PhysioFlow® Hemodynamics Redefined™

SCIENTIFIC LITERATURE REVIEW

PhysioFlow® Signal-Morphology Impedance Cardiography

A multidisciplinary review of validation, clinical applications,

exercise haemodynamics and integrative physiology

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Scientific and educational publication
Not a Clinical Evaluation Report or regulatory dossier

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1. Executive Summary

Version 1.0 18 September 2026 — Initial controlled edition.

Take-home conclusion. PhysioFlow should be considered a mature platform for continuous, non-invasive haemodynamic measurement and physiological phenotyping—especially during exercise and other dynamic challenges—not a technology awaiting its first validation. Its most consistent strengths are repeatability, sensitivity to within-person change and the ability to add a continuous circulatory dimension to integrated testing. Comparative studies generally report acceptable or clinically coherent performance under defined conditions, while a small number of discordant results remain important. Absolute values are not universally interchangeable with every comparator.

Evidence at a glance

Documented corpus	Records classified as articles	Abstract-related records	Records evaluable for result orientation	Human enrolments
328 unique records	262	49	314 of 328	≈9,000 reported (range 8,000–10,000)

The publication matrix contains 328 records in total. Of these, 314 are eligible for classification as favourable, neutral, mixed/non-conclusive or adverse; 12 contextual records and two concerning other devices are excluded from that calculation. Records are not necessarily independent studies or unique cohorts. The enrolment estimate is approximate because cohorts may overlap and some reports lack extractable sample sizes.

Take-home messages

- PhysioFlow has been used for more than twenty-five years across validation, cardiology, pulmonary medicine, systemic disease, paediatrics, rehabilitation, human performance, hypoxia, environmental physiology and experimental research.
- Its strongest recurring use is dynamic interpretation: following stroke volume, cardiac output, cardiac time intervals and derived variables across exercise, recovery, posture, treatment or serial testing.
- Across the comparative literature, acceptable or clinically coherent performance is reported in most defined settings, with a small number of clearly identified discordant results. Findings are most consistent with contemporary device generations, appropriate electrodes, careful skin preparation, stable calibration and documented adherence to the current IFU.
- Because most comparison studies were not designed as formal non-inferiority trials, the appropriate conclusion is broad comparability under defined conditions—not statistical proof of universal non-inferiority or numerical identity.

Clinical interpretation and use

- Integrated CPET and continuous haemodynamics can help distinguish the contributions of stroke-volume reserve, chronotropic response, ventilation and peripheral oxygen utilisation to exercise limitation. The arteriovenous oxygen-content difference calculated from oxygen uptake and cardiac output is a whole-body derived variable, not a direct measurement of skeletal-muscle extraction. These complementary measurements add mechanistic information beyond peak oxygen uptake alone.
- The best-developed clinical signals include heart-failure phenotyping and prognosis, CTi/stroke-volume profiling in rehabilitation, cardiopulmonary limitation in COPD and pulmonary hypertension, and integrative exercise physiology. Evidence maturity nevertheless differs by application.
- PhysioFlow is an adjunct to clinical reasoning. It does not replace invasive pressure measurements, imaging or disease-specific diagnostic standards when those are required.
- An unexpected early or disproportionate deterioration in the exercise haemodynamic trajectory—particularly a fall in CTi or stroke volume while heart rate and workload continue to rise—should not be dismissed solely because ECG, symptoms or conventional endpoints remain reassuring. The finding is not diagnostic and does not constitute an automatic stopping rule, but it may warrant greater caution, closer recovery observation, a more conservative initial exercise prescription or additional contextual assessment.
- Future studies should no longer default to generic feasibility work. The highest-value questions concern prespecified haemodynamic profiles, decision impact, transparent IFU compliance, data sharing and implementation in clinical gaps that remain poorly resolved by current pathways.

Chapter 8 provides the full cross-domain synthesis, including evidence-accounting definitions, adoption bias, limitations and the targeted research programme. This Executive Summary is a navigation aid; it does not replace the detailed methodological and application chapters.

Acknowledgments and Document Status

Acknowledgments

A special acknowledgment is owed to Dr Jean Bour, MD, whose technical and clinical intuitions were foundational to PhysioFlow. Without his contribution, neither the technology nor the body of work synthesised here would have existed.

We also thank the investigators, clinicians, engineers, technicians, research participants and patients who have studied PhysioFlow or contributed to this multidisciplinary evidence base. Its breadth reflects their collective work across laboratories, clinics, hospitals, rehabilitation programmes and field environments worldwide.

Document status

Version 1.0 · 18 September 2026 — Initial controlled edition.

Versioning note. Version 1.0 is the first officially numbered and controlled edition of the PhysioFlow Scientific Literature Review. It supersedes the unnumbered 2024 PhysioFlow Clinical Studies Reference Guide and marks the transition from a compilation to a structured critical synthesis.

Primary evidence register: Master Evidence Matrix v15.1 (3 September 2026), document-control edition with fields for CER screening. These fields do not constitute a completed regulatory CER reconciliation.

This publication is a scientific and educational literature review intended for clinicians, distributors and industrial partners. It is not a Clinical Evaluation Report (CER), a regulatory dossier, a substitute for the current Instructions for Use, or individual medical advice. Device use, interpretation and claims must remain consistent with the intended purpose, current labelling and applicable local requirements.

The matrix is maintained as a living evidence register. Later discoveries, full-text confirmations, author responses and publication-family reconciliation may change documentary counts or the interpretation of individual records without invalidating the structure of the synthesis.

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2. Scope, Methodology and Evidence Accounting

2.1. Purpose and scope

This report synthesises the documented scientific literature involving PhysioFlow and closely related signal-morphology impedance cardiography applications. It is designed to help readers understand what the corpus collectively establishes, where evidence is application specific, which methodological boundaries remain material, and how continuous non-invasive haemodynamics may complement established physiological and clinical assessment.

The report is not a catalogue in which publication count substitutes for appraisal. Validation, reproducibility, physiological application, prognostic association, implementation and economic relevance answer different questions and are therefore interpreted separately. The same publication may inform more than one question, but it is not counted as an independent replication merely because it appears in more than one chapter.

2.2. Sources and device identification

The publication matrix reconciles the 2024 Clinical Studies Reference Guide, successive historical Excel surveillance files, the Zotero collection supplied by collaborators, conference abstracts and photographed posters, author- or investigator-provided material, and targeted bibliographic and full-text searches. The historical compilation and supplementary files contain references whose use of PhysioFlow had already been confirmed by the manufacturer's scientific team. Newly discovered records were assessed separately; where publications use only the generic term impedance cardiography, device identification may require full-text review or direct confirmation from the investigators.

Two records concerning other devices (BioZ and pOpmetre) are retained in the matrix for traceability and excluded from the PhysioFlow result-orientation denominator. Records for which device use remains unresolved are labelled accordingly rather than silently accepted or discarded.

2.3. Units of evidence and publication families

Unit	Definition and use
Documentary record	One unique article, abstract, thesis, report, protocol, correspondence item or other citable source.
Publication family	Records that report the same, overlapping or enlarged cohort; retained for traceability but not treated automatically as independent replication.
Independent study/cohort	A distinct participant dataset and protocol. This is the more relevant unit for replication, but it is not recoverable with certainty for every historical record.
Reported enrolment	The participant number reported in a source. The global estimate reconciles obvious overlap where possible but is not an exact count of unique individuals.

2.4. Orientation of results

Orientation is coded from the device-relevant measurement question, not from whether an intervention or clinical hypothesis succeeded. A null treatment effect is not adverse evidence against PhysioFlow when the participant may genuinely have remained unchanged. Conversely, a favourable intervention result does not validate measurement accuracy by itself.

Documentary orientation	Operational definition	Evaluable records, n (%)
Favourable	Agreement with a credible reference, reproduction of an established response, or coherent and useful physiological, clinical or prognostic information.	281 (89.5%)
Neutral	No device-relevant discrepancy; a stable or null result is compatible with an unchanged physiological state or a non-device primary question.	18 (5.7%)
Mixed / non-conclusive	Supportive and discordant findings coexist, or protocol, comparator, IFU, software generation or data availability prevents confident attribution.	12 (3.8%)

Documentary orientation	Operational definition	Evaluable records, n (%)
Adverse	A material PhysioFlow result conflicts with a credible external truth or firmly established standard without an adequate methodological explanation.	3 (1.0%)

The matrix contains 328 documentary records: 314 are evaluable for PhysioFlow result orientation, while 12 contextual records and two concerning other devices are excluded from that analysis. All orientation percentages therefore use 314, not 328, as their denominator. These proportions describe audited records, not independent trials, unique cohorts, formal diagnostic accuracy or a commercial success rate.

2.5. Evidential weight, landmark markers and affiliation flags

Each result is weighted according to design, sample, comparator, simultaneity, protocol relevance, device generation, signal quality, IFU compliance, statistical approach, publication status, data transparency and independence from prior cohorts. Abstracts and case reports remain visible but cannot carry the same weight as complete peer-reviewed datasets.

★ identifies a landmark/core publication whose design, size, originality, clinical relevance or integrative value makes it structurally important to this synthesis. The marker is an editorial navigation aid—not a formal risk-of-bias grade, regulatory endorsement or assertion that the study is methodologically flawless.

Small flags at the end of bibliography entries indicate the countries of the first- and last-author affiliations where this information is available. A single flag is shown when both are identical. Flags refer to reported institutional affiliation, not personal nationality.

2.6. IFU, comparators and claim boundaries

PhysioFlow performance is interpreted in relation to device generation and acquisition quality. Electrode type and condition, skin preparation, placement within recommended anatomical areas, lead integrity, patient position, demographic inputs, calibration or autocalibration, exercise protocol and signal-quality criteria can materially affect inference. Results obtained with legacy hardware, non-commercial software or uncertain IFU compliance remain part of the historical record but should not be projected uncritically onto current systems.

No practical cardiac-output comparator is error free. Measured-variable Fick, thermodilution, rebreathing, Doppler and magnetic-resonance methods have different assumptions, timing constraints and sources of uncertainty. Agreement, tracking and repeatability are therefore separated. Formal statistical non-inferiority is claimed only when a study was designed for that purpose; elsewhere, the report uses the more appropriate language of comparability, coherence and context-dependent agreement.

3. Clinical Validation, Reproducibility and Methodological Considerations

3.0. How to read the validation evidence

Validation of a cardiac output measurement method cannot be reduced to a single correlation coefficient or to a binary conclusion that the device “works” or “does not work”. Cardiac output is not directly observable, and all available reference methods are themselves affected by measurement uncertainty. The somehow incorrectly named “direct” Fick method remains a calculation rather than a direct measurement of cardiac output: it depends on accurate and appropriately timed measurements of oxygen uptake and arteriovenous oxygen content difference. Thermodilution is sensitive to injection technique, respiratory variation, intracardiac or valvular abnormalities, and physiological instability. Rebreathing, indicator-dilution and imaging methods also have method-specific limitations. Disagreement between PhysioFlow and a comparator therefore does not necessarily identify which method produced the less accurate value.

Three complementary aspects should be distinguished. Absolute agreement assesses whether two methods provide sufficiently similar cardiac output values at a given time. Tracking ability assesses whether PhysioFlow appropriately detects the direction and magnitude of a physiological change, particularly from rest to exercise. Reproducibility determines whether repeated measurements obtained under comparable conditions remain sufficiently stable. A method may track exercise-induced changes reliably without being strictly interchangeable with every comparator at the individual level.

The studies reviewed in this chapter are therefore interpreted according to the reference method, study population, protocol, simultaneity of measurements, device generation, signal-quality conditions and statistical approach. Particular attention is paid to whether measurements were obtained during physiological steady state and whether the limits of agreement are clinically interpretable. The overall evidence is considered as a body of converging or conflicting results rather than as a succession of isolated verdicts.

3.1. Comparative validation studies

The comparative evidence is presented first through the foundational exercise studies and then across protocols and populations that impose distinct methodological constraints. Particular attention is given to chronic obstructive pulmonary disease (COPD), pulmonary hypertension, paediatric and congenital heart disease, and intensive-care settings. Favourable, discordant and inconclusive findings are retained and interpreted according to the comparator, protocol, device generation and measurement conditions.

3.1.1. Foundational validation against the measured-variable Fick method

The first peer-reviewed validation studies established the methodological basis for subsequent use of PhysioFlow at rest and during exercise. ★ Charloux et al. compared cardiac output obtained by the original signal-morphology impedance cardiography system with values derived using the measured-variable Fick method. This comparator is particularly relevant because cardiac output is calculated from measured oxygen uptake and measured arteriovenous oxygen-content difference rather than from another non-invasive estimation technique. The conventionally termed “direct Fick” method does not measure cardiac output directly: it calculates $\dot{Q}c = \dot{V}O_2 / [CaO_2 - C\bar{v}O_2]$ from three measured variables, each carrying uncertainty. Here, “direct” distinguishes measured oxygen uptake from an estimated-$\dot{V}O_2$ Fick calculation.

The study showed close relationships between PhysioFlow and Fick-derived measurements across resting and exercise conditions. Importantly, agreement was maintained when cardiac output increased, supporting the ability of the method to follow a substantial physiological response rather than merely reproduce resting values. The study nevertheless needs to be interpreted within its experimental setting: carefully controlled measurements and an experienced investigation team cannot automatically represent every clinical or field-use condition.

★ Richard et al. subsequently evaluated PhysioFlow during maximal progressive exercise. This study extended the initial findings by examining the full transition from rest to maximal exertion, when motion, ventilation and rapid haemodynamic changes make non-invasive measurement particularly demanding. PhysioFlow followed

the expected increase in cardiac output throughout the test and provided reproducible measurements, without evidence of a systematic loss of performance at the highest exercise intensities.

Together, these two studies constitute the foundational evidence for PhysioFlow. They support both the estimation of cardiac output and, more specifically, the measurement of its dynamic response to exercise. Their main contribution is not to establish universal interchangeability with the Fick method, but to demonstrate that signal-morphology impedance cardiography can capture physiologically coherent haemodynamic changes over a wide range of cardiac outputs.

3.1.2. Validation during steady-state and graded exercise

Subsequent studies examined PhysioFlow under a broader range of exercise protocols and against several alternative comparators. This expansion is important because agreement observed under one protocol cannot automatically be extrapolated to constant-load exercise, incremental exercise or rapidly changing physiological conditions.

★ Tordi et al. compared PhysioFlow with an independent non-invasive cardiac output method during constant-load exercise. The study reported satisfactory agreement across successive exercise levels and supported the ability of PhysioFlow to follow cardiac output during steady-state conditions. Such protocols are methodologically favourable because both techniques can be compared after the cardiovascular response has stabilised.

Other investigations extended this assessment to progressive or more demanding exercise. Robach and colleagues obtained physiologically coherent PhysioFlow responses in an experimental setting involving substantial changes in oxygen transport. Broeder et al. reported favourable agreement during submaximal steady-state exercise, although the limited publication format and use of an estimated Fick comparator restrict the depth of methodological appraisal. Kapchinsky et al. also found supportive results when PhysioFlow was compared with rebreathing techniques, while showing that different cardiac output methods should not necessarily be considered individually interchangeable.

More recently, ★ Filaire et al. compared concomitant PhysioFlow and Innocor measurements in 50 healthy adults during incremental cycling, with repeat constant-load measurements in a subgroup of 12. Mean between-method differences were small and non-significant (0.002 ± 0.98 L/min at rest and 0.38 ± 1.31 L/min during incremental exercise), and the correlation was stronger during exercise ($r = 0.83$) than at rest ($r = 0.40$). Intra-individual variability was below 6% during the repeated exercise conditions, whereas resting Innocor measurements were more variable (CV = 18%, compared with 4.5% for PhysioFlow). These findings support concordant exercise tracking and useful repeatability under controlled conditions, but not automatic numerical interchangeability. The methods use different physiological and modelling assumptions—thoracic signal morphology for PhysioFlow and inert-gas rebreathing for Innocor—which may contribute to method-specific values even when trends agree.

Siebenmann et al. simultaneously compared the measured-variable Fick method, inert-gas rebreathing, PhysioFlow and pulse-contour analysis during incremental exercise in normoxia and hypoxia. All four methods detected increasing cardiac output, but the cardiac-output-to-oxygen-uptake slopes differed by as much as 50%. PhysioFlow produced a physiologically plausible slope in normoxia and detected the expected increase in hypoxia, which pulse-contour analysis did not. The study primarily demonstrates method dependence rather than the superiority of any single comparator.

Del Torto et al. compared repeated, parallel measurements by PhysioFlow and inert-gas rebreathing in seven young, fit subjects during submaximal and supramaximal cycling. At submaximal workloads, the two methods showed similar coefficients of variation (8.6% and 7.7%, respectively), and the authors considered PhysioFlow a valuable alternative for assessing cardiac output under these conditions. At supramaximal intensity, PhysioFlow values were on average 9% lower and the relationship between methods showed proportional bias. This difference should not be attributed to PhysioFlow alone, however, because repeatability at that intensity was substantially better for PhysioFlow than for rebreathing (coefficients of variation 7.6% versus 27.7%). The study therefore supports submaximal use while illustrating the difficulty of assigning accuracy when the comparator becomes unstable at extreme intensity.

Wang et al. reported poor absolute agreement between PhysioFlow and single-breath acetylene uptake in 20 moderately trained men at rest and during cycling, with lower PhysioFlow values and wide between-method limits of agreement. Both methods nevertheless showed broadly similar test–retest reliability. The study therefore separates a reproducible within-method response from interchangeability between methods. Its

applicability is further limited by a subsequently identified ECG-detection defect in the firmware of the early Enduro unit used, which affected heart-rate calculation and signal-filter triggering; retrospective recalculation was not informative because a true resting condition had not been maintained after calibration.

Overall, the exercise validation literature is most consistent when measurements are obtained under well-defined conditions, with appropriate signal quality and sufficient physiological stabilisation. The evidence is particularly strong for following the direction and amplitude of the haemodynamic response from rest to exercise. This capacity is central to the assessment of exercise haemodynamics and haemodynamic reserve, while remaining compatible with the device's intended use.

3.1.3. Validation in chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease is a particularly demanding validation context. Hyperinflation, large ventilatory excursions and altered thoracic geometry may affect signal acquisition, while rapidly changing exercise conditions can also weaken the assumptions of the comparator. The studies in this population are therefore best read according to protocol rather than combined into a single favourable or unfavourable verdict.

★ Louvaris et al. directly addressed cardiac output measurement during cycle exercise in patients with COPD, using concomitant indocyanine-green dye-dilution measurements. PhysioFlow showed acceptable agreement from rest to peak exercise. This study is important because it evaluates the dynamic response in the target physiological setting with a simultaneously applied indicator-dilution comparator. The sample was limited and acceptable agreement does not imply strict interchangeability of every individual value, but the findings provide central supportive evidence for exercise haemodynamics in COPD.

Kapchinsky et al. provide complementary evidence under submaximal steady-state conditions. Eight stable patients with COPD completed two sessions with measurements at rest and after five-minute stages at 20, 35, 50 and 65% of peak work rate. All three methods produced physiologically plausible values, and test–retest reproducibility was highest for PhysioFlow ($R^2 = 0.80$), compared with inert-gas rebreathing ($R^2 = 0.72$) and CO_2 rebreathing ($R^2 = 0.53$). However, systematic differences in absolute values remained between methods, and the evidence is limited by the small sample and abstract-only publication.

Bougault et al. reported overestimation at high intensity in eight patients with moderate-to-severe COPD and hyperinflation. This finding should remain visible, but its interpretation is constrained by the maximal and intermittent exercise protocol. These rapidly changing conditions do not ensure the metabolic and haemodynamic steady state required for robust application of the measured-variable Fick calculation. The study therefore identifies a boundary condition rather than establishing a general invalidation of PhysioFlow. Considered together, the COPD literature is most coherent when measurements are concomitant and obtained under physiologically interpretable conditions.

3.1.4. Pulmonary hypertension: apparently conflicting evidence

The pulmonary-hypertension studies appear conflicting if their conclusions are read without regard to reference method, simultaneity and device generation. They should not be averaged into a single estimate or used selectively; each addresses a different measurement context.

Tonelli et al. prospectively studied 39 patients undergoing evaluation for pulmonary hypertension. Mean cardiac output was 5.9 ± 2.2 L/min by thermodilution and 5.6 ± 1.5 L/min by PhysioFlow, with a bias of 0.3 L/min and limits of agreement from −2.2 to +2.8 L/min. These results support reasonable group-level accuracy but only moderate individual precision. PhysioFlow measurements were obtained immediately after, rather than simultaneously with, catheterisation, and the secondary Fick comparison used estimated VO_2. Both points limit the inference of individual interchangeability.

★ Dupuis et al. subsequently compared impedance cardiography with both the measured-variable Fick method and thermodilution during right-heart catheterisation. In this resting pulmonary-hypertension cohort, PhysioFlow cardiac output was considered reliable relative to the invasive comparators. This study provides the principal favourable evidence in this population, while remaining limited by its sample size and resting protocol.

By contrast, Panagiotou et al. found poor agreement with cardiac magnetic resonance imaging in pulmonary arterial hypertension, with a reported bias of approximately 1.40 L/min and wide limits of agreement. This unfavourable result must be retained. Its direct transposition to current systems is nevertheless limited because the study used an earlier Enduro hardware configuration with a less capable amplifier in a population in which

signal acquisition is particularly demanding. The three studies therefore support cautious use under documented conditions and close attention to signal quality, rather than either an unrestricted claim or a blanket rejection.

3.1.5. Paediatric and congenital heart disease evidence

The paediatric evidence illustrates why population, age, anatomy and device evolution must be considered explicitly. Taylor et al. reported insufficient agreement between PhysioFlow and cardiac magnetic resonance imaging for stroke volume and cardiac output. The adverse result remains part of the evidence record, but its weight is limited by an unusually weak audit trail. According to the manufacturer's historical records, the recordings originated as pilot or preparatory observations in congenital patients using a 2004–2006-generation system. By the time the analysis was undertaken, the original signal files were no longer available and only a residual spreadsheet could be reviewed. Signal quality, cycle selection, configuration, IFU compliance and reprocessing could therefore not be audited retrospectively.

★ Ebrahim et al. later reported favourable agreement with cardiac magnetic resonance imaging in children with a range of congenital heart diseases, and subsequent paediatric application studies produced more coherent exercise-haemodynamic findings. Taylor should therefore remain visible as an adverse historical report, but not be treated as an evidentially equivalent counterweight to later datasets whose source signals, methods and clinical context were more fully documented. The contrast argues for data preservation and transparent acquisition records rather than for selective exclusion of an inconvenient result.

Additional observations are supportive but less definitive. Haraldsdottir et al. reported favourable absolute and trend relationships with cardiac magnetic resonance imaging in adolescents born prematurely, whereas Haynes et al. reported favourable correlation with thermodilution in a paediatric conference abstract. Their limited publication formats and specific populations prevent broad extrapolation. Overall, the evidence is more reassuring in older children and selected congenital populations than in very young children; below the age boundary specified in the current clinical documentation, further performance evidence remains necessary.

Longitudinal reliability of peak stroke volume index after congenital heart disease repair was additionally examined by ★ Legendre et al.; because this study addresses repeatability and minimum detectable change rather than agreement with a comparator, it is discussed in Section 3.2.2.

3.1.6. Resting and intensive-care comparisons

Resting and intensive-care comparisons extend the evidence to heterogeneous patients and technically difficult environments, although much of this material is available only as conference abstracts or regulatory documentation. It should therefore corroborate, rather than replace, the peer-reviewed validation literature.

Bogui et al. compared PhysioFlow-derived stroke volume index and cardiac index with Doppler echocardiography in 25 healthy participants and 32 patients with chronic anaemia, predominantly sickle-cell disease. PhysioFlow did not reproduce the between-group differences identified by echocardiography, and the methods were not interchangeable. The reported dependence of stroke volume on body surface area was also inconsistent with the intended calculation. From the manufacturer's perspective, the study used a non-commercial development software version containing erroneous algorithms, which had circulated inadvertently and should never have been used for clinical or research measurements. The investigators did not subsequently provide sufficient information to identify the exact version or permit reprocessing of the recordings. The findings must remain visible, but they cannot be considered representative of a released commercial PhysioFlow configuration.

Moreau et al. reported a series of 107 medical and surgical intensive-care patients at the University Hospital of Angers, with bolus or continuous Swan–Ganz thermodilution as the comparator. The reported correlation was $r = 0.88$ and the mean bias was close to zero. The abstract format, heterogeneous thermodilution procedures and absence of individual-level data limit a more complete appraisal. Haynes et al. subsequently reported a multicentre comparison in 112 patients across four American and French hospitals. Mean cardiac output was 5.41 versus 5.31 L/min, the reported correlation was $r = 0.85$, and 75% of measurements differed by less than 20%. This study was likewise published only as an abstract.

The later MUSC–UPMC controlled study submitted to the US Food and Drug Administration provides additional, unpublished regulatory corroboration. In the 64 paired cases in which both PhysioFlow and the predicate Philips impedance device produced measurements under acceptable conditions, PhysioFlow was in "very close agreement" with thermodilution when the predicate was not in 22 cases, whereas the reverse occurred in three cases (exact McNemar test $p < 0.0001$). Across the 84 acceptable PhysioFlow measurements, 64 (76.2%) met

the FDA-defined agreement criterion. PhysioFlow also produced measurements in more patients than the predicate device. These findings supported regulatory clearance, but they should be identified transparently as a controlled regulatory study rather than a peer-reviewed publication.

Heshmati et al. assessed dynamic stroke-volume change during passive leg raising in 50 patients shortly after cardiac surgery. Relative stroke-volume change measured by PhysioFlow discriminated preload responders, defined by echocardiographic velocity-time integral change, with an area under the receiver-operating-characteristic curve of 0.818; a threshold of 20.7% provided 86.2% sensitivity and 90.5% specificity. This conference report supports tracking of an acute preload response rather than absolute interchangeability with echocardiography.

Together, these data support feasibility and provide supportive evidence of resting agreement in difficult care settings. Because the principal sources are abstracts and a regulatory report, they remain corroborative and should not be treated as the main evidence for exercise performance.

3.1.7. The isolated unresolved negative signal

In ten men with chronic heart failure, Kemps et al. reported marked overestimation of absolute cardiac output at rest and during exercise relative to the Fick-based comparator (bias approximately +48%, with wide limits of agreement). Unlike the methodologically inconclusive studies discussed above, no established technical or protocol-related explanation accounts for this discrepancy.

The study used early PhysioFlow Lab1 hardware and software; configuration and post-production verification procedures have since evolved substantially. From the manufacturer's perspective, an undetected configuration or calibration issue remains possible, but cannot be verified retrospectively. The finding must therefore remain classified as unexplained.

Tracking of intra-individual exercise-induced changes was more acceptable (bias −2%; limits of agreement approximately ±36%), reinforcing the distinction between absolute agreement and tracking ability. Kemps remains the principal unexplained cautionary signal in the corpus, without constituting a general invalidation.

3.2. Reproducibility and measurement reliability

Reproducibility addresses a question that is distinct from comparative agreement: whether repeated PhysioFlow measurements obtained in the same person under comparable conditions remain sufficiently stable. It depends not only on the measurement technology, but also on protocol standardisation, electrode condition, positioning within the recommended anatomical areas, resting calibration, signal quality and the magnitude of the physiological change being assessed.

3.2.1. Evidence supporting repeatability

Welsman et al. examined maximal exercise measurements in 20 children aged 10–11 years across three tests separated by one week. No systematic drift was observed. The reported typical error was 9.3% for maximal cardiac output and stroke volume, compared with 4.1% for peak oxygen uptake. Although the study used an older protocol and a specific paediatric population, it provides early evidence that repeated PhysioFlow measurements can remain stable across separate maximal exercise tests.

★ Tan et al. specifically investigated the effect of electrode repositioning in 30 subjects. Changing electrode placement produced a bias of 0.046 L/min, limits of agreement from −0.24 to 0.34 L/min and a mean difference of 0.86%. The study does not test accuracy against an invasive reference, but shows that modest repositioning had only a limited effect on cardiac output under controlled conditions. Electrode placement nevertheless remains a factor that should be standardised whenever small serial changes are interpreted.

More recent studies extend these findings. In addition to the comparative results discussed in Section 3.1, ★ Filaire et al. found low within-subject variability during repeated exercise. Del Torto et al. likewise found repeatability comparable to inert-gas rebreathing at submaximal workloads and markedly better repeatability for PhysioFlow at supramaximal intensity, although the small sample limits precision. Together, these studies support useful repeatability of cardiac output and stroke volume from rest to exercise when acquisition conditions are controlled.

McCarthy et al. focused specifically on duplicate-measurement error in 60 healthy adults (30 women), comparing PhysioFlow Enduro with nitrous-oxide inert-gas rebreathing (Innocor) at rest, 50 W and 90% of peak power output. Typical error was lower for PhysioFlow at all three levels: 0.4 versus 0.6 L/min at rest, 0.5 versus

0.8 L/min at 50 W, and 0.7 versus 1.2 L/min at 90% of peak power. At the highest intensity, relative typical error was 4.0% for PhysioFlow and 7.5% for Innocor, with ICC values of 0.96 and 0.89, respectively. The overall error variance was significantly greater with Innocor ($p < 0.0001$). However, duplicate values could still differ by approximately 3 L/min (24%) with PhysioFlow and 4 L/min (38%) with Innocor. The study therefore supports better group-level precision for PhysioFlow under this protocol, while also showing why isolated individual measurements should not be over-interpreted.

★ Hsu et al. also reported a separate reproducibility series conducted within the 2006 altitude/sildenafil programme. Twenty healthy, fit men completed repeat cycle-ergometer VO_2peak tests at least two days apart. At peak exercise, the coefficients of variation were 3.6% for stroke volume and 3.4% for cardiac output. These results describe favourable best-case repeatability during a highly standardised maximal exercise protocol. Because the series is reported only briefly within the methods of a paper whose primary objective was not reproducibility, it should be treated as supportive evidence rather than as a standalone validation study.

Additional protocol-specific evidence is directionally supportive. Wang et al. found similar test–retest reliability for PhysioFlow and acetylene uptake despite poor between-method agreement, subject to the firmware limitation described in Section 3.1.2. Aron et al. reported reproducible cardiac output, stroke volume and heart-rate responses across three visits during repeated Müller manoeuvres in 15 healthy men. In an unpublished university study of 21 men, Rodriguez reported coefficients of variation below 8% for primary haemodynamic variables during repeated moderate and vigorous treadmill exercise, with weaker findings for some secondary or derived variables. Aron provides narrow population-specific support; Rodriguez remains low-level documentary evidence rather than a peer-reviewed validation study.

3.2.2. Individual-level sensitivity and parameter-specific limitations

★ Legendre et al. provided clinically relevant information on the magnitude of change required to exceed expected variability in 30 young patients with residual right ventricular outflow tract lesions after congenital heart disease repair. Overall reliability of peak stroke volume index was high (ICC = 0.80), but depended strongly on the measured value. At peak SVi ≤ 50 mL/m², the ICC was 0.95 and the minimum detectable difference was 7.3%, whereas reliability was substantially lower at higher SVi values; cardiac index also showed wider minimum detectable differences. These results support parameter- and value-specific thresholds for individual follow-up. However, the approximately one-year interval between tests, during a period of growth, means that the study reflects longitudinal stability under clinical conditions rather than short-term instrumental repeatability alone.

Repeatability should not be assumed to be identical for every PhysioFlow parameter. Gordon et al. reported good intrarater reliability for heart rate, stroke volume, cardiac output, left cardiac work index and end-diastolic volume in 19 analysable participants from rest to high-intensity exercise, but less consistent results for other variables. More importantly, some findings are not mathematically coherent: cardiac output and stroke volume were classified as reliable whereas cardiac index and stroke volume index were not. Because body surface area is constant between repeated tests, indexing is only a linear rescaling and cannot alter true reproducibility when the same observations and analytical approach are used. This points to an analytical, classification or reporting issue rather than a physiological difference. Similar caution applies to discordant derived parameters sharing the same inputs. Gordon therefore supports selected primary variables, but not a parameter-by-parameter interpretation of reproducibility.

★ Schoch et al. more recently assessed 31 healthy, well-trained adults during two identical incremental cycle tests performed seven days apart. Mean intraclass correlation coefficients were good for heart rate, stroke volume and cardiac output at VT1, VT2 and peak exercise (approximately 0.77–0.93), but the wide individual limits of agreement and detectable changes led the authors to conclude that reliability was insufficient for individual comparisons. The study is therefore an important counterpoint, particularly against over-interpretation of small changes in a single patient. Its conclusion should nevertheless be confined to the protocol investigated. Reliability was a secondary, exploratory outcome without a dedicated sample-size calculation, and measurements were compared between two visits. Matching external work rate does not ensure an identical internal physiological state; the observed dispersion therefore combines instrument-related variability with day-to-day biological and exercise-response variability.

The article reports PhysioFlow HTFS50PF electrodes, recommended skin preparation and a 30-beat resting calibration. Post-publication clarification sought by the manufacturer did not establish the electrodes' provenance or labelled-expiry status, and the published report does not provide enough operational detail to

determine whether resting and calibration conditions were reproduced identically at both visits. Participant-level data were not available to the manufacturer for independent technical reanalysis. These unresolved points do not invalidate the reported variability; they limit attribution of its full magnitude specifically to the measurement technology.

The results should also be considered alongside the nearly contemporaneous study by ★ Filaire et al. In 50 healthy adults, with repeat constant-load exercise measurements in a subgroup of 12, PhysioFlow cardiac output showed intra-individual variability below 6% during the repeated exercise conditions. The protocols are not directly equivalent—between-day incremental testing in Schoch versus repeated controlled constant-load bouts in Filaire—so neither study cancels the other. Together, they indicate that individual repeatability is materially influenced by protocol, physiological standardisation, calibration and acquisition conditions, and should not be inferred from a single study design.

Overall, reproducibility is most extensively documented for cardiac output and stroke volume. Controlled protocols include best-case peak-exercise coefficients of variation of 3.4–3.6% in the Hsu series and a 4.0% typical error for cardiac output at 90% of peak power in McCarthy, whereas other populations and protocols yield larger errors. As a cautious practical guide, changes of less than approximately 7% in these primary variables should generally not be over-interpreted at the individual level, because they may remain within expected repeatability limits even under controlled conditions. This value is an interpretive reference rather than a universal cut-off: repeatability varies with the parameter, population, exercise protocol, signal quality and interval between measurements, and some published estimates are higher. Conversely, a change exceeding 7% is not by itself proof of physiological or clinical significance and should be assessed against the complete haemodynamic and exercise response. Published reporting is less consistent for some indexed or derived variables; because indexing by a constant body-surface area is a linear rescaling, it cannot by itself change true reproducibility. Serial studies should use a standardised protocol, fresh electrodes, recommended positioning, skin preparation and stable calibration.

3.3. Methodological considerations and boundary conditions

The evidence reviewed above does not support a single context-independent estimate of validity. Each comparison tests a combination of device generation, population, protocol, reference method and acquisition conditions. The most useful boundary conditions concern the uncertainty of the comparator, the timing and physiological relevance of the protocol, and the conditions under which a usable impedance signal is obtained.

3.3.1. Reference methods and simultaneity

No comparator provides a direct and error-free measurement of cardiac output. The measured-variable Fick method, thermodilution, indicator dilution, inert-gas rebreathing, cardiac magnetic resonance imaging and Doppler-based methods each rely on different assumptions and sources of uncertainty. Agreement must therefore be interpreted in relation to the comparator used rather than against an abstract error-free truth. Correlation alone is insufficient to establish agreement, while differences in absolute values do not preclude useful tracking of physiological change.

Timing is equally important. Concomitant measurements, as in the more recent study by ★ Filaire et al., reduce the risk that physiological variation is mistaken for disagreement. Sequential comparisons become more difficult during exercise or clinical instability. The measured-variable Fick calculation additionally requires appropriately matched gas-exchange and blood measurements and a sufficiently stable physiological state. Conversely, use of estimated oxygen uptake introduces a further source of error, as in the Tonelli comparison. Bougault illustrates how absence of a clear steady state at high-intensity exercise can make a nominal Fick comparison methodologically inconclusive.

3.3.2. Protocol relevance and physiological plausibility

A comparison informs performance only within the population and physiological challenge that it actually examines. Cheung et al. reported an unfavourable comparison during successive head-up tilt positions in trained athletes. The result remains relevant, but its interpretation was contested because head-up tilt is not equivalent to exercise and because USCOM had not been adequately established as a reference under those specific conditions. Moreover, the mean USCOM cardiac index was below 2.0 $L \cdot min^{-1} \cdot m^{-2}$ in three reported positions—1.96 supine, 1.67 at 70° and 1.91 at 30°—despite a young, trained population without a corresponding abnormal heart-rate response. These unexpectedly low values raise a physiological-plausibility

concern about the comparator measurements themselves. The study therefore identifies an unresolved protocol-dependent disagreement rather than a general verdict on exercise measurement.

The same restraint applies to other specialised designs. Gonzalez-Represas compared resting measurements before and after cardiac rehabilitation with non-continuous echocardiographic and tonometric assessments; the methods were not interchangeable and did not track all longitudinal changes consistently, while the comparator itself remained subject to temporal and operator variability. Małek et al. found coherent associations but imperfect absolute agreement in wheelchair rugby players with tetraplegia, using echocardiography only at rest. Together with Bougault, these studies show that population specificity, lack of simultaneity and rapidly changing physiology can materially limit the scope of a conclusion.

3.3.3. Device generation, electrodes and signal quality

Results obtained with early hardware or software configurations should remain visible but should not be assumed to quantify the performance of the current system. The unfavourable Panagiotou study in pulmonary arterial hypertension used an earlier Enduro configuration with a less capable amplifier in a particularly demanding population. Bougault also used an early configuration under difficult high-intensity conditions. Wang used an early Enduro unit with a subsequently identified ECG-detection firmware defect. Bogui is the clearest software-specific case: measurements were generated by an inadvertently circulated development version containing erroneous algorithms, not by released commercial software. These studies define historical and technical boundary conditions; they are not dismissed, but their direct transposability to current devices is limited.

Signal quality also depends on skin preparation, electrode condition, positioning within the recommended anatomical areas, cable integrity and an appropriate resting calibration. This does not imply that placement must be exact to the millimetre: ★ Tan et al. found only a small effect of modest repositioning under controlled conditions. It does mean that unexplained outliers or poor reproducibility should prompt review of the acquisition and signal-quality record before being attributed to physiology or to the measurement principle. Performance claims should therefore be understood as conditional on use within the recommended operating procedures and on acquisition of an interpretable signal.

Overall, the main methodological lesson is not that discordant studies should be excluded, but that their evidential weight depends on what was actually tested. The strongest conclusions concern controlled, concomitant measurements and changes larger than expected measurement variability. Greater caution is required for small individual changes, non-simultaneous comparators, unstable physiological states, specialised populations and legacy device configurations.

Practical take-home. Contemporary PhysioFlow systems, used with appropriate electrodes, skin preparation, placement and signal-quality control, generally provide clinically coherent cardiac-output values and reproducible within-person trends. Interpret absolute agreement in relation to the comparator and protocol; do not assume universal numerical interchangeability.

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4. Clinical Applications

The application literature asks what continuous non-invasive haemodynamics contributes once the measurement platform is used in a clinical or functionally relevant population. The chapters below distinguish mechanistic phenotyping, prognosis, longitudinal monitoring and decision support. They should be read with the validation and reproducibility boundaries in Chapter 3: application evidence can demonstrate clinical coherence and usefulness, but does not by itself establish interchangeability with every reference method.

Across specialties, the strongest recurring contribution is the ability to observe the trajectory of stroke volume, cardiac output and related variables during a physiological challenge. Peak values and rest-to-peak deltas remain informative, but the timing and shape of the response—interpreted alongside heart rate, gas exchange, blood pressure, symptoms and signal quality—often contain the more discriminating information.

4.1. Cardiology

Cardiology contains the most clinically developed PhysioFlow applications: heart-failure phenotyping and prognosis, exercise haemodynamics in coronary disease, rehabilitation response, hypertrophic cardiomyopathy, and selected structural or pacing applications. No single study establishes a universal pathway. Collectively, however, the corpus shows repeated feasibility and clinically coherent information under demanding exercise and disease conditions.

4.1.1. Heart failure

Heart failure is characterised by impaired functional capacity, but the mechanisms responsible for exercise intolerance vary markedly between patients. A reduced peak oxygen uptake may reflect an inadequate increase in cardiac output, chronotropic limitation, abnormal ventricular filling, impaired peripheral oxygen extraction, ventilatory inefficiency, skeletal-muscle dysfunction, or several of these factors in combination. Resting left ventricular ejection fraction alone cannot resolve this heterogeneity. The principal application of PhysioFlow in this field has therefore been to add continuous, non-invasive haemodynamic information to cardiopulmonary or functional exercise testing, rather than to replace established diagnostic procedures.

The 2016 focused update jointly developed by the American Heart Association and the European Association for Cardiovascular Prevention and Rehabilitation provides the appropriate clinical context. It reaffirmed the central role of cardiopulmonary exercise testing in heart failure, promoted multivariable interpretation rather than reliance on peak VO_2 alone, and discussed the synergistic value of combining CPET with complementary assessments. The statement did not recommend a specific cardiac-output technology and should not be presented as validation of PhysioFlow. Its relevance here is contextual: it explains why continuous haemodynamic measurements may enrich an already established clinical test by identifying the circulatory component of limitation.

The evidence below is consequently divided into exercise haemodynamic phenotyping, prognostic and risk-stratification applications, functional and advanced-heart-failure assessment, and mechanistic or acute-intervention studies. Validation and reproducibility findings are not re-analysed here; they are addressed in Chapter 3 and are invoked only when they materially constrain interpretation of an application study.

4.1.1.1. Exercise haemodynamic phenotyping

★ Schoch et al.analysed baseline data from 43 patients with heart failure with preserved ejection fraction (HFpEF) enrolled in the HIT-HF programme. CPET was combined with impedance-derived stroke volume, haemoglobin mass, near-infrared spectroscopy and lower-limb functional measurements. In this cohort, leg muscle power and lower-limb fat-free mass were more strongly associated with peak VO_2 than the measured central haemodynamic or ventilatory variables. The study therefore supports a predominantly peripheral contribution to exercise limitation in the population examined, while also illustrating the feasibility of integrating PhysioFlow into a multicomponent oxygen-pathway assessment.

This result should be interpreted as a cross-sectional association, not as evidence that central haemodynamic reserve is unimportant in HFpEF. The sample was small, several variables required imputation, and the relative contribution of each physiological domain depends on the selected tests and statistical model. The investigators reported skin preparation, calibration over more than 30 cycles and a signal-integrity threshold of at least 95%. Nevertheless, the methodological and IFU-compliance questions raised by this research programme, together with the unresolved issues discussed in Sections 3.2.2 and 3.3.3, remain relevant. The application study is

retained on its own scientific merits, but its use of PhysioFlow does not constitute independent validation of reproducibility.

★ Kwast et al. studied 62 Stage B patients at risk of heart failure with non-reduced ejection fraction using symptoms, echocardiography, CPET and continuous cardiac-output monitoring. The cohort already showed abnormalities in total exercise capacity, cardiac performance and calculated arteriovenous oxygen difference. Symptom burden measured by the Kansas City Cardiomyopathy Questionnaire showed only modest relationships with physiological variables in the whole cohort, although sex-specific associations were stronger: cardiac power output was related to symptoms in men, whereas ventilatory inefficiency was more closely related in women. Stratification by objectively measured exercise capacity also identified differences in cardiac output and peripheral oxygen extraction that were not captured by symptom scores alone.

Kwast is particularly useful for positioning PhysioFlow along the continuum between cardiovascular risk, early functional impairment and established HFpEF. It does not demonstrate diagnostic accuracy for HFpEF, and the subgroup analyses should remain exploratory. It does, however, show why an integrated CPET-haemodynamic assessment may reveal a mixed central-peripheral limitation before resting ejection fraction becomes abnormal or symptoms provide a reliable indication of severity.

Sugita et al. studied 99 stable outpatients aged 65–80 years with HFpEF—51 with type 2 diabetes and 48 without—together with 50 age- and sex-matched controls. The diabetic HFpEF group had the lowest peak oxygen uptake, peak heart rate and calculated arteriovenous oxygen difference and the least efficient ventilation. Peak stroke-volume index did not differ significantly between groups. The integrated result therefore points to chronotropic and peripheral-extraction limitations rather than an isolated decrement in peak stroke volume.

This case–control study strengthens the concept of heterogeneous HFpEF phenotypes and shows why a preserved peak stroke-volume index does not make the haemodynamic assessment uninformative. It is observational and does not validate absolute accuracy or demonstrate a treatment decision, but it provides a coherent example of central, chronotropic and peripheral variables being interpreted together.

★ Fukuda et al. provided one of the clearest descriptions of the cardiac-output response to incremental exercise in chronic heart failure. Fourteen patients were divided according to peak VO_2, and seven age-matched controls were studied during symptom-limited cycling. In the lower-capacity heart-failure group, peak cardiac output and stroke volume were lower than in controls (11.3 versus 15.6 L/min and 89 versus 110 mL, respectively). Stroke volume reached a plateau during submaximal exercise in six of seven lower-capacity patients, whereas it continued to increase to peak exercise in most controls and in most patients with better exercise capacity. Across all participants, peak cardiac output was more closely related to peak stroke volume than to peak heart rate. The study therefore links impaired exercise capacity to an attenuated stroke-volume reserve rather than merely to a lower peak heart rate.

Palmieri et al. examined an earlier stage of the same pathophysiological continuum. Seventy sedentary outpatients with cardiovascular risk factors, but without congestive heart failure, systolic dysfunction, significant valvular disease or evidence of coronary ischaemia, underwent echocardiography and exercise testing with simultaneous non-invasive stroke-index and cardiac-index assessment. Isolated diastolic dysfunction, present in 26%, was independently associated with lower peak exercise stroke index and cardiac index despite no difference in achieved metabolic equivalents. These findings suggest that impaired exercise systolic performance can be present before overt heart failure and may remain invisible when exercise capacity is described only by workload or estimated METs.

Taken together, these studies do not support a single haemodynamic phenotype of heart failure. Some patients show a clear limitation of stroke-volume or cardiac-output reserve, whereas others are predominantly limited by peripheral muscle function, oxygen extraction or ventilatory efficiency. The principal value of continuous exercise haemodynamics is therefore phenotypic: it helps locate the limiting step rather than assuming that a reduced peak VO_2 has the same mechanism in every patient.

4.1.1.2. Prognostic and risk-stratification applications

★ Mapelli et al. reported a contemporary conference analysis of 174 patients with HFrEF or heart failure with improved ejection fraction. Higher NT-proBNP was associated with a smaller stroke-volume reserve ($r = -0.21$), lower chronotropic reserve ($r = -0.40$), lower peak VO_2 ($r = -0.37$) and a steeper VE/VCO_2 slope ($r = 0.39$), whereas its relationship with resting ejection fraction was weak and non-significant. The findings support the physiological relevance of dynamic reserve measurements and their convergence with an established

biomarker. Because this is a cross-sectional congress abstract without longitudinal outcomes, it does not independently demonstrate incremental prognostic value.

Chang et al. extended haemodynamic monitoring beyond daytime examination in 63 patients preparing for discharge after acute heart failure. Once clinical euvolaemia had been judged to be achieved, thoracic fluid content was monitored from evening to early morning. During a median follow-up of 16 months, an overnight increase in indexed thoracic fluid content independently predicted the composite of heart-failure hospitalisation or death and recurrent events. A rise of at least 0.5/kΩ/m² was associated with a substantially higher event rate. This small observational study suggests that nocturnal fluid redistribution may reveal residual congestion missed by conventional daytime assessment. The result concerns thoracic-fluid monitoring rather than exercise haemodynamics and requires external confirmation before clinical thresholds can be generalised.

★ Myers et al. subsequently evaluated 1,236 consecutive patients referred for heart-failure assessment using CPET and impedance cardiography; 422 composite events occurred. Conventional CPET markers, including peak VO_2 and indices of ventilatory inefficiency, were predictive, but the change in cardiac index, peak cardiac time interval and peak left cardiac work index were the strongest haemodynamic predictors. Patients with five impaired CPET and haemodynamic responses had approximately seven times the risk of those with no abnormal response. Adding the haemodynamic variables yielded net reclassification improvements ranging from 0.34 to 0.89, driven mainly by improved classification of patients who subsequently experienced events.

The 2019 study materially strengthens the earlier work because of its larger cohort and explicit reclassification analysis. Its interpretation nevertheless requires restraint. The cohort consisted of patients referred for heart-failure evaluation rather than a narrowly defined, externally validated disease population; no direct cardiac output comparator was incorporated; and an independent validation cohort was not reported. The study therefore supports incremental prognostic information from PhysioFlow-derived exercise variables within this referral setting, but does not establish universal risk thresholds or prove that management based on those variables improves outcomes.

The earlier study by ★ Myers et al. (2013) included 639 consecutive patients evaluated for heart failure and recorded 113 composite events over a mean follow-up of 460 days. Peak VO_2 and the VE/VCO_2 slope remained established CPET predictors, while peak cardiac index was the strongest haemodynamic predictor. A model combining peak VO_2, peak cardiac index and the VE/VCO_2 slope retained independent contributions from all three variables; patients with all three responses abnormal had a hazard ratio of 5.1. This study introduced the central clinical proposition later examined more formally in 2019: exercise cardiac output and conventional gas-exchange variables may provide complementary, rather than redundant, prognostic information.

The two Myers cohorts form the principal prognostic evidence in heart failure. Their consistency supports the interpretation that a low peak VO_2 has different implications when the cardiac-index response is preserved than when both oxygen uptake and haemodynamic reserve are impaired. The evidence is observational, however. It supports risk stratification and physiological interpretation, not a claim that PhysioFlow-guided decisions have themselves been shown to reduce mortality or hospitalisation.

4.1.1.3. Functional assessment and advanced-heart-failure monitoring

O'Connor et al. compared the physiological responses elicited by sit-to-stand protocols and the six-minute walk test in people with heart failure, using randomised test order and continuous haemodynamic monitoring. The tests did not produce interchangeable cardiovascular demands: differences in heart rate, gas exchange and cardiac-output response were detectable despite their shared use as simple field assessments. The study is clinically relevant because it shows that performance counts or walking distance alone do not fully describe the physiological stress imposed by different functional tests. The choice of test must therefore be considered when haemodynamic responses are compared between patients or across follow-up.

Franzoni et al. assessed 13 patients with HFrEF and 14 healthy controls before, during and after a six-minute walk test. Patients showed lower acceleration of cardiac output and heart rate, and significant group differences in stroke volume, cardiac output and cardiac index. Stroke volume accounted for only 22.9% of the change in cardiac output in HFrEF, compared with 57.4% in controls. The study illustrates how continuous cardiodynamic monitoring can enrich a six-minute walk test by showing how the circulation generates the observed performance. The small cross-sectional sample limits threshold definition, but the physiological contrast between groups is coherent with the incremental-exercise findings of Fukuda.

Piccirillo et al. evaluated 65 hospitalised NYHA class IV patients, including 39 with HFrEF and 26 with HFpEF, using short bioimpedance and ECG recordings at admission and discharge. Stroke-volume index, cardiac index

and other bioimpedance-derived variables differed between HFrEF and HFpEF, while ECG repolarisation dispersion contributed additional prognostic information. Fifty-seven percent of patients were classified as responders to optimal medical therapy and showed reductions in NT-proBNP, heart rate and Tpeak-Tend variability at discharge. Bioimpedance-derived and echocardiographic ejection fraction were correlated but showed limited agreement, illustrating again that correlation does not justify interchangeability. The study supports multidimensional bedside phenotyping, but its single-centre design and composite analytical approach do not establish a treatment-selection algorithm.

Besnier et al. explored a less conventional consequence of impaired haemodynamic reserve. Eleven patients with chronic heart failure, 11 heart-transplant recipients and 13 healthy controls underwent CPET, peak cardiac-output assessment and cognitive testing. Peak VO_2, the first ventilatory threshold and peak cardiac output were related to processing speed and executive function; in the heart-failure group, peak cardiac output statistically mediated the group difference in these cognitive domains. The sample is too small and the mediation analysis too exploratory to support causal conclusions, but it broadens the clinical relevance of exercise haemodynamics beyond dyspnoea and peak workload.

Two historical conference abstracts provide additional, lower-level observations. Bauer et al. studied six controls and 15 patients with ejection fraction below 35% and reported a strong correlation between a rapidly measured thoracic fluid index and BNP ($r = 0.93$). In a separate series of 20 patients with systolic heart failure unable to tolerate other beta-blockers, substitution with nebivolol was associated with a fall in systemic vascular resistance index, a modest increase in cardiac index, lower thoracic fluid content and improvement in NYHA class. These abstracts are valuable for historical completeness and hypothesis generation, but their small samples, incomplete reporting and absence of full peer-reviewed articles prevent them from carrying the same evidential weight as the published cohorts.

4.1.1.4. Mechanistic and acute-intervention studies

Collins et al. revisited their dopamine chemoreceptor-inhibition experiment by stratifying participants according to baseline carotid chemosensitivity. The secondary analysis suggested that exercise tolerance improved preferentially in participants with elevated chemosensitivity, thereby identifying a possible responder phenotype that was obscured in the original whole-group analysis. This is an informative example of haemodynamic phenotyping, but it is not an independent replication: it derives from the same experimental programme and should be regarded as hypothesis generating until prospectively confirmed.

Aitken et al. evaluated a two-minute uphill Dyspnea Challenge in patients with heart failure and compared their responses with those of patients with COPD. At comparable cardiac output, stroke volume and heart rate, the heart-failure group showed a greater arteriovenous oxygen difference, whereas the COPD group showed larger reductions in inspiratory capacity, oxygen saturation and breathing reserve. The test was reproducible for exertional dyspnoea. These findings illustrate how combined haemodynamic, gas-exchange and ventilatory measurements can distinguish different mechanisms producing a similar symptom during a short functional challenge.

Apostolo et al. studied 20 patients hospitalised with advanced heart failure before and shortly after levosimendan infusion using two complementary CPET protocols, continuous cardiac-output monitoring, near-infrared spectroscopy and pulmonary diffusion measurements. Peak VO_2 increased from a median of 11.3 to 12.6 $mL \cdot kg^{-1} \cdot min^{-1}$, the VE/VCO_2 slope decreased, and cardiac output increased in parallel with oxygen uptake. Measures of muscular oxygen availability and pulmonary diffusion also improved. The study therefore suggests that the clinical response to levosimendan is multisystemic, involving increased forward flow, improved muscular oxygen delivery and extraction, reduced exercise-induced pulmonary oedema and more efficient ventilation. The uncontrolled before-after design and small sample prevent attribution of every change solely to the drug.

Borghi-Silva et al. later examined proportional assist ventilation in ten men with severe HFrEF during constant-load exercise. Compared with sham ventilation, respiratory-muscle unloading prolonged exercise tolerance, accelerated post-exercise VO_2 recovery and was accompanied by faster recovery of cardiac output and leg-muscle oxygenation. The findings support interaction between respiratory work, central haemodynamics and peripheral reoxygenation. Their small, male-only experimental sample and short-term intervention limit direct clinical generalisation, but the study provides mechanistic evidence relevant to repeated exercise and rehabilitation.

In the original Collins study, 12 clinically stable patients with heart failure and 12 matched controls completed constant-load cycling with saline or low-dose dopamine. In the heart-failure group, chemoreceptor inhibition increased cardiac output, vascular conductance and oxygen delivery at symptom limitation, but did not prolong exercise time or reduce ventilatory demand. The discordance between improved central oxygen delivery and unchanged tolerance suggests that increasing cardiac output alone may be insufficient when peripheral utilisation or other limiting mechanisms remain unchanged. The later 2025 responder analysis refines, rather than overturns, this primary result.

Rocha et al. studied 51 patients with combined COPD and systolic heart failure; cardiac output was measured in a subset of 18. Patients with an abnormally low increase in oxygen uptake relative to work rate had lower stroke volume and cardiac output, slower oxygen-uptake kinetics, earlier anaerobic threshold and greater symptoms, despite similar ejection fraction and spirometric obstruction. The results identify adverse cardiopulmonary-muscular interaction rather than a single-organ limitation and reinforce the need to analyse a clearly defined heart-failure subgroup when mixed populations are included.

An earlier experiment by Borghi-Silva et al. studied nine patients with advanced chronic heart failure during high-intensity constant-load exercise. Proportional assist ventilation improved exercise tolerance and leg-muscle oxygenation and blood volume without increasing systemic cardiac output or arterial oxygen saturation. The authors interpreted this as redistribution of blood flow from the unloaded respiratory muscles toward the exercising limbs. The finding remains mechanistically important because it shows that a meaningful improvement in peripheral oxygen availability can occur without a measurable increase in total cardiac output.

Scope note. Murata et al. (2020) described ventilatory-pattern regularities in 1,111 patients undergoing CPET, but the available report does not identify a separately analysed heart-failure subgroup. In accordance with the chapter inclusion rule, it is not used as heart-failure evidence here and should be considered for a broader dyspnoea or CPET section.

4.1.1.5. Practical evidence synthesis and limitations

Across these studies, the most consistent contribution of PhysioFlow is the ability to describe the dynamic circulatory response to exercise or another physiological challenge. The evidence supports four practical observations. First, patients with similar resting ejection fractions or peak workloads may have materially different stroke-volume and cardiac-output reserves. Second, central haemodynamic impairment frequently coexists with, but does not fully explain, ventilatory and peripheral-muscle limitation. Third, adding exercise haemodynamics to CPET can improve risk classification in referral cohorts. Fourth, continuous measurement can add physiological meaning to short functional tests, therapeutic challenges and monitoring periods that would otherwise be described only by symptoms, distance, workload or resting variables.

The evidence does not establish PhysioFlow as a stand-alone diagnostic test for heart failure, a substitute for echocardiography or invasive haemodynamics, or a universally validated basis for treatment decisions. Most mechanistic and intervention studies are small, several important observations are available only as abstracts, and the largest prognostic cohorts remain observational and lack independent prospective validation. HFpEF evidence is particularly heterogeneous: the relative importance of cardiac reserve, peripheral oxygen extraction and skeletal muscle function varies with patient selection and the analytical framework used.

Methodological boundary conditions described in Chapter 3 remain applicable. Kemps et al. reported the principal unresolved unfavourable comparison of absolute PhysioFlow cardiac output with a Fick-based method in ten men with chronic heart failure, although tracking of exercise-induced change was more acceptable. This finding prevents an unqualified assumption that every absolute value is interchangeable with an invasive comparator. It does not, however, negate the internally consistent physiological and prognostic associations observed across the application studies. Interpretation should prioritise signal quality, protocol, device generation, magnitude of change and convergence with CPET and clinical findings.

Cardiac-rehabilitation studies, including training-response work and CTi-based responder phenotyping, are developed separately in Section 4.1.3. Hypertrophic cardiomyopathy, for which ★ Finocchiaro et al. provides a major prognostic exercise-haemodynamic study, is treated in Section 4.1.4. These separations preserve a neutral application-based structure while allowing cross-reference between heart-failure pathophysiology, rehabilitation response and disease-specific cardiomyopathy evidence.

Overall, the heart-failure literature supports PhysioFlow as an adjunct to integrated functional assessment—not as a diagnostic number, but as a way to characterise cardiac-output and stroke-volume reserve and their interaction with ventilatory and peripheral factors beyond resting assessment and conventional CPET.

Practical take-home. During CPET or functional exercise, PhysioFlow can add stroke-volume and cardiac-output reserve to conventional gas-exchange interpretation, supporting phenotyping and risk assessment in heart failure. It is an adjunct to—not a replacement for—imaging, invasive haemodynamics or disease-specific diagnostic criteria.

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★ = *landmark/core publication. Flags at the end of an entry indicate first- and last-author affiliation countries where available; a single flag is shown when identical.*

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4.1.2. Coronary artery disease

In coronary artery disease (CAD), exercise testing can address several distinct questions: whether symptoms are reproduced, how much functional capacity is preserved, which mechanisms limit exercise, and whether treatment or revascularisation has restored an adequate physiological response. These questions should not be conflated with the anatomical demonstration of coronary stenosis or the imaging-based assessment of inducible ischaemia. Current chronic-coronary-syndrome and chest-pain pathways rely primarily on coronary computed-tomography angiography or functional stress imaging when diagnostic clarification is required; conventional exercise electrocardiography retains selected functional and prognostic roles.

Within that framework, PhysioFlow-derived haemodynamics is best considered an adjunct to exercise or peri-interventional assessment. For ischaemia-related applications, the potentially informative signal lies less in an isolated peak value or a simple rest-to-peak increase than in the temporal profile of contractility index (CTi) and stroke volume: the timing of their peak, an inadequate rise and, most importantly, a secondary decline despite a continuing increase in heart rate and workload. A plateau is not necessarily abnormal, particularly when it occurs only late in exercise. A secondary decline may be more concerning when it appears before very high heart rates are reached. At heart rates around or above 160 beats/min in PhysioFlow clinical experience, however, such a decline may instead reflect the physiological and mechanical consequences of shortened diastolic filling time, partly modulated by ventricular compliance. Interpretation must therefore consider both the trajectory and the heart rate at which it occurs; neither can by itself identify the anatomical cause.

This distinction is essential when appraising the literature. A study that analyses only maximum values or rest-to-maximum changes can test whether those global summaries are associated with ischaemia, but it cannot determine whether the shape of the response contains clinically relevant information. The available CAD corpus is small: three full peer-reviewed clinical studies and two historical conference abstracts directly address these applications. The evidence therefore supports physiological characterisation and hypothesis generation more strongly than diagnostic classification.

This section separates three clinically different uses: exercise haemodynamic phenotyping soon after revascularisation; longitudinal monitoring after acute myocardial infarction and percutaneous coronary intervention; and the more ambitious use of impedance-derived responses to identify CAD or a high ischaemic burden. Validation and reproducibility studies are addressed in Chapter 3, while training-induced changes and responder phenotypes in patients with CAD are developed in Section 4.1.3.

4.1.2.1. Exercise haemodynamic phenotyping after revascularisation

Kurpaska et al. studied patients with CAD within six weeks of percutaneous coronary intervention or coronary artery bypass grafting, at the point of referral to phase II cardiac rehabilitation. Seventy-seven participants underwent cardiopulmonary exercise testing (CPET) with PhysioFlow; the analysis was restricted to 54 patients who reached a respiratory-exchange ratio above 1.05. Nearly two thirds had a peak oxygen uptake below 80% of the predicted value. Peak oxygen uptake correlated with peak heart rate ($r = 0.45$), cardiac output ($r = 0.33$) and left cardiac work index ($r = 0.40$). Changes in oxygen uptake from the anaerobic threshold to peak exercise were similarly related to changes in heart rate, cardiac output and left cardiac work index ($r = 0.49$-0.52).

The most clinically suggestive observation was that 31.5% of the analysed patients showed a fall in stroke volume during the final phase of exercise. This does not by itself demonstrate residual ischaemia, graft or stent dysfunction, or impaired prognosis; it identifies a heterogeneous haemodynamic response among apparently stable, recently revascularised patients. Its physiological meaning depends on whether heart rate was still increasing and on the heart rate reached, because a late decline at very high rates may reflect shortened filling time rather than disease. The study therefore supports the use of combined CPET and continuous haemodynamics to distinguish a predominantly chronotropic limitation from an inadequate stroke-volume or cardiac-output reserve and from a more peripheral limitation. Its cross-sectional design, moderate correlations, selected maximal-effort sample and absence of a simultaneous perfusion or invasive reference preclude diagnostic thresholds.

Kurpaska is consequently better placed in the CAD application section than in a generic vascular-investigation chapter. It also provides a natural bridge to Section 4.1.3: the measurements were obtained before phase II rehabilitation and may help describe the physiological starting point, but the study did not test whether haemodynamic phenotyping improved exercise prescription or outcomes.

4.1.2.2. Acute myocardial infarction and post-PCI monitoring

Lewicki et al. evaluated 27 patients with acute myocardial infarction undergoing percutaneous coronary intervention. Beat-to-beat PhysioFlow Q-Link monitoring was performed around the procedure, with repeat assessments during the first day and approximately one month later. During the first 24 hours after intervention, cardiac index, stroke-volume index, left cardiac work index, corrected flow time and ventricular ejection time were lower, while heart rate, systemic vascular-resistance index and thoracic-fluid-content index were higher. By one month, the main haemodynamic indices had moved back towards or beyond their pre-procedural values, in parallel with an increase in left-ventricular ejection fraction.

This small longitudinal series illustrates that continuous non-invasive monitoring can capture a coherent and clinically plausible circulatory trajectory through an acute coronary event and early recovery. It does not establish that any individual PhysioFlow variable detects procedural success, predicts complications or changes management. There was no control group, no independent cardiac-output reference and no attempt to separate the effects of reperfusion, medication, loading conditions and spontaneous recovery. The study should therefore be cited as evidence of feasibility and descriptive sensitivity to change, not as a validated post-PCI monitoring strategy.

4.1.2.3. Ischaemia detection: the temporal-profile hypothesis and methodological considerations

Mielniczuk et al. evaluated 50 patients with a single-vessel chronic total occlusion and no other significant coronary stenosis using clinical assessment, echocardiography, a six-minute walk test, CPET, exercise PhysioFlow Enduro monitoring and single-photon-emission computed tomography (SPECT). The prespecified comparison concerned patients with and without a high inducible ischaemic burden. Although haemodynamics was recorded continuously during CPET, the reported PhysioFlow analysis was restricted to maximum heart rate, stroke volume and cardiac output, together with their increases from rest to maximum. None of these simple summary variables differed significantly between the SPECT groups; only occlusion location and lateral-wall longitudinal strain were associated with the imaging endpoint.

The negative result is valid for the variables that were tested, but its scope is narrow. CTi was not reported, and the investigators did not analyse the stage-by-stage stroke-volume trajectory, the timing of the maximum, a premature plateau, or a secondary decline despite a continuing increase in heart rate and workload. Left cardiac work index and systemic vascular resistance were mentioned among the recorded variables but were not presented in the comparative results. Moreover, PhysioFlow was recorded during cycle-ergometer CPET, whereas SPECT stress was produced separately by a Bruce treadmill protocol or, in some patients, dipyridamole. The haemodynamic and perfusion responses were therefore neither simultaneous nor necessarily elicited by the same physiological stress.

Mielniczuk consequently shows that peak stroke volume, peak cardiac output and their rest-to-maximum increases did not discriminate a high SPECT-defined ischaemic burden in this modest chronic-total-occlusion cohort. It does not show that CTi or stroke-volume profiles were non-discriminatory, because that hypothesis was not tested. The study provides no support for replacing regional perfusion imaging with simple global haemodynamic summaries, but it should not be interpreted as negative evidence against temporal-profile analysis.

Two abstracts presented by the Angers group in 2000 provide the historical origin of the ischaemia-detection hypothesis. In a study comparing exercise PhysioFlow PF03 with thallium-201 scintigraphy, ★ Dupuis et al. classified the impedance response as abnormal when peak stroke volume was lower than an earlier exercise value separated by at least one minute. Among 36 patients, the abstract reported that the stroke-volume alteration preceded ST-segment depression or angina and yielded sensitivity of 100%, specificity of 74%, positive predictive value of 67% and negative predictive value of 100%.

A second bicycle-exercise abstract applied the same late-exercise stroke-volume criterion in 29 patients who subsequently underwent coronary angiography. Nineteen had angiographically documented CAD and ten did not. The reported sensitivity, specificity, positive predictive value and negative predictive value were respectively 100%, 50%, 79% and 100%, compared with poorer performance for exercise ECG or angina in this selected sample. The impedance abnormality again reportedly occurred before ST-segment depression.

These observations are intriguing because they propose a physiologically interpretable marker: a secondary fall in stroke volume while exercise demand and heart rate continue to increase. This is conceptually different from both peak stroke volume and the net change from rest to maximum: a patient may achieve a normal or high maximum and still develop a potentially abnormal decline during the final stages of exercise. This interpretation

is not universal: at very high heart rates, approximately 160 beats/min or above in PhysioFlow clinical experience, a decline in CTi or stroke volume may be physiological because diastolic filling time becomes mechanically constrained, with the magnitude of the effect depending partly on ventricular compliance. The reports remain preliminary: both are small conference abstracts with limited methodological reporting and no independent replication. In the angiography study, coronary angiography was clinically indicated only after an abnormal exercise ECG or typical angina. This ethically understandable work-up design confined the analysis to a conventionally positive referral subgroup, leaving PhysioFlow-positive patients with otherwise negative findings unverified and precluding estimation of incremental diagnostic performance. The two studies also addressed the presence of CAD, whereas Mielniczuk assessed a high SPECT-defined ischaemic burden within an already established chronic-total-occlusion population. Their numerical results are therefore not directly contradictory. Mielniczuk did not analyse the late-exercise pattern used by Dupuis, while the absence of full publication and independent replication prevents the historical diagnostic estimates from being generalised.

A complementary rationale is developed in the cardiac-rehabilitation literature reviewed in Section 4.1.3. In that different clinical context, baseline CTi profiles have shown an association with the subsequent response to exercise-based rehabilitation, suggesting some predictive value for the dynamic contractile response. This does not validate CTi as a marker of myocardial ischaemia. It nevertheless supports the broader positioning of CTi and stroke-volume profiles as candidate markers of a functional cardiac abnormality during exercise, and strengthens the case for studying the complete trajectory rather than reducing the recording to a peak and a rest-to-peak delta.

4.1.2.4. Practical evidence synthesis and research priorities

The CAD literature supports a narrow but clinically coherent application of PhysioFlow:characterising how the cardiac response develops throughout exercise or acute care, rather than merely reporting a maximum or determining whether a coronary stenosis or regional perfusion defect is present. After revascularisation, combined CPET and impedance monitoring can reveal heterogeneity in chronotropic, contractile, stroke-volume and cardiac-output reserve that peak oxygen uptake alone does not fully describe. A plateau should be interpreted according to how early it occurs and is not intrinsically pathological. A secondary decline in CTi or stroke volume despite a continuing increase in heart rate is more physiologically concerning than the absolute maximum, except at very high heart rates where shortened diastolic filling may provide a physiological explanation. This profile-based hypothesis still requires prospective confirmation against an appropriate reference. Following acute myocardial infarction and PCI, serial measurements can document the direction and time course of haemodynamic recovery.

The evidence does not establish PhysioFlow as a stand-alone diagnostic test for CAD, inducible ischaemia or post-PCI complications. The historical Dupuis abstracts generated a physiologically plausible temporal stroke-volume signal, but their diagnostic estimates remain exploratory because of small, selected cohorts, limited reporting and no independent replication. In the angiography abstract, an ethically understandable work-up design left PhysioFlow-positive patients with otherwise negative findings unverified. The recent chronic-total-occlusion study found no discrimination of high SPECT-defined ischaemic burden by maxima or simple rest-to-maximum increases, but did not evaluate the CTi or stroke-volume profiles of primary interest. These data are most consistent with current diagnostic pathways: anatomy and perfusion should be established with validated coronary or stress-imaging methods, while exercise haemodynamics may provide complementary functional information.

The section is also limited by the small number of studies, modest sample sizes, heterogeneous clinical stages and non-equivalent endpoints. Studies that do not examine the temporal profile have limited impact on the central functional hypothesis. Absolute values, changes and profiles remain subject to the methodological boundary conditions detailed in Chapter 3, including attention to signal quality, protocol compliance and the distinction between agreement, repeatability and clinical association. No study has shown that adding PhysioFlow to a CAD pathway improves decisions or patient outcomes.

Overall, the most promising CAD signal is CTi and stroke-volume morphology in relation to the simultaneous heart-rate trajectory, not an isolated maximum. Section 4.1.3 develops the corresponding rehabilitation evidence.

Practical take-home. In coronary disease, the most informative candidate signal is the temporal CTi/stroke-volume profile alongside heart rate and workload. A plateau is not automatically pathological; an early relapse despite increasing heart rate is more concerning, except where very high heart rates plausibly shorten diastolic filling. PhysioFlow is not a stand-alone ischaemia test. An unexpected early or disproportionate deterioration should not be dismissed solely because ECG or symptoms are otherwise reassuring; it may warrant caution during testing and contextual clinical review.

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4.1.3. Cardiac rehabilitation

Exercise-based cardiac rehabilitation improves functional capacity, symptoms and clinical status, but the change in peak oxygen uptake (VO_2peak) varies considerably between patients. A similar gain in VO_2peak may arise through different combinations of increased cardiac output, improved peripheral oxygen extraction, enhanced muscle oxygen diffusion, chronotropic adaptation and ventilatory efficiency. Conversely, an apparently small change in VO_2peak does not necessarily imply absence of cardiovascular adaptation. This heterogeneity is the principal clinical rationale for adding continuous non-invasive haemodynamics to cardiopulmonary exercise testing (CPET) before and after rehabilitation.

The 2016 EACPR/AHA focused update on CPET emphasised integrated interpretation, the synergistic value of combining CPET with other assessments, and the use of exercise data to characterise limitation and support safe, effective exercise prescription. The 2026 ESC Guidelines on cardiac rehabilitation now strengthen this framework: CPET is described as the gold standard for risk stratification, assessment of global functional capacity and exercise-tolerance limits, evaluation of chronotropic response, and prescription of endurance training; exercise prescription should be tailored to the patient's goals, medical needs, capabilities and phenotype. Neither document recommends PhysioFlow specifically, and the 2026 Guidelines do not endorse non-invasive exercise haemodynamics as a standard component of rehabilitation. They nevertheless provide an appropriate clinical framework for this literature: PhysioFlow-derived variables should complement established CPET measures rather than displace them, and their value depends on the incremental physiological question they answer (Bäck et al., 2026; doi:10.1093/eurheartj/ehag099).

Three related but distinct applications should therefore be separated. First, haemodynamic measurements can explain which step of oxygen transport adapts during training. Second, the baseline exercise response may identify patients who are more or less likely to increase VO_2peak. Third, serial measurements can describe the cardiovascular adaptation that accompanies response. Evidence for the first application is the most mature. Prediction from baseline exercise CTi or stroke-volume profiles is promising but remains investigator-led and exploratory. The use of haemodynamics to prescribe a superior training programme is still hypothesis-generating.

The corpus also requires careful accounting. Several articles and conference abstracts are successive reports from the same institutional cohorts. The French provincial mixed-cardiac rehabilitation cohort conducted at Fondation Léopold Bellan in Tracy-le-Mont, the HFrEF cohort conducted at Corentin-Celton in Paris, and the Montreal coronary-heart-disease cohort should each be treated as a separate family of related evidence. Repeated presentation within one family can deepen the analysis but does not constitute independent replication. The Fondation Léopold Bellan and Corentin-Celton cohorts, however, are clinically and institutionally distinct and therefore constitute independent datasets.

4.1.3.1. Beyond $\dot{V}O_2$peak: identifying the mechanism of training response

The Fick principle provides the organising framework: oxygen uptake is the product of cardiac output and the arterial-venous oxygen-content difference. A change in VO_2peak can therefore result from central oxygen delivery, peripheral extraction and diffusion, or both. Continuous haemodynamics adds stroke volume, heart rate, cardiac output and vascular-resistance behaviour to the conventional CPET response. These variables should be interpreted together, because an isolated value cannot establish which component limited the patient or caused the training effect.

★ Legendre et al. applied this framework to patients with HFrEF before and after cardiac rehabilitation. Approximately half increased VO_2peak, cardiac oxygen delivery at peak exercise or muscle oxygen diffusion, but the responses were not concordant in every patient: some improved both delivery and diffusion, others improved only one component, and a small subgroup improved neither. The change in peak oxygen delivery was strongly related to changes in exercise stroke volume and cardiac power and inversely related to the change in systemic vascular resistance. These findings show why VO_2peak response should not be treated as a single biological phenotype. They also suggest that a patient can improve peripheral utilisation despite limited central adaptation, or improve central delivery without a proportionate gain in VO_2peak.

In the Montreal coronary-heart-disease programme, Girault et al. classified 82 patients across a graded spectrum of VO_2peak response rather than a binary responder/non-responder definition. High, moderate, low and absent responses were observed. Peripheral and ventilatory adaptations explained more of the variation in VO_2peak change than central haemodynamic changes. This is an important counterweight to an exclusively

cardiac interpretation: PhysioFlow can show that cardiac output or stroke volume changed, but it can also help demonstrate that the dominant training effect occurred elsewhere in the oxygen-transport pathway.

In HFrEF, ★ Kirsch et al. divided 76 participants according to the median improvement in VO_2peak. Responders increased peak cardiac output by approximately 25%, compared with about 4% in non-responders, and also showed larger increases in peak heart rate. The change in peak cardiac output discriminated the post hoc response groups with an area under the receiver-operating-characteristic curve reported as 0.77. This is evidence of different physiological adaptation, not prospective prediction: the groups were defined after training by the same VO_2peak change that the haemodynamic changes were used to discriminate, and the median split was cohort-specific.

A related Montreal analysis by ★ Kirsch et al. (2024) in 72 patients with coronary heart disease reached a similar mechanistic conclusion. Patients with the larger VO_2peak response had greater increases in peak cardiac output, cardiac index and stroke volume, whereas systemic vascular resistance decreased in both response groups. Girault and Kirsch should not be counted as two wholly independent replications because the samples probably overlap substantially. Together, however, they show that a programme-level average conceals distinct combinations of central, peripheral and ventilatory adaptation.

Sugita et al. extended this approach to HFpEF in a non-randomised controlled study of 99 older Japanese patients. After five months, the intervention group improved peak oxygen uptake and several central and peripheral components, including peak stroke index, heart rate, cardiac index and estimated arterial-venous oxygen difference. Only about 30% met the study's clinically meaningful response threshold. Diabetes and poorer ventilatory efficiency were associated with a lesser response, while left-atrial strain differed in responders. The study supports multidimensional phenotyping in HFpEF, but its non-randomised, single-centre design and population-specific sample limit causal and external inference.

4.1.3.2. Baseline exercise CTi and stroke-volume profiles as candidate predictors

A more ambitious application is to use the shape of the baseline exercise response to estimate the probability of subsequent improvement. The relevant signal is not simply the resting CTi, the peak CTi, or the rest-to-peak difference. It is the temporal relationship among CTi, stroke volume, heart rate and workload. Two abnormal CTi patterns should be distinguished. A compromised CTi response is characterised by the absence of a significant CTi increase, or even by a decrease early in exercise. A CTi relapse is a secondary decline after an initial increase, despite a continuing rise in heart rate and external work. These patterns differ from a late plateau, which is not intrinsically pathological, particularly when it is not premature. Stroke-volume morphology should be interpreted in parallel. Even a late CTi or stroke-volume decline requires contextual interpretation: at heart rates around or above 160 beats/min in PhysioFlow clinical experience, shortened diastolic filling time can produce a physiological or mechanical decline, partly influenced by ventricular compliance.

In the French provincial mixed-cardiac rehabilitation cohort conducted at Fondation Léopold Bellan, Tracy-le-Mont, ★ Bour et al. retrospectively studied 58 patients, with 57 included in the analysis. Baseline exercise CTi trajectories were classified as normal or altered, with altered profiles including a compromised response or a CTi relapse. VO_2peak increased by 24.1% in the normal-profile group and by 3.4% in the altered-profile group. A normal baseline exercise profile was associated with an odds ratio of 8.7 for achieving more than a 5% improvement in VO_2peak. The study is clinically important because it analyses response morphology rather than reducing the exercise recording to a maximum or a delta. It positions the dynamic CTi profile as a candidate marker of functional cardiac reserve.

The result should nevertheless be described as exploratory prediction. The classification was retrospective, the sample was small and heterogeneous, the response threshold was modest, and the analysis came from a single expert environment. One author was a co-inventor of the technology and a co-founder and managing director of Manatec; this declared conflict of interest does not invalidate the data but strengthens the need for blinded, multicentre and investigator-independent replication. The profile definition and the heart-rate context of any late decline should also be prespecified before external validation.

An HFrEF congress report from Corentin-Celton subsequently described 65 patients with a mean left-ventricular ejection fraction of approximately 29%. Patients classified as having a normal baseline exercise CTi profile showed a larger mean increase in VO_2peak than those with an abnormal profile, and the reported odds ratio for response was 3.3. Because this HFrEF population is entirely distinct from the mixed-cardiac cohort at Fondation Léopold Bellan, the finding constitutes an independent clinical replication at cohort and site level. It is not yet an investigator-independent external validation, because both analyses arose from the same research programme.

The later Corentin-Celton HFrEF abstracts include 73 participants and probably represent an enlarged or overlapping version of the 65-patient cohort; these successive HFrEF reports should therefore remain one evidence family when the final count is frozen.

The interpretation also links to the CAD evidence in Section 4.1.2. The historical Dupuis abstracts used a late-exercise fall in stroke volume as a candidate signal of ischaemia, while the rehabilitation studies use CTi morphology to characterise functional reserve and training responsiveness. Rehabilitation findings do not validate CTi or stroke-volume profiles as diagnostic tests for myocardial ischaemia. They do, however, support the broader hypothesis that the complete dynamic profile can contain clinically relevant information that is lost when only a peak value or a rest-to-peak delta is analysed.

4.1.3.3. CTi and contractile reserve as markers of training adaptation

Baseline prediction and longitudinal monitoring are not the same question. A baseline scalar CTi may fail to distinguish future responders, while the direction and magnitude of the CTi change after training may still identify an acquired contractile adaptation. The recent reports from the two French rehabilitation cohorts are particularly useful when read in this way. CTi remains a signal-morphology-derived surrogate index; it should not be presented as a direct measurement of myocardial contractility or as an interchangeable substitute for an invasive pressure-volume assessment.

In a 2025 EAPC abstract, Bour, Milstein and Leprêtre reported 42 patients with complete pre- and post-rehabilitation CPET and signal-morphology impedance cardiography. Seventeen had a normal baseline exercise CTi profile and 25 an altered profile. Sixteen of the 25 patients with an altered profile nevertheless met the VO_2peak response criterion. Within this subgroup, responders showed a marked increase in the rest-to-peak CTi difference, whereas non-responders showed a decrease. This analysis is best regarded as an extension or subset of the Fondation Léopold Bellan mixed-cardiac cohort rather than a new independent validation. It adds an important nuance: an altered initial profile does not make adaptation impossible, and serial CTi behaviour may help explain why some patients improve despite an initially unfavourable trajectory.

A 2026 EAPC abstract, now formally published in the European Journal of Preventive Cardiology supplement (doi:10.1093/eurjpc/zwag249.049),analysed 73 patients with HFrEF. Thirty-two were classified as responders. Resting CTi, peak CTi and CTi reserve at baseline did not differ between response groups. After rehabilitation, responders increased peak cardiac index, cardiac-index reserve, stroke-volume-index reserve and CTi reserve, whereas non-responders showed an opposite CTi direction. Almost all responders increased CTi reserve and almost all non-responders decreased it. Estimated arterial-venous oxygen difference and systemic vascular resistance did not distinguish the groups in this analysis.

The same 73-patient HFrEF analysis was also prepared for the 2025 AACVPR meeting. The AACVPR and EAPC versions should therefore be cited as parallel dissemination of one dataset, not as two positive studies. The longitudinal result is striking, but the endpoint remains association with a post-training VO_2peak classification. It does not yet show that following CTi improves clinical decisions, that the observed changes exceed all relevant measurement variability at the individual level, or that a CTi-targeted programme produces better outcomes.

Taken together, the profile studies suggest two complementary propositions. The shape of the baseline CTi trajectory may identify a patient more likely to respond, while the change in CTi reserve may describe one mechanism through which response occurred. These propositions should remain separate in future protocols. Prospective prediction requires a baseline rule fixed before training; response monitoring requires a predefined change threshold that incorporates test-retest variability and signal-quality criteria.

4.1.3.4. Haemodynamics-guided exercise prescription and modality selection

The most operationally attractive hypothesis is that haemodynamics could help prescribe the training stimulus itself. A historical 2018 pilot abstract compared training intensity set at the first ventilatory threshold with intensity set near the workload at maximal stroke volume (pSVmax) in 12 frail patients with heart failure. Six patients were allocated to each strategy. The pSVmax workload was below the ventilatory threshold before and after training. Peak oxygen uptake improved significantly only in the pSVmax group and its change correlated with the stroke-volume change. The observation is intriguing because it proposes a patient-specific central haemodynamic target, but the extremely small groups, short four-week intervention, dropouts and abstract-only reporting make it insufficient to establish a prescription method.

Acute exercise-comparison studies provide complementary feasibility information. Gayda et al. compared optimised high-intensity interval exercise with moderate continuous exercise in 13 patients with HFrEF. Cardiac

output, stroke volume and estimated arterial-venous oxygen difference were broadly similar between sessions, while oxygen uptake and ventilation were lower during the interval condition; both were tolerated. This supports acute physiological comparison of exercise formats, but it cannot determine which format produces superior chronic adaptation.

The 2025 Baduanjin study similarly showed that matched or clinically comparable exercise modalities can achieve different central-peripheral combinations: cardiac output was lower and estimated peripheral oxygen extraction higher during Baduanjin than during cycle exercise in patients with chronic heart failure. Such studies demonstrate why heart rate or external workload alone may not fully specify the physiological dose. They do not yet justify selecting a modality from a PhysioFlow threshold without longitudinal outcome data.

Hargens et al. identified lower resting cardiac output, cardiac index, stroke volume, CTi and left cardiac work index in cardiac-rehabilitation entrants with obstructive sleep apnoea than in controls. This is a useful example of comorbidity-related haemodynamic phenotyping at programme entry. It is not a training-response or exercise-prescription study, and should be used as contextual evidence rather than as proof that PhysioFlow-guided rehabilitation improves outcomes.

4.1.3.5. Practical evidence synthesis and research priorities

The strongest current application of PhysioFlow in cardiac rehabilitation is mechanistic phenotyping. Combined CPET and continuous haemodynamics can distinguish whether improvement is accompanied mainly by greater stroke volume and cardiac output, chronotropic adaptation, lower vascular resistance, enhanced peripheral extraction or a combination of these responses. This can make the physiological effect of a programme more intelligible than VO_2peak alone and can identify clinically relevant adaptation even when the global VO_2peak change is modest.

Baseline exercise CTi and stroke-volume profiles are promising candidate predictors. The abnormal patterns of interest include a compromised CTi response with no meaningful rise or an early fall, and a CTi relapse after an initial increase despite rising heart rate and workload. A late plateau is not necessarily abnormal, and a decline at very high heart rates may reflect shortened filling rather than pathological loss of reserve. Positive findings have been reproduced in two distinct French clinical cohorts, although several reports overlap within each evidence family and the work remains investigator-led. They support multicentre, investigator-independent prospective validation of a prespecified profile rule; they do not yet support a universal clinical threshold or a stand-alone treatment decision.

Serial CTi reserve may be useful as a marker of acquired cardiac adaptation. The 2026 HFrEF report is especially informative because baseline scalar CTi values were not discriminatory, whereas the direction of their change was strongly associated with the VO_2peak response group. This distinction prevents two common overinterpretations: a normal baseline CTi does not guarantee response, and an abnormal baseline profile does not preclude improvement. CTi is a candidate functional marker that should be interpreted within the full CPET and haemodynamic trajectory, not a direct measure of contractility.

The evidence remains insufficient to claim that PhysioFlow-guided prescription improves rehabilitation outcomes. The 2026 ESC Guidelines provide a clear framework for personalised rehabilitation based on CPET, ventilatory thresholds, patient phenotype, goals and clinical context, but they do not endorse PhysioFlow-guided prescription. The pSVmax pilot and acute modality studies therefore define testable strategies, not standards of care. Future trials should prospectively specify the response endpoint, preserve continuous CTi and stroke-volume trajectories, report the heart rate and workload at profile transitions, and distinguish prediction from post-training discrimination. They should also address test-retest error, protocol and IFU compliance, signal quality, medication and rhythm effects, sex representation, external adjudication and clinically meaningful outcomes beyond VO_2peak.

Overall, PhysioFlow adds its greatest value when it is used to explain how a patient responds to exercise and training. The present evidence supports physiological stratification and longitudinal monitoring, with encouraging replication of CTi-profile prediction across two clinically and institutionally distinct cohorts but no multicentre, investigator-independent external validation. The next decisive step is not another retrospective reclassification of an overlapping report, but a multicentre prospective study in which the profile definition and its intended clinical use are fixed before rehabilitation begins.

Practical take-home. In cardiac rehabilitation, serial exercise haemodynamics can help distinguish central from chronotropic or peripheral adaptation. Baseline exercise CTi and stroke-volume profiles are promising candidate predictors, but thresholds and prescription algorithms are not yet universal standards of care. A clearly abnormal or discordant profile may justify a more conservative initial prescription and closer observation, but does not by itself define a treatment limit or mandate escalation.

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4.1.4. Hypertrophic cardiomyopathy

Exercise intolerance in hypertrophic cardiomyopathy (HCM) is rarely explained by one mechanism. Dynamic left-ventricular outflow-tract obstruction, diastolic dysfunction, mitral regurgitation, chronotropic limitation, an inadequate stroke-volume reserve and impaired peripheral oxygen utilisation may coexist in different proportions. Resting measurements may therefore underestimate the functional abnormality. Contemporary HCM guidance appropriately places exercise testing within functional and prognostic assessment, while stress echocardiography remains the established method for detecting provocable obstruction. PhysioFlow-derived exercise haemodynamics should be considered an adjunct to these evaluations, not a substitute for imaging or a stand-alone diagnostic test.

The PhysioFlow HCM literature addresses a narrower and clinically useful question: can continuous stroke-volume and cardiac-output behaviour help explain exercise capacity and refine the interpretation of conventional cardiopulmonary exercise testing (CPET)? Three full publications currently provide the principal evidence: the Stanford cohort reported by ★ Finocchiaro et al. in 2015, the multicentre Italian RoMa phenotyping study reported by ★ Willixhofer et al. in 2025, and the 2026 stroke-volume-kinetics analysis reported by ★ Mapelli et al. Two 2025 conference abstracts arise from the later Italian research programme and substantially overlap with the population subsequently reported in full. They add developmental context but should not be counted as independent studies.

Across this corpus, the most defensible contribution is physiological phenotyping. Continuous haemodynamics may reveal whether a low oxygen pulse reflects an abnormal stroke-volume response, whether chronotropic and stroke-volume reserves fail together, and whether stroke volume declines while workload and heart rate continue to rise. The evidence is not yet sufficient to define universal abnormality thresholds, demonstrate outcome improvement from PhysioFlow-guided decisions, or establish device-specific prognostic value independent of established CPET and imaging variables.

4.1.4.1. Integrated exercise haemodynamics, functional capacity and prognosis

★ Finocchiaro et al. prospectively evaluated 156 consecutive patients with HCM using resting and exercise echocardiography, CPET and impedance-derived haemodynamics. Thirty-nine per cent had a peak oxygen uptake below 80% of predicted and 19% had a ventilation-to-carbon-dioxide-output slope above 34. Peak cardiac index was the strongest measured correlate of peak oxygen uptake ($r = 0.61$), supporting the physiological importance of cardiac-output reserve in this population. During 27 ± 11 months of follow-up, 21 patients reached a composite outcome comprising cardiac death, transplantation or functional deterioration leading to septal-reduction therapy.

The prognostic interpretation requires precision. Reduced peak oxygen uptake, an elevated ventilation-to-carbon-dioxide-output slope and enlarged left-atrial volume were independent predictors of events. Peak cardiac index helped explain exercise capacity, but it was not reported as an independent outcome predictor in the final model. The study therefore supports an integrated exercise assessment and shows that measured haemodynamics can clarify the mechanism of functional limitation. It should not be presented as proof that PhysioFlow alone provided incremental prognostic discrimination.

The composite outcome also included clinical deterioration leading to an intervention, and the number of events was modest. Treatment practice, referral thresholds and the HCM phenotype of a specialist-centre population may affect generalisability. Nevertheless, this remains the foundational HCM application study because haemodynamics, gas exchange and stress imaging were acquired within the same clinical assessment and related to both functional capacity and follow-up.

4.1.4.2. Oxygen pulse, chronotropic reserve and RoMa phenotyping

Oxygen pulse is often used as a non-invasive surrogate for stroke volume during CPET, but by the Fick principle it is the product of stroke volume and the arterial-venous oxygen-content difference. Its magnitude and trajectory can therefore change because of central haemodynamics, peripheral extraction or both. ★ Willixhofer et al. studied 90 clinically stable patients with HCM and combined the percentages of predicted peak heart rate and predicted oxygen pulse in a four-group rate-of-magnitude (RoMa) classification. Stroke volume was measured simultaneously with PhysioFlow Q-Link.

From RoMa group I to group IV, peak oxygen uptake decreased from approximately 29.7 to 16.2 $mL \cdot kg^{-1} \cdot min^{-1}$ and ventilatory inefficiency increased. Peak stroke volume and the exercise-related increase in stroke volume also declined across the groups. Stroke volume and oxygen pulse were only moderately correlated ($r = 0.48$).

This partial correspondence is physiologically plausible and is central to the study: oxygen pulse cannot be assumed to represent stroke volume faithfully in every individual, while direct tracking of the stroke-volume curve may help distinguish a predominantly central response from altered peripheral oxygen extraction.

RoMa was derived as a functional phenotyping tool, not originally as a validated outcome score. A subsequent 2026 study evaluated the CPET classification in an independent cohort of 292 patients with HCM and found progressively higher clinical risk in RoMa groups II to IV over approximately six years. That later study did not use PhysioFlow. It therefore strengthens the clinical relevance of the chronotropic-response/oxygen-pulse construct, but it does not independently validate PhysioFlow measurement or show that adding stroke volume improves prediction. This distinction should be retained whenever the two reports are discussed together.

The two 2025 conference abstracts in the matrix describe related analyses from the Italian programme, including comparison of Fick-derived variables and the proposed added value of non-invasive stroke-volume assessment. Their populations and scientific questions overlap substantially with the later peer-reviewed reports. They should be retained for traceability and historical development, but not used to inflate the number of independent datasets.

4.1.4.3. Stroke-volume kinetics beyond oxygen pulse

★ Mapelli et al. extended this programme by examining exercise stroke-volume kinetics in 102 patients with HCM, most of whom had non-obstructive disease and mild functional impairment. Only 12 patients displayed an abnormal oxygen-pulse trajectory, whereas 40 were classified as having an abnormal stroke-volume response measured with PhysioFlow: 14 showed an early plateau and 26 a downsloping pattern. Thus, 28 patients with an apparently preserved oxygen-pulse pattern were additionally identified by the stroke-volume analysis. Abnormal stroke-volume kinetics were associated with poorer CPET performance and ventilatory efficiency, but did not differ clearly according to the presence of left-ventricular outflow-tract obstruction.

This finding illustrates the potential value of measuring rather than inferring stroke volume. It does not, however, mean that any plateau is pathological. Stroke volume commonly approaches a plateau during progressive exercise, and the timing, workload and accompanying heart-rate response determine its meaning. A more concerning pattern is a definite relapse or downsloping of stroke volume despite increasing workload and heart rate, particularly when it occurs early or accompanies other evidence of cardiac limitation. At very high heart rates - around 160 beats/min in the authors' practical experience - a late decrease may also be physiological or mechanical because shortened diastolic filling limits preload; ventricular compliance may influence the extent of this response. These possibilities argue for interpretation of the complete curve rather than a binary label based on a single feature.

Several limitations prevent immediate clinical thresholding. The study did not include simultaneous exercise echocardiography or an invasive reference, normal ranges for the slope analysis are not established, and approximately 10% of the initially enrolled population was excluded because mean signal quality was below 80%. The cohort was predominantly mildly symptomatic, outcome data were not available, and the classification partly depended on investigator-defined curve behaviour. Conversely, acquisition procedures and signal-quality criteria were clearly described, alternative electrode configurations were used when necessary, and the underlying dataset was made openly available. This transparency should facilitate independent reanalysis and methodological scrutiny.

The result is best interpreted as evidence that oxygen pulse and measured stroke-volume kinetics are complementary. It remains to be shown whether the additional abnormal profiles are reproducible between tests, correspond to abnormalities on simultaneous imaging, predict clinical outcomes, or change management.

4.1.4.4. Practical evidence synthesis and research priorities

The HCM corpus supports four cautious conclusions. First, an inadequate cardiac-output or stroke-volume reserve is an important contributor to exercise limitation in at least a subset of patients. Second, oxygen pulse provides useful but incomplete information because peripheral oxygen extraction also contributes to its trajectory. Third, continuous stroke-volume measurement can expose abnormal exercise patterns that are not apparent from peak values or oxygen pulse alone. Fourth, established CPET and imaging markers currently carry the stronger evidence for prognosis and clinical decision-making.

In practice, PhysioFlow is most plausibly used to answer a targeted mechanistic question during CPET: did stroke volume rise appropriately, plateau at a physiologically credible point, or fall despite continued increases in heart rate and workload? Interpretation should integrate signal quality, the full stroke-volume and cardiac-output

curves, heart rate, blood pressure, oxygen pulse, ventilatory variables, symptoms, rhythm and stress-imaging findings. A scalar peak value or an unqualified plateau label is insufficient.

Future studies should prospectively test curve reproducibility and prespecified abnormality criteria, use simultaneous stress imaging or invasive haemodynamics where feasible, and determine whether the profiles predict outcomes beyond conventional CPET and imaging. Serial assessment before and after septal-reduction therapy, cardiac myosin inhibition or structured rehabilitation may be particularly informative. Until such evidence is available, the technology provides a promising physiological lens rather than an autonomous diagnostic or prognostic pathway.

Practical take-home. In hypertrophic cardiomyopathy, a measured stroke-volume trajectory can clarify whether oxygen-pulse and exercise limitation reflect impaired cardiac reserve, peripheral extraction or both. Interpretation should remain integrated with rhythm, blood pressure, symptoms and imaging.

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4.1.5. Cardiac resynchronisation and selected cardiac applications

The residual cardiology literature does not form a single evidence domain comparable with heart failure, coronary artery disease, cardiac rehabilitation or hypertrophic cardiomyopathy. It comprises small historical studies of acute cardiac-resynchronisation-therapy (CRT) optimisation, a conceptual paper on impedance-waveform morphology, and an exercise-haemodynamic application in pectus excavatum. Retaining these reports in one compact closing section preserves clinically relevant signals without implying a level of maturity or coherence that the corpus does not possess.

The common rationale is dynamic assessment: PhysioFlow is used to observe within-patient changes in cardiac output or waveform behaviour during a pacing adjustment or physiological challenge. This can generate useful mechanistic information. It is not equivalent to showing diagnostic accuracy, durable treatment benefit or improved outcomes from a PhysioFlow-guided strategy.

4.1.5.1. Acute haemodynamic assessment during cardiac resynchronisation

Adachi et al. reported an 83-year-old woman with dilated cardiomyopathy in whom quantitative tissue Doppler imaging and PhysioFlow were used to assess acute responses to different pacing configurations. Cardiac output increased from approximately 3.5 L/min without pacing to about 4.5-4.6 L/min during biventricular pacing with atrioventricular delays of 120 or 180 ms. Tissue-Doppler measures of intraventricular phase difference changed in parallel. The report showed that rapid, repeated non-invasive haemodynamic measurements could be obtained during device programming and could complement mechanical-synchrony assessment.

This was a single case with sequential, non-randomised pacing conditions. It establishes feasibility and an internally coherent acute signal, but cannot determine precision, an optimal programming algorithm or patient benefit. The large percentage change within the individual is more informative than the absolute cardiac-output value; even so, order effects, short stabilisation periods and spontaneous variation cannot be excluded.

Bauer et al. subsequently assessed 10 symptomatic patients six to twelve months after CRT across 78 steady-state combinations of atrioventricular and interventricular delay. Optimal settings derived from echocardiography and tissue Doppler were close, on average, to those identified by PhysioFlow: the reported mean differences were approximately 2 ± 22 ms. This suggests that thoracic bioimpedance could track acute haemodynamic responses during repeated programming changes and might reduce the burden of a lengthy echocardiographic protocol.

The evidence level remains low. Bauer is a conference abstract, the sample was small, multiple settings were tested within the same patients, and no prospective clinical outcomes were reported. More importantly, agreement between two methods for an acute optimum does not demonstrate that systematic optimisation improves symptoms, remodelling, hospitalisation or survival. Contemporary pacing guidance does not support routine atrioventricular or interventricular optimisation for every CRT recipient. These PhysioFlow studies should therefore be presented as historical proof-of-concept for within-patient trending, not as evidence for routine device programming.

4.1.5.2. Waveform morphology as a historical interpretive concept

★ Bour and Kellett described a signal-averaged impedance waveform and proposed that its A, S and O components might convey information about atrial contraction, systolic ejection, diastolic filling and mechanical dyssynchrony. The paper is historically relevant because it frames impedance cardiography as more than a source of averaged cardiac-output values: waveform morphology may contain timing information related to the cardiac cycle.

The article is principally narrative and hypothesis-generating. It does not provide a prospective diagnostic cohort, blinded interpretation, prespecified thresholds or estimates of sensitivity, specificity and reproducibility for the proposed patterns. The waveform concepts may inform later signal analysis, but they should not be used as validated screening criteria for cardiac disease or as an independent basis for diagnosing diastolic dysfunction or dyssynchrony.

4.1.5.3. Exercise haemodynamics in pectus excavatum

Pectus excavatum provides a distinct structural setting in which resting evaluation may not reveal the functional consequence of reduced intrathoracic space or cardiac compression. Tardy et al. reported exercise cardiac-output limitation in patients with pectus excavatum, using PhysioFlow during exercise to examine whether impaired augmentation of stroke volume and cardiac output contributed to reduced aerobic capacity. The report

introduced a potentially useful application: testing the cardiovascular consequence of the deformity under physiological stress rather than inferring it from anatomy alone.

★ Filaire et al. revisited this question in 2024 by relating exercise haemodynamics to chest-wall deformity indices. Their findings suggest that exercise limitation is multifactorial and cannot be reduced to a single anatomical severity index. This is clinically plausible: cardiac compression, ventricular filling, chronotropic compensation, deconditioning, ventilatory mechanics and peripheral factors may interact, while static morphology may correlate imperfectly with function.

The evidence should remain proportionate. These are focused application reports rather than trials showing that PhysioFlow improves selection for surgery or predicts postoperative benefit. Exercise stroke-volume and cardiac-output profiles may complement CPET, imaging and anatomical assessment when the functional relevance of pectus excavatum is uncertain, but they do not replace them. The broader musculoskeletal and functional implications belong in Section 4.5; the present discussion is limited to the cardiac mechanism.

4.1.5.4. Practical evidence synthesis and close of the cardiology section

The CRT reports show technical feasibility for rapid, repeated assessment of acute within-patient haemodynamic change, but they are too small and methodologically limited to support routine PhysioFlow-guided optimisation. The historical waveform paper offers a concept for morphology-based interpretation, not a validated diagnostic method. The pectus-excavatum studies illustrate how exercise haemodynamics can test a structural hypothesis under physiological load, while also showing that functional limitation may not follow anatomy in a simple linear manner.

None of these applications currently supports stand-alone screening, treatment allocation or outcome prediction. Their value lies in generating or refining a mechanistic question and in complementing established clinical assessment. Across cardiology as a whole, the more developed evidence remains concentrated in heart failure, exercise-related coronary physiology, cardiac rehabilitation and HCM. The selected applications in this closing section should be retained as promising, low-volume evidence and revisited if larger prospective datasets emerge.

Practical take-home. Selected cardiac applications support rapid within-patient mechanistic assessment and hypothesis testing, particularly under physiological load. The present evidence does not support routine stand-alone screening or universal device-guided treatment algorithms.

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4.2. Pulmonary and respiratory diseases

Exercise intolerance and exertional dyspnoea in pulmonary disease rarely arise from a single failed organ. Ventilatory mechanics, gas exchange, pulmonary vascular load, right- and left-heart reserve, systemic oxygen delivery, respiratory-muscle work and peripheral extraction may all contribute. Conventional pulmonary function tests and peak oxygen uptake describe important parts of this system, but neither directly shows how cardiac output and stroke volume respond while symptoms develop.

This is the principal contribution of continuous non-invasive haemodynamics in the pulmonary literature. PhysioFlow has been used not only to estimate cardiac output at peak exercise, but also to follow the kinetics and morphology of the cardiac response throughout exercise and recovery: during incremental exercise, constant-work exercise, walking, respiratory unloading, positive-pressure support, oxygen or helium-oxygen breathing, pulmonary vasodilation and rehabilitation. The resulting corpus is unusually broad. Much of its value lies in resolving physiological mechanisms; whether a particular interpretation changes management is a separate, application-specific question.

The chapter therefore separates three questions. First, can the measurement be interpreted with sufficient confidence in the relevant population and protocol? Second, what physiological mechanism does it reveal beyond conventional exercise variables? Third, is that information mature enough to support a practical role in phenotyping, treatment selection or follow-up? This distinction prevents a mechanistically elegant experiment from being presented as a validated clinical pathway, while also avoiding the opposite error of dismissing a coherent body of physiological evidence because no single trial was designed as a definitive implementation study.

4.2.1. Chronic obstructive pulmonary disease

4.2.1.1. A circulatory component across the severity spectrum

The COPD evidence has developed from studies of advanced, mechanically constrained disease towards integrated phenotyping in earlier stages. The recurring observation is that oxygen transport cannot be inferred from spirometry or ventilation alone. Cardiac output may be preserved through compensation, limited by dynamic hyperinflation and impaired filling, or redistributed between respiratory and locomotor muscles according to the imposed task.

★ Richard et al. (2024) studied 207 CanCOLD participants: 88 ever-smokers without COPD, 63 with GOLD 1 and 56 with GOLD 2 COPD. Concurrent gas exchange and cardiac-output measurements allowed comparisons at matched metabolic demand, rather than only at each group's exercise endpoint. GOLD 1 responses resembled those of smokers without obstruction. GOLD 2 participants showed a lower calculated arteriovenous oxygen difference and blunted stroke-volume expansion associated with hyperinflation; compensatory heart-rate responses did not fully preserve end-exercise output. The study therefore reveals both compensation and its limits in relatively early COPD. Its distinctive contribution is integrated central–peripheral phenotyping, not proof of a treatment-selection rule. The oxygen-extraction interpretation remains indirect, and arterial oxygen content or saturation was not available in the analysed dataset.

Combining measured oxygen uptake with simultaneous cardiac output gives a calculated whole-body arteriovenous oxygen-content difference, $(a–v)O_2$ diff = $\dot{V}O_2/\dot{Q}c$. This helps interpret the balance between systemic oxygen delivery and utilisation, but does not independently measure skeletal-muscle extraction or mitochondrial function. It inherits error from both measurements and must be interpreted with haemoglobin, arterial oxygenation and regional blood-flow distribution in mind. Its value here is mechanistic; the pulmonary corpus does not establish this derived variable as a stand-alone clinical decision marker.

Vasilopoulou et al. examined on- and off-exercise cardiac-output kinetics during cycling and walking across GOLD stages I-IV. Together with work on exercise-mode selection and intermittent versus continuous walking, these studies show why a single rest-to-peak difference is an incomplete description. The speed of the response, the task used and the recovery trajectory may each reveal limitations that a peak value obscures.

4.2.1.2. Respiratory-muscle work and competition for blood flow

A substantial part of the COPD corpus concerns the respiratory muscle metaboreflex and competition for a finite cardiac output. Borghi-Silva et al. showed that unloading the respiratory muscles during high-intensity exercise improved locomotor-muscle oxygenation. Chiappa et al. linked accelerated muscle deoxygenation kinetics at

exercise onset to central cardiovascular dynamics, while ★ Louvaris et al. later documented impaired perfusion of extradiaphragmatic respiratory muscles during high-intensity exercise. These experiments are complementary: they place the cardiac response within a distribution problem rather than treating output as an isolated endpoint.

The resulting interpretation is clinically useful. A patient may stop because ventilation is mechanically constrained, because the cardiac response is insufficient, because an adequate output is preferentially directed towards the work of breathing, or because peripheral extraction remains impaired despite adequate delivery. Simultaneous CPET, continuous haemodynamics and local oxygenation measurements can separate these possibilities more convincingly than any component alone.

4.2.1.3. Hyperinflation, pressure support and lung deflation

The studies of Oliveira, Carrascosa and colleagues provide one of the clearest examples of haemodynamic heterogeneity hidden within a respiratory intervention. Inspiratory pressure support or proportional assist ventilation did not produce a uniform response. In less hyperinflated patients, unloading could preserve or increase stroke volume and improve endurance; in more hyperinflated patients, positive intrathoracic pressure could reduce venous return, stroke volume and cardiac output, with little or no gain in tolerance. The same intervention may therefore improve endurance or impose an unfavourable preload effect, depending on the balance between respiratory unloading and preload limitation.

Berton et al. provide an important counterweight. Lung deflation induced by tiotropium/olodaterol did not translate into a clear increase in stroke volume, cardiac output or leg blood flow at a given metabolic demand. This negative physiological result matters: relief of dynamic hyperinflation does not automatically imply a measurable central haemodynamic gain, and symptom improvement should not be retrospectively attributed to a cardiac mechanism that was not demonstrated.

High-intensity interval exercise offers a related example. Nasis et al. studied patients who developed dynamic hyperinflation and showed that exercise format modifies the haemodynamic burden. Alexiou et al. subsequently reported greater tolerance during intermittent than continuous shuttle walking in a proof-of-concept study. The corpus supports task-specific haemodynamic assessment, not a universal response inferred from one laboratory protocol.

4.2.1.4. Oxygen, helium-oxygen and pulmonary vasodilation

Hyperoxia studies add another layer to the oxygen-transport model. Siqueira et al. found that oxygen accelerated the cardiac-output response and improved arterial oxygenation at the onset of heavy exercise, without a corresponding significant acceleration of pulmonary oxygen-uptake kinetics. Queiroga et al. compared helium-hyperoxia with hyperoxia in hypoxaemic advanced COPD, building on an earlier congress report focused on cardiocirculatory responses. The reports should be treated as a publication family rather than as fully independent experiments.

The 2026 randomised, placebo-controlled, double-blind crossover trial by Collins et al. tested inhaled nitric oxide in 61 patients with mild-to-severe COPD. The unadjusted mean effect on peak oxygen uptake was neutral, but response varied with pulmonary microvascular phenotype; participants with a larger small-vessel volume fraction showed an improvement in peak oxygen uptake. This is a valuable example of why a null average effect can conceal a biologically plausible responder subgroup. PhysioFlow-derived haemodynamics contribute to the integrated phenotype, but the trial does not yet establish a stand-alone haemodynamic rule for selecting inhaled pulmonary vasodilation.

4.2.1.5. Rehabilitation, dyspnoea provocation and practical interpretation

The historical Nasis rehabilitation abstract and the supplemental-oxygen rehabilitation report suggest that serial cardiac-output responses can be followed during pulmonary rehabilitation, but the limited methodological detail prevents strong conclusions. The two 2022 Dyspnoea Challenge papers by Aitken et al. are useful chiefly because they standardise symptom provocation during a short uphill treadmill protocol. PhysioFlow was used within the broader physiological instrumentation; haemodynamics were not the sole or necessarily dominant determinant of the published dyspnoea findings.

Practical synthesis - COPD. The strongest current role is mechanistic and phenotypic: identifying whether impaired exercise tolerance reflects an insufficient flow response, compensatory haemodynamics, preload limitation during positive pressure, respiratory-locomotor competition, or a predominantly peripheral limitation. The evidence does not support interpreting one rest-to-peak delta as a complete phenotype, and it does not yet show that a PhysioFlow-guided treatment algorithm improves outcomes.

Methodological confidence in COPD is protocol-dependent. ★ Louvaris et al. found acceptable agreement between PhysioFlow and indocyanine-green dye dilution during concomitant cycling measurements. Kapchinsky et al. reported better test-retest reproducibility with PhysioFlow than with CO2 or inert-gas rebreathing in eight stable patients studied at five-minute submaximal stages, although absolute values differed between methods. By contrast, Bougault et al. reported overestimation during maximal or intermittent high-intensity exercise in eight hyperinflated patients; the absence of a stable metabolic and haemodynamic state seriously weakens the Fick comparison in that protocol. These findings are not contradictory enough to be averaged into one verdict: they define conditions under which comparison is more or less interpretable.

4.2.2. Pulmonary hypertension

4.2.2.1. Exercise stroke-volume and cardiac-index reserve

Pulmonary hypertension is a particularly demanding application because right-ventricular afterload can rise disproportionately during exercise, while resting measurements may underestimate functional limitation. Ferreira et al. evaluated signal-morphology impedance cardiography during incremental CPET in 50 patients with pulmonary arterial hypertension and 21 controls. Abnormal stroke-volume responses and a cardiac-index increase of no more than approximately 1.5-fold were associated with greater disease severity and with adverse clinical events during one-year follow-up. The study is clinically suggestive, but eight events are too few for a definitive prognostic rule and 12 of 50 patient recordings were technically unacceptable. Signal availability is therefore part of the result, not a footnote.

The central message remains important: in pulmonary arterial hypertension, distance or peak oxygen uptake alone cannot show whether the right ventricle has generated an adequate flow response. Continuous stroke volume and cardiac index can describe reserve and the temporal pattern by which reserve is lost. The measurement is most informative when interpreted with symptoms, oxygen uptake, ventilatory efficiency and established markers of right-heart and pulmonary vascular disease.

4.2.2.2. Enriching the six-minute walk test

Tonelli et al. instrumented the six-minute walk test in patients with pulmonary hypertension. The change in cardiac index correlated with distance walked and percentage-predicted distance, showing that a familiar submaximal test can be decomposed into more informative physiological components. A subsequent analysis compared beat-by-beat heart-rate slopes in pulmonary arterial hypertension, other lung diseases and healthy controls; the slower acceleration pattern in pulmonary arterial hypertension was associated with clinical worsening. The associated Arelli congress abstract represents the same six-minute-walk dataset as the full 2013 article and should not be counted as a separate confirmation.

The operational attraction is obvious: a scalable test already used in routine follow-up could provide both performance and flow-response information. The evidence supports feasibility and physiological enrichment, but it has not yet established thresholds that are sufficiently validated to replace established risk models or invasive assessment.

4.2.2.3. Training response, vasodilator response and pulmonary perfusion

Woolstenhulme et al. studied women with pulmonary arterial hypertension before and after supervised aerobic training. Training reduced peak systemic vascular resistance index and did not produce evidence of deteriorating left-ventricular systolic or diastolic function. Morris et al.analysed respiratory-buffering indices in the broader training programme and showed that ventilatory adaptation differed according to the magnitude and direction of six-minute-walk change. These reports are complementary products of a related programme and should not be presented as independent replication.

Historical abstracts proposed that exercise haemodynamics might detect vasodilator response more sensitively than resting measurements. Their limited detail makes them hypothesis-generating rather than practice-changing. Farina et al. used a novel combination of electrical impedance tomography and non-invasive haemodynamic assessment to study intrapulmonary perfusion distribution during exercise. This technically

ambitious study extends PhysioFlow from global flow estimation towards multimodal pulmonary vascular phenotyping, but remains small and exploratory.

4.2.2.4. Validation context and the current clinical pathway

Comparative evidence in pulmonary hypertension is more heterogeneous in design than uniformly discordant in result. In Tonelli et al., mean cardiac output values were close and the mean bias versus thermodilution was small, supporting reasonable group-level accuracy, although the limits of agreement indicated only moderate precision for individual measurements. Because PhysioFlow was recorded immediately after rather than simultaneously with catheterisation, physiological variation between acquisitions may have contributed to the observed dispersion; the secondary Fick comparison was also weakened by estimated rather than measured oxygen uptake. ★ Dupuis et al., using better-controlled resting measurements during right-heart catheterisation, reported favourable agreement with both the measured-variable Fick method and thermodilution and therefore provides the principal supportive evidence in this population. Panagiotou et al. found poor agreement with cardiovascular magnetic resonance, but the study used an earlier Enduro amplification configuration. Potential departures from current conditions of use and signal-quality procedures, discussed in Chapter 3, may also have contributed and limit direct transposition to current devices. Overall, these studies should be interpreted according to their specific measurement conditions rather than summarised as a simple positive-versus-negative balance. PhysioFlow adds continuous non-invasive flow information to routine clinical and exercise assessment. It complements, but does not replace, right-heart catheterisation when pulmonary pressures, pulmonary-artery wedge pressure or pulmonary vascular resistance must be determined.

The 2022 ESC/ERS pulmonary-hypertension guidelines retain right-heart catheterisation as the reference procedure for diagnosis and haemodynamic classification. Exercise or provocative invasive assessment is particularly relevant when exertional symptoms remain unexplained despite normal or borderline resting haemodynamics. PhysioFlow does not measure pulmonary-artery or wedge pressure, and flow alone cannot determine pulmonary vascular resistance, which requires pressure and cardiac-output data. Its complementary role is to add a continuous, non-invasive flow response to CPET or walking tests. An abnormal pattern can support further targeted assessment, but does not by itself distinguish pulmonary vascular disease, HFpEF, preload limitation or isolated right-ventricular dysfunction.

Practical synthesis - pulmonary hypertension. The evidence supports exercise haemodynamic phenotyping and physiological enrichment of functional tests. It does not support replacing catheterisation, pressure-based classification or validated risk assessment. The most credible near-term use is to expose impaired flow reserve during symptoms and to guide the escalation of testing.

4.2.3. Unexplained exertional dyspnoea and integrated cardiopulmonary phenotyping

Persistent exertional dyspnoea after unrevealing resting tests is a clinical problem defined partly by what standard assessment has failed to explain. Conventional CPET can determine whether limitation is ventilatory, gas-exchange, circulatory or deconditioning-dominant, but the circulatory inference often relies on indirect surrogates. Invasive CPET can resolve pressure-flow mechanisms, but its expertise, cost and invasiveness limit scalability. This leaves a clinically meaningful space for continuous non-invasive cardiac-output measurement, provided its findings are used to refine rather than close the diagnosis.

Kurpaska et al. studied 114 patients with arterial hypertension and showed that women with dyspnoea had a shorter six-minute-walk distance, a steeper VE/VCO2 slope, lower peak stroke volume and cardiac output, and a smaller rest-to-peak cardiac-output change than other subgroups. Resting biomarkers, conventional diastolic-function assessment and several standard CPET variables did not explain the difference. Exercise impedance cardiography therefore identified a circulatory abnormality that was largely invisible at rest. Skalska et al. later described an unfavourable central blood-pressure response in hypertensive women with dyspnoea. The studies arise from the same Polish research lineage and should be treated as convergent extension, not automatic independent validation.

The defensible clinical proposition is modest but important. In a patient with exertional symptoms and a non-diagnostic resting evaluation, adding continuous stroke volume and cardiac output to a standard exercise test may help determine whether central flow limitation is plausible, whether the response is compensatory but inefficient, or whether an adequate flow response makes a predominantly central limitation less likely. This information can support the choice between exercise echocardiography, pulmonary vascular assessment, autonomic evaluation, rehabilitation or invasive CPET.

An apparently preserved stroke-volume and cardiac-output response at the achieved metabolic demand makes marked forward-flow limitation less likely. It does not establish normal filling pressures or exclude HFpEF on its own. Exercise studies and the HFA–PEFF diagnostic framework show why left-sided filling-pressure assessment may be needed when HFpEF remains suspected despite reassuring resting findings (Borlaug et al., 2010; Pieske et al., 2019). Neither establishes a normal PhysioFlow exercise profile as a validated rule-out test. Conversely, an abnormal flow profile can reveal functional limitation without identifying its pressure mechanism. Flow and pressure assessment answer complementary questions; this distinction preserves the value of exercise phenotyping without turning it into an unsupported exclusion claim.

Contextual recommendation "in the gap". Current diagnostic pathways acknowledge that resting evaluation may not explain exertional dyspnoea and that exercise haemodynamics can reveal early pulmonary vascular or left-heart disease. They do not yet specify a validated scalable non-invasive flow step. This unresolved interval is the most strategically coherent application to test prospectively: does adding continuous non-invasive haemodynamics reduce diagnostic uncertainty, improve selection for advanced testing, or change management?

4.2.4. Cystic fibrosis, post-COVID conditions and other chronic respiratory disorders

4.2.4.1. Cystic fibrosis: central delivery versus peripheral utilisation

The cystic-fibrosis evidence is small but conceptually coherent. An early congress abstract reported lower cardiac output and left cardiac work index, higher systemic vascular resistance and an abnormal exercise haemodynamic response in people with cystic fibrosis, with exploratory normalisation after sildenafil in a very small treated subgroup. A related abstract described impaired mixed-venous oxygen saturation during maximal exercise.

Rodriguez-Miguelez et al. subsequently studied 15 people with mild-to-moderate cystic fibrosis and 18 controls during incremental exercise, followed by four weeks of sildenafil in the cystic-fibrosis group. PhysioFlow showed that maximal exercise limitation was not primarily explained by an inadequate central haemodynamic or chronotropic response; reduced skeletal-muscle oxygen extraction and utilisation were more closely related to exercise capacity. Sildenafil improved peripheral oxygen utilisation. The full article should replace the earlier abstract as the principal citation while the abstract remains linked as part of the same publication family.

This is an instructive negative central finding. PhysioFlow added value not by demonstrating cardiac failure, but by helping show that oxygen delivery was relatively preserved and directing interpretation towards the periphery. Such exclusionary physiological information is clinically meaningful when the alternative would be to attribute reduced oxygen uptake nonspecifically to lung disease.

Clayton et al. examined a different question in the current CFTR-modulator era. In 15 people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor and 15 matched controls, resting stroke-volume index and cardiac-index values did not differ, whereas microvascular acetylcholine-mediated vasodilation and flow-mediated dilation normalised to shear rate were impaired. The study is not an exercise application, but it reinforces the central-peripheral distinction: normal resting flow indices do not exclude vascular dysfunction in contemporary cystic fibrosis.

4.2.4.2. Post-COVID functional limitation

Nascimento et al. compared 36 adults after COVID-19 with 11 controls during the one-minute sit-to-stand test and six-minute walk test. PhysioFlow was explicitly identified in the methods. The post-COVID group completed fewer sit-to-stand repetitions and a shorter walking distance, and showed lower stroke-volume index, cardiac index, contractility index and ejection fraction with higher systemic vascular resistance indices during the sit-to-stand protocol. Tissue-oxygenation patterns did not differ significantly between groups.

The study demonstrates feasibility in a simple functional test and suggests that post-COVID limitation can include a central and vascular component. Interpretation must remain cautious because the groups were small, differed in age and body size, and the cross-sectional design cannot distinguish persistent disease effects from baseline differences or deconditioning. The results support a phenotype to investigate, not a diagnostic signature of long COVID.

4.2.5. Sleep-disordered breathing and positive airway pressure

Sleep-disordered breathing provides a different application: rapid haemodynamic changes during apnoea or positive airway pressure rather than incremental exercise. A historical abstract described a distinctive cardiac

response during obstructive apnoeas. Digby et al. subsequently published a small proof-of-concept study of acute continuous positive airway pressure in three postoperative cardiac-surgery patients, three patients with severe obstructive sleep apnoea and three healthy participants. Increasing positive end-expiratory pressure reduced stroke volume and cardiac index; in postoperative patients, PhysioFlow and pulmonary-artery-catheter measurements tracked the direction of change similarly.

A case report by Yoshida et al. used continuous PhysioFlow monitoring in obesity hypoventilation syndrome and described immediate restoration of cardiac output after non-invasive positive-pressure ventilation. The apparent contrast with pressure-induced reductions in stroke volume is physiologically credible: positive pressure can improve output when relief of severe hypoventilation, hypoxaemia and right-heart stress dominates, but reduce preload when intrathoracic pressure itself becomes the limiting factor. These tiny studies establish responsiveness and mechanistic plausibility, not outcome efficacy or a dosing algorithm.

Hargens et al., discussed in the cardiac-rehabilitation section, also found lower resting cardiac output, stroke volume and contractility-related indices in rehabilitation entrants with obstructive sleep apnoea. Together, the evidence supports considering sleep-disordered breathing as a modifier of haemodynamic phenotype, while keeping acute pressure-response experiments separate from chronic cardiovascular risk assessment.

4.2.6. Overall pulmonary evidence synthesis

Across pulmonary and respiratory disease, the literature is stronger as a coherent physiological corpus than as a set of isolated decisive clinical trials. COPD studies show compensation, limitation and redistribution of flow under varied ventilatory loads. Pulmonary-hypertension studies show that stroke-volume and cardiac-index reserve can enrich CPET and walking tests. Dyspnoea studies illustrate how exercise haemodynamics may reveal abnormalities missed at rest. Cystic-fibrosis and post-COVID studies demonstrate the value of separating central delivery from peripheral utilisation, while sleep and positive-pressure studies show rapid preload-sensitive responses.

The breadth of contexts is itself informative. PhysioFlow has continued to generate physiologically plausible responses during cycle ergometry, walking, sit-to-stand testing, respiratory unloading, non-invasive ventilation, supplemental gases, vasodilation and rehabilitation. No single application study proves that the technology should be used routinely in every patient. Conversely, the accumulated evidence is no longer well described as mere feasibility. It supports a mature measurement platform capable of contributing to integrative phenotyping when the protocol, signal quality and clinical question are explicit.

The next research step need not be one prohibitively large generic trial. More actionable studies would embed PhysioFlow in a defined clinical pathway and test a decision: selection for invasive CPET in unexplained dyspnoea; identification of preload-sensitive responses to positive pressure; recognition of a pulmonary-vascular responder phenotype in COPD; or distinction between central delivery and peripheral utilisation during rehabilitation. Outcomes should include diagnostic reclassification, change in management, resource use and patient-relevant benefit, not only correlation with another device.

For current practice, four principles emerge:

- Interpret trajectories and response patterns, not only resting values or rest-to-peak deltas.
- Combine flow with CPET, symptoms, ventilatory mechanics, oxygenation and, when relevant, local tissue oxygenation.
- Treat signal availability, protocol design and the validity of the comparator as part of the evidence.
- Use non-invasive haemodynamics to refine phenotype and escalation of testing, not to claim pressure-based diagnoses that the device does not measure.

Bottom line. The pulmonary corpus supports PhysioFlow as a scalable integrative measurement of the circulatory component of exercise and respiratory interventions. Its most credible clinical opportunity is not to replace established pulmonary or invasive testing, but to make functional assessment physiologically more specific and to reduce the number of patients whose exertional limitation remains unexplained.

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4.3. Internal and systemic medicine

The conditions gathered in this chapter differ clinically, but they share an integrative problem: symptoms and functional limitation frequently reflect interactions among cardiac reserve, vascular regulation, autonomic control, oxygen transport, metabolism and skeletal-muscle function. Resting blood pressure, ejection fraction or routine laboratory values may remain reassuring while the dynamic response to exercise, posture, dialysis, heat or medication is abnormal.

PhysioFlow is used in this literature less as a disease-specific diagnostic instrument than as a continuous flow layer within a physiological assessment. Its principal contribution is to help separate central oxygen delivery from peripheral utilisation, to follow the time course of compensation or failure, and to identify different haemodynamic routes to a superficially similar symptom or blood-pressure response. This is a clinically relevant contribution, but it must not be confused with proof that a PhysioFlow-guided pathway improves outcomes.

Three interpretive rules are especially important. First, indexed and non-indexed values answer different questions in obesity, pregnancy and other states in which body size or composition changes. Second, calculated arteriovenous oxygen difference is derived from measured oxygen uptake and estimated cardiac output; it is not an independent tissue measurement. Third, trajectories during the stress and recovery phases are usually more informative than a single resting value or a rest-to-peak difference.

4.3.1. Arterial hypertension

4.3.1.1. Why resting haemodynamics are insufficient

The Polish hypertension programme provides a coherent sequence of studies showing that resting haemodynamics alone do not adequately predict functional capacity. Kurpaska et al. evaluated controlled hypertensive patients with resting impedance cardiography, echocardiography, laboratory testing and CPET. Resting variables showed only weak relationships with exercise capacity and did not provide an independent explanation of performance after multivariable analysis. This negative result is useful: the clinical question is not whether a resting cardiac-output estimate can replace CPET, but whether adding a dynamic flow response makes exercise assessment more physiologically resolved.

A separate multiparameter study in 98 patients demonstrated relationships between exercise cardiac output, stroke volume and oxygen uptake. The work supports interpretation of hypertension as a heterogeneous functional phenotype rather than a single pressure value. It does not establish a unique PhysioFlow signature of hypertension, because exercise capacity is also influenced by age, body composition, medication, chronotropic response and peripheral conditioning.

4.3.1.2. Exercise trajectories, dyspnoea and central pressure

The most informative application is the symptomatic patient whose resting assessment does not explain exertional limitation. In hypertensive patients with dyspnoea, exercise impedance cardiography identified lower peak stroke volume and cardiac output and a smaller output increase alongside poorer walking performance and ventilatory efficiency. A later analysis described an unfavourable central blood-pressure response in hypertensive women with dyspnoea. These related studies are discussed in Section 4.2.3 because their primary clinical entry point is unexplained exertional dyspnoea.

The methodological lesson is transferable to hypertension: a rest-to-peak delta is not a complete phenotype. The timing and morphology of the stroke-volume and contractility responses, their relationship to heart rate and workload, and their recovery pattern may discriminate compensation from early functional limitation more plausibly than two isolated time points. Prospective thresholds and decision rules have not yet been validated in hypertension.

4.3.1.3. Acute intervention studies

Gayda et al. studied sauna alone and post-exercise sauna in untreated hypertension. Blood-pressure changes were accompanied by measurable haemodynamic adjustments, illustrating how non-invasive monitoring can identify the mechanism of an acute response rather than record pressure alone. The study is physiological and short term; it should not be interpreted as evidence for sustained antihypertensive efficacy or outcome benefit.

The proposed comparison of high-intensity interval training with hydrochlorothiazide is represented in the matrix by a protocol publication. It is useful context for the type of pragmatic intervention study that could connect

haemodynamic phenotype to treatment, but it contributes no outcome evidence until results are published and audited.

Practical synthesis - hypertension. PhysioFlow does not diagnose hypertension and should not replace validated blood-pressure assessment. Its plausible value is to expose how the circulation responds during symptoms, exercise or an intervention when resting measurements are insufficient. The evidence supports physiological enrichment; it does not yet support a treatment-selection algorithm.

A historical resistant-hypertension trial by Taler et al. is deliberately not cited as PhysioFlow evidence. The study used CardioDynamics BioZ impedance cardiography. It may remain relevant to the broader concept of haemodynamically guided antihypertensive care, but attributing its results to PhysioFlow would be incorrect.

4.3.2. Neurovascular, autonomic and orthostatic disorders

4.3.2.1. Cardiodynamic response to walking after stroke

Liu et al. instrumented the six-minute walk test in 29 people after stroke on two occasions. Heart rate, cardiac output and cardiac index rose progressively during the first approximately 90 seconds, whereas stroke volume reached a plateau much earlier. Test-retest reliability was high for the principal cardiodynamic variables, and the cardiac-output and cardiac-index responses correlated with walking distance. Participants assessed within one year of stroke also differed from those later in recovery.

This study is useful because it transforms a global functional result into a time-resolved physiological test. The early stroke-volume plateau is not, by itself, proof of pathology; the response must be interpreted with heart rate, workload, neurological impairment and deconditioning. The sample was small and did not establish a threshold that predicts rehabilitation outcome. A later Longshi Scale study extends the association between activity dependence and cardiac-function indices, but its cross-sectional design likewise cannot establish causality.

4.3.2.2. Orthostatic stress and respiratory-pump support

Orthostatic regulation is a natural application for continuous beat-to-beat trends because blood pressure alone cannot distinguish reduced cardiac filling from inadequate vasoconstriction or chronotropic compensation. Rodrigues et al. examined older women during orthostatic stress with and without inspiratory resistance. The study supports a role for the respiratory pump in maintaining central and cerebrovascular responses, while later work from the same programme explored sympathovagal balance and slow haemodynamic oscillations after inspiratory-muscle training. In some of these reports, PhysioFlow-derived ECG or heart-rate variability was more central than the flow estimates; they should therefore not all be counted as independent demonstrations of cardiac-output utility.

A historical tilt-test abstract reported that sublingual nitroglycerin altered haemodynamic responses during head-up tilt. The report remains hypothesis-generating because the available documentation is insufficient for a full appraisal. In Parkinson disease, Wolf et al. combined postural and venous-volume measurements to show that L-dopa can influence venous tone. These studies illustrate mechanistic sensitivity, not a validated stand-alone test for syncope or autonomic failure.

4.3.2.3. Neurological disability and exercise modality

★ Astorino (2019) examined haemodynamic and cardiorespiratory responses to different arm-cycling regimens in men with spinal-cord injury. The work reinforces a broader methodological point: the exercise modality and available muscle mass materially shape stroke-volume, heart-rate and output responses. Comparisons with able-bodied leg exercise or conventional reference values can therefore misclassify a population-specific but physiologically coherent response.

Practical synthesis - neurovascular and autonomic disorders. The evidence supports continuous haemodynamics as an adjunct to walking, posture and autonomic provocation when the aim is to distinguish filling, flow, vascular and chronotropic components. It does not support using PhysioFlow alone to diagnose stroke-related disability, syncope, Parkinson-related dysautonomia or spinal autonomic dysfunction.

4.3.3. Metabolic and endocrine disorders

4.3.3.1. Obesity, diabetes and metabolic syndrome

Besnier et al. combined maximal CPET, PhysioFlow haemodynamics, cerebrovascular measurements and cognitive testing in adults with type 2 diabetes. The diabetic group showed an altered cardiac response to exercise, including a lower peak cardiac-index response, within a broader pattern involving cerebral perfusion and cognitive performance. This integrative application is useful because it does not treat the metabolic phenotype as either exclusively cardiac or exclusively peripheral. The study is mechanistic and comparatively small; it does not constitute an independent validation of absolute cardiac output.

Metabolic disease illustrates why oxygen uptake should be decomposed into delivery and utilisation. In obese adults, Vella et al. showed that reduced peak oxygen uptake can coexist with altered cardiac function and arteriovenous oxygen difference. In men with type 1 diabetes, Niedzwiecki et al. found that greater insulin resistance was associated with lower cardiac output during maximal exercise and recovery. In metabolic syndrome, Chen et al. reported lower maximal exercise capacity despite broadly preserved ejection fraction and differences in stroke volume, cardiac work and vascular resistance.

These cross-sectional studies identify associations rather than a common causal pathway. Body size is especially important: a larger absolute stroke volume or cardiac output may coexist with an unfavourable indexed response, and conventional body-surface-area indexing may itself be difficult to interpret in obesity. Medication, duration of diabetes, autonomic dysfunction, vascular stiffness and fitness can all contribute.

★ Kwast et al. combined CPET and impedance cardiography in patients with obesity or type 2 diabetes and in healthy controls. Patients had markedly lower maximal work and calculated arteriovenous oxygen difference; the type 2 diabetes group also showed lower peak cardiac output and cardiac power than the obese group. After an exercise intervention, improved work capacity was explained mainly by a rise in calculated peripheral oxygen extraction rather than by a measurable change in cardiac parameters. This central-negative result is valuable, but the healthy controls were younger and not closely age-matched, limiting attribution of between-group differences to metabolic disease alone.

4.3.3.2. Acute and repeated interventions

Perissiou et al. used a double-blind, placebo-controlled crossover design in 13 adults with type 2 diabetes. Acute ketone-monoester ingestion increased cardiac index and stroke-volume index, reduced systemic vascular resistance index and improved muscle oxygenation, without improving the endothelial-function endpoint. The design is rigorous for an acute mechanistic question, but a one-dose response does not establish chronic benefit, safety or treatment value.

James et al. assessed repeated hot-water immersion in 14 people with type 2 diabetes. Resting blood pressure and several central haemodynamic indices changed after the intervention, whereas macrovascular and microvascular endothelial-function measures did not improve. The uncontrolled pre-post design prevents separation of intervention effects from time, familiarisation or regression to the mean. Whole-body vibration and interval-training studies add physiological detail, but PhysioFlow was one component of broader immune, metabolic, cognitive or cerebral-oxygenation protocols rather than the decisive endpoint.

4.3.3.3. Inherited metabolic disease and mitochondrial function

Imbard et al. provide one of the most clinically interesting metabolic applications. In 27 patients with fatty-acid beta-oxidation disorders, the slope relating cardiac output to oxygen uptake during incremental exercise was associated with disease severity and differed in relation to triheptanoin treatment. The authors propose this integrated response as a follow-up biomarker of mitochondrial dysfunction. The informative signal lies in the relationship between flow and oxygen uptake, not in an isolated change in cardiac output.

The interpretation requires discipline. The calculated relationship depends on accurate synchronisation of gas exchange and PhysioFlow, and it is an indirect systemic surrogate rather than a direct assay of mitochondrial function. The cohort combines rare disorders and is too small to establish disease-specific thresholds. Nevertheless, the study moves beyond descriptive physiology towards a plausible monitoring application in a field with few scalable functional biomarkers.

Smaller studies in mitochondrial myopathy and lipin-1 deficiency extend the same central-peripheral framework. Bravo et al. used exercise and recovery measurements to investigate skeletal-muscle reoxygenation. Renard et al. described hydroxychloroquine treatment in lipin-1 deficiency within a much broader molecular and clinical

evaluation. These studies are important for hypothesis generation and individual follow-up, but they cannot establish general treatment efficacy from haemodynamic change alone.

Practical synthesis - metabolic disease. The strongest contribution is integrative phenotyping: distinguishing insufficient central delivery from impaired peripheral utilisation and following how that balance changes with intervention. Derived arteriovenous oxygen difference and flow-to-oxygen-uptake slopes must be interpreted as model-dependent composite measures, not independent direct measurements.

4.3.4. Systemic and chronic disease applications

4.3.4.1. Renal disease and haemodialysis

Bayya et al. prospectively monitored 48 chronic haemodialysis patients before, during and after a dialysis session. Eighteen developed a systolic-pressure fall of at least 20%. Among these unstable patients, 11 showed a fall in cardiac output, whereas seven showed a significant fall in peripheral resistance. A lower baseline end-diastolic filling ratio was associated with instability and was interpreted as a marker of reduced preload.

The clinically important finding is heterogeneity: the same hypotensive endpoint arose through different combinations of flow and vascular resistance. Continuous non-invasive monitoring could therefore support mechanism-based investigation of recurrent intradialytic hypotension. However, the proposed filling index is device-derived, the population was heterogeneous, and the study did not test whether PhysioFlow-guided preventive actions improved dialysis tolerance or outcomes.

A later congress abstract examined the short-term haemodynamic effect of liraglutide in diabetic nephropathy. It remains supporting evidence only: the abstract format, brief exposure and incomplete methodological detail do not permit a robust clinical conclusion.

4.3.4.2. Cirrhosis and multisystem exercise intolerance

Couret et al. compared 45 patients with cirrhosis with 45 age- and sex-matched controls. Peak oxygen uptake was markedly reduced and declined with Child-Pugh severity. Cardiac output at exercise was relatively preserved, whereas chronotropic incompetence was frequent and calculated arteriovenous oxygen difference was reduced. Heart-rate reserve and lower-limb functional performance independently explained much of the variation in peak oxygen uptake.

This is another informative central-negative result. Reduced aerobic capacity in cirrhosis should not automatically be attributed to an inadequate cardiac-output response. The integrated data point towards chronotropic and peripheral-muscle limitations and support a cirrhosis-induced myopathy phenotype. Cross-sectional associations cannot determine whether targeted rehabilitation changes the physiology or clinical course.

4.3.4.3. Fibromyalgia, cancer and post-infectious conditions

In women with fibromyalgia, Lehto et al. found substantially lower peak oxygen uptake than in controls, with contributions from both lower peak cardiac output and lower calculated arteriovenous oxygen difference. The haemodynamic response remained qualitatively preserved, supporting severe deconditioning and combined central-peripheral limitation rather than a single disease-specific cardiac abnormality. The study helps resist overinterpretation: a lower value in a symptomatic group is not necessarily evidence of intrinsic myocardial disease.

Falz et al.randomised 148 patients after breast, prostate or colorectal cancer surgery to a six-month home-based online strength-endurance programme or control; 122 completed follow-up. Oxygen uptake improved more in the intervention group and rate-pressure product decreased, but cardiac output did not show a significant between-group interaction. The trial supports scalable rehabilitation and reduced myocardial workload during exercise, while showing that PhysioFlow need not change for an intervention to be clinically or functionally beneficial.

Lässing et al. repeatedly tested young competitive handball players with and without SARS-CoV-2 infection. Small group size and the athletic population limit clinical generalisation, but the study illustrates the sensitivity of serial integrated measurements to transient post-infectious changes. It should not be extrapolated into a diagnostic signature for long COVID or systemic inflammation.

4.3.4.4. Rare systemic and autonomic case evidence

A historical case of familial amyloid polyneuropathy used continuous monitoring during posture and exercise. The fall in exercise blood pressure with little increase in cardiac index and reduced vascular resistance was interpreted as evidence of peripheral sympathetic denervation. Such case material demonstrates mechanistic plausibility and preserves the historical breadth of PhysioFlow use, but it has no population-level diagnostic performance.

Practical synthesis - systemic and chronic disease. Across dialysis, cirrhosis, fibromyalgia, cancer rehabilitation and rare systemic disease, PhysioFlow is most useful when identical symptoms or pressure responses may arise through different mechanisms. The evidence supports mechanistic stratification and monitoring; prospective studies must still show that acting on the phenotype improves care.

4.3.5. Pregnancy and maternal haemodynamics

4.3.5.1. Normal early-pregnancy adaptation

Bijl et al. compared 20 healthy women in the first trimester with 20 non-pregnant controls during submaximal CPET. Stroke volume, cardiac output and heart-rate responses to exercise were broadly similar, while early pregnancy was characterised by a larger ventilatory response and a tendency towards slower cardiac-output and heart-rate recovery. The study establishes feasibility and a physiological reference direction; it was not designed to predict obstetric complications.

The recovery finding is a useful reminder that pregnancy changes the baseline physiological context. Gestational age, posture, blood volume, vascular tone and exercise intensity must be explicit before an individual trace is labelled abnormal. Reference values from non-pregnant adults cannot simply be transferred.

4.3.5.2. Pregnancy-related cardiovascular risk, pre-eclampsia and later functional phenotype

Dos Santos et al. followed B-type natriuretic peptide, exercise and haemodynamic variables in low-risk pregnancy and in pregnancy complicated by congenital heart disease. The absence of a decisive relationship between BNP and the reported haemodynamic or exercise variables is an informative neutral result: it does not indicate that PhysioFlow failed, and it cautions against assuming that a single biomarker and dynamic maternal adaptation must move in parallel. The application is longitudinal and clinically relevant, but the primary question concerns BNP and pregnancy rather than device validation.

Grønningsæter et al. assessed 62 women approximately seven years after severe pre-eclampsia and 35 controls. The former pre-eclampsia group had lower peak oxygen uptake and lower peak cardiac output, and 19% met the study definition of cardiac limitation. They were also less active, more sedentary and more frequently unfit; body mass index and physical activity explained a substantial part of peak oxygen uptake.

The study supports long-term cardiovascular follow-up after severe pre-eclampsia, but does not show that the PhysioFlow phenotype is specific to prior placental disease or independently predicts events. A historical pilot abstract reproduced in the 2024 PhysioFlow guide compared ten women with pre-eclampsia, ten women with an uncomplicated delivery and ten non-pregnant controls during supine-to-lateral postural changes. It suggested that the cardiac-index response to position might carry prognostic information, but no indexed abstract or complete proceedings record was located and the date cannot be verified from the reproduced source. A later publication from the same Rouen programme, led by Tith et al. in 2013, focused on indexed systemic vascular resistance as an early discriminator of pre-eclampsia (doi:10.1016/j.annfar.2013.07.357). The later abstract should be treated as a related development of the programme, not assumed to be an exact duplicate or an independent validation without cohort-level confirmation.

4.3.5.3. Caesarean section, oxytocin and acute monitoring

McLeod et al.randomised 74 women undergoing elective caesarean section to different oxytocin infusion strategies after a 5-unit bolus. Spinal anaesthesia and oxytocin produced rapid, measurable changes in heart rate, cardiac index, cardiac work and systemic vascular resistance. The additional 30-unit infusion did not produce adverse haemodynamic effects in this study. Continuous non-invasive monitoring was well matched to the short time scale of the pharmacological response.

This remains a small perioperative trial in a selected elective population. It does not establish the safety of all oxytocin regimens or replace clinical blood-pressure monitoring, obstetric assessment and escalation when haemodynamic instability occurs. A separate LCHADD pregnancy case illustrates individualised monitoring

during a rare metabolic condition and high-intensity exercise, but is not generalisable evidence for routine pregnancy care.

Practical synthesis - pregnancy. PhysioFlow can describe maternal flow responses continuously during exercise, recovery and acute obstetric interventions without invasive instrumentation. Current evidence supports research, physiological reference development and selected monitoring questions. It does not yet validate screening for pre-eclampsia, prediction of maternal events or replacement of established obstetric and echocardiographic assessment.

4.3.6. Overall evidence synthesis

Section 4.3 is heterogeneous by diagnosis but coherent by function. Across hypertension, stroke, orthostatic stress, metabolic disease, dialysis, cirrhosis, chronic pain, cancer rehabilitation and pregnancy, the recurrent value of PhysioFlow is to make a dynamic stress response more specific. It can show whether cardiac output is insufficient, preserved through compensation, unchanged despite functional improvement, or dissociated from peripheral oxygen utilisation and vascular control.

Several apparently negative findings are therefore scientifically constructive. Preserved output in cirrhosis redirects attention towards chronotropy and muscle; unchanged output after cancer rehabilitation shows that improved oxygen uptake and lower myocardial workload need not require a larger peak flow; similar exercise haemodynamics in early pregnancy help define normal adaptation. A technology intended for integrative phenotyping should not be judged only by how often it produces an abnormal central value.

The evidence is nevertheless not equivalent to routine clinical utility. Most studies are single-centre, small or cross-sectional; interventions are often acute; historical abstracts lack full methodological detail; and derived indices can amplify uncertainty from multiple inputs. Disease-specific thresholds, reproducible classification rules and management consequences are largely absent. The broad corpus supports maturity of measurement across demanding contexts, but not a universal decision algorithm.

For current interpretation, five principles emerge:

- Use continuous trajectories and recovery patterns rather than relying only on resting values or rest-to-peak differences.
- Interpret absolute and indexed values together when body size, obesity, pregnancy or fluid shifts materially alter the denominator.
- Treat calculated arteriovenous oxygen difference and flow-to-oxygen-uptake slopes as integrated derived measures, not direct independent assays of peripheral extraction or mitochondrial function.
- Preserve central-negative findings: demonstrating adequate flow can be valuable when it redirects investigation towards chronotropic, vascular, ventilatory or peripheral mechanisms.
- Test clinical value through defined decisions - escalation of exercise testing, mechanism-specific management of dialysis hypotension, rehabilitation targeting or longitudinal monitoring - rather than through another undirected correlation study.

Bottom line. The internal and systemic medicine corpus supports PhysioFlow as a flexible, scalable tool for integrative haemodynamic phenotyping across exercise, posture, fluid removal and intervention. Its most credible role is to resolve mechanism within a defined clinical problem; its main research need is evidence that this additional specificity changes decisions, efficiency or outcomes.

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4.4. Critical care, perioperative medicine and anaesthesia

Critical care and anaesthesia appear, at first sight, to be natural environments for continuous non-invasive haemodynamic monitoring. Patients may change within minutes; arterial pressure can remain an incomplete surrogate for flow; and repeated invasive measurements are not always justified. The relevant question, however, is not whether continuous cardiac output is conceptually attractive. It is whether PhysioFlow provides sufficiently dependable and actionable information under the specific conditions in which a decision is being made.

The present PhysioFlow corpus establishes feasibility across spontaneous-breathing trials, sepsis, acute dyspnoea, spinal anaesthesia and major surgery. It also demonstrates genuine constraints, including small samples, old or incompletely reported abstracts, electrical interference during electrocautery, non-equivalent comparators and a lack of trials in which PhysioFlow-guided management was shown to improve patient outcomes. This section therefore distinguishes physiological observation from validated decision support.

In this setting, trends and internally coherent responses are generally more defensible than isolated absolute values. Flow must be interpreted with blood pressure, heart rate, oxygenation, clinical examination and, when indicated, echocardiography or invasive monitoring. A non-invasive device without pressure waveforms, alarms or validated shock-specific treatment thresholds should not be presented as a stand-alone intensive-care monitor.

4.4.1. Critical care, weaning and acute haemodynamic assessment

4.4.1.1. Weaning from mechanical ventilation

Two early conference reports explored the haemodynamic transition during spontaneous-breathing trials. Le Tacon et al. described ten trials in seven patients. In patients without respiratory distress, heart rate rose modestly and stroke volume fell while cardiac index remained broadly stable. Lee et al. compared successful and failed weaning in 19 patients: the failure group showed a persistent increase in heart rate, stroke volume and cardiac output during the trial, whereas the success group remained comparatively stable. The physiological interpretation is plausible: liberation from positive-pressure ventilation can increase venous return, left-ventricular afterload and respiratory-muscle demand, so an apparently vigorous cardiac response may represent excessive cardiovascular work rather than reserve.

These reports support continuous observation because the trajectory during the trial is more informative than a measurement obtained only before and after it. They do not establish a validated prediction rule. Both are small abstracts, the case mix and adjudication procedures are incompletely described, and no PhysioFlow threshold has been prospectively tested against a contemporary weaning protocol. They should therefore be retained as historical proof of concept, not as evidence that the device can independently determine extubation readiness.

4.4.1.2. Sepsis, acute critical illness and response to intervention

Shoemaker and colleagues placed non-invasive haemodynamic monitoring within a broader programme of outcome prediction and therapy guidance in acute critical illness. The report is relevant historically because it emphasised flow, oxygen transport and tissue oxygenation rather than arterial pressure alone. Its broad claims are difficult to grade using modern evidence standards, because the design, selection process and treatment consequences are insufficiently detailed in the available record. It is best used as conceptual context rather than as a pivotal efficacy study.

Butz et al. prospectively evaluated nine septic patients before and one hour after two litres of crystalloid. Systemic vascular resistance and indexed resistance increased significantly, whereas heart rate, mean arterial pressure and left cardiac work index did not change significantly. The study illustrates a potential advantage of multiparametric monitoring: a blood-pressure response can result from different combinations of flow and vascular tone, and a fluid challenge does not imply a uniform stroke-volume response. It also illustrates the limits of the evidence. The cohort was extremely small, used historical systemic inflammatory response criteria, had no control group, and did not validate PhysioFlow-derived treatment targets or demonstrate improved outcomes.

The passive-leg-raise study after cardiac surgery belongs primarily to Chapter 3 because its central question is the ability of signal-morphology impedance cardiography to detect stroke-volume variation against a comparison method. Its clinical relevance to this chapter is nonetheless clear: reversible preload manipulation is a more

useful test of dynamic responsiveness than a static preload surrogate. Any bedside use should follow the validated protocol and methodological boundaries described in Chapter 3.

4.4.1.3. Acute dyspnoea in the emergency department

Vorwerk et al. conducted the most clinically oriented study in this section. In 52 adults presenting with acute breathlessness, 51 of whom had analysable data, discharge diagnoses were classified as cardiac or non-cardiac. Cardiac causes were associated with lower cardiac output and cardiac index and higher systemic vascular resistance. Cardiac index showed an area under the receiver-operating-characteristic curve of 0.906; a value at or below 3.2 $L \cdot min^{-1} \cdot m^{-2}$ produced a positive likelihood ratio of 7.9 and a negative likelihood ratio of 0.14 in this cohort.

This is a promising diagnostic-enrichment result, not a definitive diagnostic test. The study was single-centre, modest in size and used the final clinical diagnosis rather than a uniform independent gold standard. The threshold requires external validation and may be sensitive to age, body size, medication, acute loading conditions and the prevalence of cardiac disease. PhysioFlow should therefore be viewed as an adjunct to the emergency assessment of dyspnoea, not as a replacement for electrocardiography, biomarkers, imaging or clinical judgement. The study also provides a natural bridge to the integrative symptom-based synthesis proposed for Section 4.7.

Practical synthesis - acute care. The corpus supports feasibility and physiological discrimination during rapidly changing conditions. Its strongest use case is the interpretation of a haemodynamic trajectory alongside standard monitoring. It does not yet support autonomous shock classification, a validated weaning decision rule, or a PhysioFlow-guided resuscitation algorithm.

4.4.2. Perioperative and anaesthetic applications

4.4.2.1. Spinal anaesthesia and caesarean delivery

Terblanche et al. continuously monitored ten elective caesarean deliveries under spinal anaesthesia. Systolic pressure fell by approximately 25%, with accompanying changes in cardiac index, heart rate, stroke volume and systemic vascular resistance index; the greatest haemodynamic transition occurred around delivery. The pilot demonstrates that PhysioFlow can describe the mechanism and timing of hypotension, but its sample size and uncontrolled design preclude a management recommendation.

McLeod et al. subsequently used continuous haemodynamic monitoring in a randomised comparison of two oxytocin regimens during elective caesarean delivery. That trial is analysed in Section 4.3.5 because its primary question concerns maternal physiology and drug exposure. Its relevance here is that non-invasive flow monitoring can reveal treatment effects not fully represented by arterial pressure. The application remains investigational unless monitoring is tied prospectively to a protocol and clinically important maternal outcomes.

4.4.2.2. Preoperative risk signals

A 2006 SFAR abstract evaluated 67 patients before abdominal or vascular surgery. Nearly half developed intraoperative hypotension. Preoperative heart rate, stroke volume and early-diastolic-filling/preload-related indices were associated with subsequent events, whereas cardiac index and several other resting variables were not; CTi showed only a statistical trend. This pattern is informative because it argues against reducing perioperative risk to a single resting output value. It remains hypothesis-generating: the endpoint was broad, the model was not externally validated, and the incremental value beyond standard risk assessment was not established.

4.4.2.3. Pharmacodynamic and mechanistic studies

Komatsu et al. used impedance cardiography while testing whether ephedrine accelerated vecuronium-induced neuromuscular block. Ephedrine increased cardiac index by 17%, but did not accelerate the onset of 90% neuromuscular block. For PhysioFlow, the useful result is not a claim of anaesthetic benefit; it is the ability to register the expected haemodynamic effect while showing that a larger flow response did not translate into the hypothesised pharmacodynamic outcome. The study is therefore a mechanistic application rather than evidence for perioperative haemodynamic guidance.

4.4.2.4. Major surgery, comparators and hostile measurement conditions

Gratz et al. compared PhysioFlow, third-generation FloTrac/Vigileo and central venous oxygen saturation during major intra-abdominal surgery. PhysioFlow values were less variable and tracked central venous oxygen saturation more closely than FloTrac/Vigileo in the reported analysis. This finding should be framed carefully. Central venous oxygen saturation is not a reference cardiac-output method; close co-variation may be physiologically useful but does not demonstrate agreement or accuracy. The authors also excluded PhysioFlow data during electrocautery, which is an important operational limitation rather than a minor technical detail.

The abstract therefore supplies two complementary messages. First, non-invasive impedance monitoring may preserve a physiologically coherent trend when an arterial pulse-contour device is affected by changing vascular tone. Second, the measurement environment determines usability: electrical interference, ventilation, patient movement, electrode access and rapid changes in vascular state must all be documented. A future perioperative study should use simultaneous reference measurements, report data availability and artefact burden, predefine acceptable trending performance, and test whether the information changes fluid or vasoactive management.

4.4.3. Overall evidence synthesis

- Feasibility is demonstrated across weaning, sepsis, acute dyspnoea, spinal anaesthesia and major abdominal surgery, including clinically demanding measurement conditions.
- The most persuasive clinical signal is the emergency-dyspnoea study, but its diagnostic threshold remains single-centre and unvalidated externally.
- Historical weaning and perioperative abstracts are useful for mechanism and hypothesis generation, but should not be weighted as prospective decision-impact evidence.
- Continuous trajectories, responses to reversible interventions and concordance with the whole physiological picture are more defensible than isolated absolute values.
- No study in this corpus demonstrates that a PhysioFlow-guided critical-care or perioperative algorithm improves complications, length of stay or survival.

Editorial conclusion. The critical-care and perioperative evidence remains application-specific and developmental. PhysioFlow has shown that meaningful non-invasive haemodynamic information can be obtained in selected acute and perioperative settings. The remaining gap is not another feasibility series; it is a well-defined decision-impact study in which data availability, action thresholds, treatment changes and patient-centred outcomes are prospectively recorded.

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4.5. Musculoskeletal and functional rehabilitation

In musculoskeletal rehabilitation, walking distance, workload and symptom scores are composite outcomes. They may improve because pain falls, gait mechanics recover, muscle conditioning increases, confidence returns, or cardiovascular reserve changes. Conversely, a poor test may reflect a locomotor constraint rather than impaired cardiac output. Continuous haemodynamic assessment is potentially valuable because it adds a central-circulatory response to a functional test without requiring the patient to exercise inside an imaging system.

The PhysioFlow evidence is small but conceptually diverse: one randomised rehabilitation study after knee arthroplasty, two reports on exercise limitation in pectus excavatum, and exploratory exercise studies after transtibial amputation and spinal cord injury. Together they support physiological phenotyping and protocol design. They do not yet establish a general rehabilitation algorithm or prove that measuring cardiac output is necessary in all musculoskeletal patients.

Functional rehabilitation after knee arthroplasty

Lin et al.randomised 66 patients undergoing total knee arthroplasty to a multidisciplinary home rehabilitation programme based on the six-minute walk test and non-invasive cardiac output, with full supervision through WeChat, or to a rehabilitation manual completed independently. Sixty participants completed training and symptom follow-up. Because COVID-19 restrictions prevented 36 participants from returning for the instrumented six-month assessment, the principal six-minute-walk and haemodynamic analysis was restricted to 12 patients per group.

At six months, the intervention group achieved a longer walking distance than controls (413.9 versus 375.0 m), higher activity-equivalent intensity, greater end-test stroke volume (115.0 versus 98.4 mL) and greater cardiac output (11.9 versus 9.8 L/min). Pain and WOMAC outcomes also favoured the intervention. The study is important because it embeds PhysioFlow in an actual rehabilitation pathway rather than using the device only to describe physiology.

The causal attribution is nonetheless limited. The intervention combined haemodynamic testing, multidisciplinary prescription, repeated professional contact, digital supervision and likely improved adherence, whereas the control group received a manual. The trial therefore demonstrates benefit of the bundled programme, not the independent contribution of PhysioFlow. The severe loss of instrumented follow-up also weakens the randomised comparison. A definitive study would keep contact intensity equivalent, predefine how haemodynamic findings change the exercise prescription, and report adherence and adverse events by treatment arm.

Practical interpretation. The six-minute walk test becomes more informative when its distance is interpreted with the cardiac response, particularly when pain or locomotor impairment prevents a conventional maximal test. The current trial supports feasibility and a promising care model, but it does not isolate the effect of PhysioFlow-guided prescription from the effect of supervision.

Pectus excavatum and exercise haemodynamics

Pectus excavatum provides a more specific mechanistic application. A patient may report exercise limitation despite relatively preserved resting tests, while the depressed sternum may constrain cardiac filling and displacement during exertion. In a 2015 JACC report, Tardy et al. reported exercise cardiac-output limitation in pectus excavatum. The contribution was to move the discussion beyond resting anatomy or spirometry and show that an exertional central haemodynamic constraint can be present.

★ Filaire et al. extended this work in 2024 by relating exercise haemodynamic changes to chest-wall deformity indices. Their findings did not favour impaired peripheral oxygen extraction as the main explanation and instead supported a central cardiovascular contribution linked to the deformity. The two publications are concise and observational, and neither proves that a PhysioFlow phenotype should determine surgical referral. Nevertheless, they form a coherent application-level sequence: dynamic cardiac output may identify a physiologically relevant consequence that a static anatomical index alone may not capture.

The next clinically decisive step would be a prospective pre- and post-repair study with standardised maximal testing, symptom and quality-of-life outcomes, prespecified haemodynamic trajectories, and a comparator able

to confirm change in cardiac filling or forward flow. The aim should not be to replace anatomical evaluation, but to determine whether exercise haemodynamics identifies the patients in whom the deformity is functionally consequential and whether it predicts benefit from correction.

Exercise prescription after amputation or spinal cord injury

Storey et al. studied five men with unilateral transtibial amputation and six controls during moderate continuous cycling and high-intensity intervals. Heart rate and oxygen uptake responses were similar between groups, whereas absolute stroke volume and cardiac output were higher in controls, a difference plausibly influenced by body size. Participants with amputation reached vigorous intensities during bilateral cycling without reported adverse events. The study is too small and male-only to define a disease phenotype, but it provides useful feasibility evidence for vigorous lower-limb cycling and shows why absolute flow values should not be interpreted without body-size and workload context.

★ Astorino et al. assessed different arm-cycling regimens in active men with spinal cord injury. This work fits at the boundary between neurological physiology and functional rehabilitation. Its practical value lies in comparing the haemodynamic demand of exercise formats in a population with altered active muscle mass and autonomic control. As in the amputation study, the result should guide protocol selection and physiological understanding rather than imply a diagnostic role for PhysioFlow.

Across these populations, exercise mode is part of the measurement. Arm cycling, bilateral leg cycling and walking recruit different muscle masses and venous-pump mechanisms; the same cardiac output cannot be assumed at a matched rating of perceived exertion. Within-person trends under a standardised protocol are therefore more interpretable than comparisons with generic reference values.

Overall evidence synthesis

- PhysioFlow can add a central haemodynamic dimension to functional tests when distance or workload is strongly influenced by pain, gait, prosthesis or active muscle mass.
- The knee-arthroplasty trial is the only randomised care-pathway study, but it evaluates a multicomponent supervised programme and cannot isolate the contribution of haemodynamic guidance.
- Pectus excavatum is the most coherent disease-specific application in this section: two reports support exercise cardiac-output limitation and favour a central rather than peripheral explanation.
- Amputation and spinal-cord-injury studies support exercise-mode selection and within-person physiological assessment, not diagnostic thresholds.
- The clinically important future question is whether haemodynamic phenotyping changes rehabilitation prescription or selection for corrective intervention and improves meaningful functional outcomes.

Editorial conclusion. The unifying message is not that PhysioFlow is an orthopaedic monitor, but that it can help distinguish cardiovascular response from locomotor limitation during rehabilitation and functional testing.

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4.6. Paediatric and congenital conditions

Paediatric and congenital cardiology is one of the clearest examples of why resting anatomy and peak oxygen uptake do not answer the same question as exercise haemodynamics. Surgical repair may correct the primary lesion while leaving residual obstruction, regurgitation, abnormal pulmonary blood-flow distribution, chronotropic limitation or a preload-constrained circulation. Growth further changes body size, heart rate and expected output. A child can therefore have reassuring resting imaging but an abnormal mechanism of exercise limitation.

PhysioFlow has been used in this field to measure stroke volume continuously during upright exercise, calculate peak indexed cardiac output, distinguish central oxygen delivery from peripheral utilisation, and relate functional reserve to residual anatomy or earlier treatment history. The evidence is predominantly observational and concentrated in a small number of expert centres. Its value lies in mechanistic phenotyping and in generating candidate decision variables; prospective proof that it improves timing of intervention is still limited.

Interpretation requires paediatric-specific discipline. Values should be indexed appropriately, peak effort and protocol quality must be documented, and a single low value should not be detached from heart rate, workload, oxygen uptake and the shape of the stroke-volume response. Chapter 3 should be consulted for the mixed comparative and reliability findings in children. Repeated tests are most credible when change exceeds the population- and range-specific measurement error established for the relevant protocol.

4.6.1. Congenital heart disease and Fontan physiology

4.6.1.1. Repaired congenital heart disease: central and peripheral determinants

Guirgis et al. studied 77 children after open-heart repair, including 55 with residual lesions, and compared them with 44 healthy peers. In children with residual lesions, maximal oxygen uptake, maximal oxygen delivery and estimated peripheral diffusion capacity were all reduced. Lower maximal oxygen delivery reflected both lower peak indexed stroke volume (48 versus 53 $mL \cdot m^{-2}$) and lower peak heart rate (171 versus 185 beats/min). By contrast, the 22 children without residual lesions had normal maximal aerobic capacity despite a lower maximal heart rate, because stroke volume increased sufficiently to compensate.

This study makes an important clinical distinction. A reduced peak oxygen uptake can arise from impaired stroke volume, chronotropic limitation, peripheral deconditioning or a combination; the same global CPET result may therefore imply different management. Exercise cardiac-performance measurement helped identify children with altered reserve who might merit reassessment of a residual lesion, while a predominantly peripheral phenotype could support rehabilitation. The wording "can improve management" remains a physiological and selection argument: the study did not randomise patients to PhysioFlow-guided decisions or demonstrate better long-term outcomes.

4.6.1.2. Severe pulmonary regurgitation and repaired tetralogy of Fallot

Karsenty et al. assessed 82 patients aged 10 to 54 years with a pulmonary regurgitant fraction above 40%, using cardiac magnetic resonance and CPET with peak cardiac-index measurement. Eighteen had a low peak cardiac index below 7 $L \cdot min^{-1} \cdot m^{-2}$. Peak oxygen uptake only partly reflected cardiac output, particularly in adults, and no resting MRI measurement predicted the low exercise response. Age was the only independent predictor, with the risk increasing continuously over time.

The result supports exercise haemodynamics as a complementary functional layer when considering pulmonary-valve replacement: resting ventricular size and function do not fully describe forward-flow reserve. It does not establish a replacement threshold. The proposed peak cardiac-index cut-off was applied within one observational cohort, and the study did not show that intervention selected by this variable improves symptoms, ventricular remodelling or prognosis.

Panaioli et al. then linked branch pulmonary-flow distribution after Fallot repair to peak exercise stroke volume. Pulmonary regurgitation, right-ventricular ejection fraction and a predominantly rightward pulmonary perfusion pattern independently predicted peak indexed stroke volume; rightward imbalance was associated with a better exercise stroke-volume response. This counterintuitive finding illustrates the added value of combining anatomical flow imaging with dynamic systemic output. It should be interpreted as a mechanistic association, not as a target for deliberately creating perfusion asymmetry.

4.6.1.3. Fontan circulation: a preload-limited response

★ Legendre et al. compared 25 young patients with non-failing Fontan circulation with matched healthy controls during upright ramp cycling. Patients had lower maximal oxygen uptake (24 versus 32 mL·kg^{-1}·min^{-1}) and lower peak cardiac index (6.4 versus 9.9 L·min^{-1}·m^{-2}), reflecting both reduced peak indexed stroke volume (42 versus 54 mL·m^{-2}) and chronotropic limitation (154 versus 184 beats/min). Increased calculated arteriovenous oxygen difference partly compensated for the impaired central delivery.

Continuous monitoring also exposed heterogeneity that a peak value would miss. Some patients continued to augment stroke volume beyond the ventilatory threshold, whereas others reached an earlier plateau. A plateau is not automatically pathological; its timing, workload and relationship to heart rate matter. The study nevertheless supports the physiological model of Fontan exercise limitation as a constrained ability to increase preload and forward flow, variably compounded by chronotropic limitation and peripheral compensation.

David et al. extended this programme in 57 consecutive Fontan patients by relating exercise cardiac performance to pre- and post-Fontan history. Longer duration of cyanosis and lower pre-Fontan oxygen saturation were associated with impaired peak stroke volume and heart-rate response, partly through ventricular dysfunction; a cyanosis duration of 6.9 years or less predicted a peak indexed stroke volume of at least 45 mL·m^{-2}, with an area under the curve of 0.747. The study is clinically valuable because it links a current dynamic phenotype to timing earlier in the treatment pathway. Its retrospective design and centre-specific management history limit causal inference.

Practical synthesis - congenital heart disease. The strongest role supported by the corpus is not lesion diagnosis but functional phenotyping after repair. Exercise stroke volume and cardiac index can reveal impaired reserve that resting imaging or peak oxygen uptake alone may not explain, and can separate central limitation from chronotropic or peripheral components. The evidence supports multidisciplinary interpretation and closer follow-up; prospective intervention thresholds remain to be validated.

4.6.1.4. Methodological boundary for serial decisions

The clinical promise of repeated testing depends on measurement reliability. ★ Legendre et al. reported an intraclass correlation of 0.80 and a standard error of measurement of 10.5% for peak indexed stroke volume in 30 young patients with residual right-ventricular outflow-tract lesions tested approximately one year apart. Reliability was substantially better in the subgroup with peak indexed stroke volume below 50 mL·m^{-2} than above that range. This is a useful but non-uniform result: a change that is meaningful in a low-output subgroup may fall within measurement variability at higher values.

Comparative studies in congenital heart disease have not been uniformly favourable across all ages, anatomies and reference methods. Those data are analysed in Chapter 3 and should not be selectively cited here. For an individual management decision, the device signal, electrode configuration, exercise protocol, achieved effort and compatibility with the broader clinical picture must be reviewed. PhysioFlow can add dynamic evidence; it does not invalidate discordant imaging or catheterisation data by itself.

The early Taylor comparison deserves particularly conservative weighting. The recordings originated as pilot or preparatory observations in congenital patients using a 2004–2006-generation system, and the original signal files were no longer available when the later publication analysis was performed; only a residual spreadsheet could be reviewed. The adverse result remains transparent in Chapter 3, but it cannot support retrospective audit of signal quality, acquisition choices, IFU compliance or reprocessing. Later paediatric datasets with more complete methods and preserved clinical context are therefore more informative for contemporary application.

4.6.2. Paediatric exercise, prematurity, transplantation and systemic conditions

4.6.2.1. Prematurity from childhood to young adulthood

Narang et al. studied 14 children born prematurely and 15 term-born controls during maximal cycling in normoxia and normobaric hypoxia. Hypoxia reduced peak power in both groups. Peak oxygen uptake fell significantly in controls but not in the preterm group, and the heart-rate and stroke-volume changes between normoxia and hypoxia also differed by birth status. The authors concluded that preterm birth did not exacerbate the acute hypoxic reduction in exercise capacity. The small study is mechanistically interesting but cannot be taken as evidence that prematurely born children are protected from altitude-related risk.

A historical cardiac-MRI abstract reported a blunted stroke-volume response to exercise in adolescents born prematurely and favourable agreement of the PhysioFlow exercise trend with imaging. PhysioFlow use is

confirmed by its inclusion in the historical manufacturer-audited corpus. Because only an abstract is available, however, the acquisition details, analysis and numerical agreement cannot be appraised with the weight of a full report; it should therefore remain supporting context.

Delfrate et al. provided a larger young-adult perspective in 71 participants aged 18 to 29 years who had been born before 30 weeks of gestation, including 24 with bronchopulmonary dysplasia, and 73 term-born controls. Cardiac haemodynamic data were available in 52 preterm and 48 control participants. Preterm participants had lower peak oxygen uptake, while the integrated analysis favoured impaired peripheral oxygen utilisation rather than an isolated central cardiac-output deficit as the dominant explanation. This finding is important precisely because PhysioFlow did not simply label every reduction in exercise capacity as cardiac.

4.6.2.2. Rare disease and childhood cancer survivorship

★ Legendre et al. evaluated eight children with biallelic LPIN1 mutations outside acute rhabdomyolysis. Resting echocardiography was normal in all but one child. That child showed mild left-ventricular dysfunction and failed to augment stroke volume during ramp exercise, with later worsening. In a rare condition in which acute crises can include cardiac arrest, the report illustrates how exercise haemodynamics may uncover limited reserve despite a largely reassuring resting phenotype. The sample is necessarily very small and does not establish a screening interval or outcome threshold.

Drinkard et al. studied exercise capacity in 48 children and adolescents with Friedreich ataxia within a randomised, double-blind idebenone trial. Baseline peak oxygen uptake was low and related to neurological and genetic disease severity; idebenone did not improve exercise capacity over the study period. PhysioFlow contributed to the physiological assessment, but the publication primarily informs disease burden and treatment response rather than a device-specific clinical pathway.

Artz et al. combined cardiac magnetic resonance, CPET haemodynamics and the CircAdapt model in 53 survivors of childhood acute lymphoblastic leukaemia exposed to doxorubicin. The model suggested subtle differences in left-ventricular mechanical properties and possible preservation among survivors who had received cardioprotective agents, although group differences were not statistically significant. This is an advanced integrative research application: PhysioFlow-derived exercise data contribute boundary conditions for modelling, but the final mechanical parameters are model-derived and should not be treated as direct device outputs or validated screening thresholds.

4.6.2.3. Paediatric heart transplantation

Coppola et al. reported a 2025 transplant-congress abstract describing serial CPET in paediatric heart-transplant recipients. Median peak oxygen uptake at the first test was 26.8 $mL \cdot kg^{-1} \cdot min^{-1}$, approximately 68% of predicted, with a peak heart rate around 80% of predicted and reduced oxygen pulse. The title and longitudinal framing emphasise slow recovery of exercise capacity. PhysioFlow use has been confirmed in the source audit, but the short abstract provides insufficient detail to determine the independent contribution of stroke volume, denervation-related chronotropic limitation, peripheral conditioning or time since transplantation. It should remain a recent supporting signal pending a full publication.

4.6.3. Overall evidence synthesis

- The paediatric congenital corpus contains a coherent application sequence: exercise haemodynamics reveals reserve that resting anatomy and peak oxygen uptake do not fully describe.
- In repaired congenital heart disease, low exercise performance may reflect reduced stroke volume, chronotropic limitation, peripheral deconditioning or combinations that imply different clinical responses.
- Fontan studies consistently position limited stroke-volume augmentation and chronotropic response as central determinants, while showing heterogeneous trajectories and compensatory peripheral oxygen extraction.
- In severe pulmonary regurgitation, resting MRI did not predict low peak cardiac index; this supports complementary functional assessment but not a validated intervention threshold.
- Prematurity, rare disease, cancer survivorship and transplantation demonstrate broader feasibility and mechanistic value, but their clinical evidence remains heterogeneous and sometimes abstract- or model-based.
- Serial use requires paediatric-specific protocols and an explicit measurement-error framework; apparent change should not be equated automatically with disease progression or therapeutic response.

Editorial conclusion. Section 4.6 is one of the stronger arguments for PhysioFlow as an exercise-phenotyping technology. Its distinctive contribution is to expose how the circulation performs after complex repair or across developmental disease, not merely to reproduce a resting cardiac-output value. The next step is prospective evidence that a prespecified exercise-haemodynamic phenotype changes surveillance, rehabilitation or timing of reintervention and leads to better outcomes.

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4.7. Integrated assessment of unexplained dyspnoea and exercise intolerance

Unexplained exertional dyspnoea and reduced exercise capacity are clinical presentations, not single diagnoses. Similar symptoms may result from impaired cardiac output reserve, chronotropic limitation, abnormal filling or pulmonary vascular loading, ventilatory mechanics, gas-exchange abnormality, impaired peripheral oxygen extraction, locomotor limitation, deconditioning, or several mechanisms acting together. Resting echocardiography, pulmonary function, biomarkers and vascular measurements may be normal or only mildly abnormal because the relevant failure of physiological reserve appears while the symptom is being reproduced.

Cardiopulmonary exercise testing (CPET) is central to this problem because it measures the integrated response of ventilation, gas exchange and external work. Yet several familiar CPET variables remain physiological surrogates. Oxygen pulse, for example, is influenced by both stroke volume and peripheral oxygen extraction. A peak value can also conceal an early failure, compensation, plateau, secondary decline or abnormal recovery. Continuous SM-ICG adds explicit estimates of stroke volume and cardiac output to the same exercise trajectory. Its proposed role is therefore to explore the haemodynamic contribution to limitation, not to claim that every cause of dyspnoea has been diagnosed.

Clinical proposition. When symptoms remain insufficiently explained after resting assessment and conventional exercise testing, simultaneous non-invasive haemodynamics may help determine whether the circulation fails to augment, compensates appropriately, or is unlikely to be the principal limiting system. That information may focus the next diagnostic question, but it does not replace the method required to confirm a pressure-, perfusion-, anatomical- or tissue-specific diagnosis.

4.7.1. The clinical gap between conventional CPET and invasive haemodynamics

The 2016 AHA/EACPR CPET recommendations emphasise multiparametric interpretation and the synergistic value of combining CPET with other assessments where appropriate. At the other end of the pathway, invasive CPET and exercise right-heart catheterisation can measure intracardiac and pulmonary vascular pressures—including pulmonary-artery wedge pressure as a surrogate of left-sided filling pressure—together with blood oxygen content when non-invasive evaluation has not resolved the cause. They remain the reference approach for selected questions such as exercise-induced pulmonary hypertension, occult HFpEF, preload failure or a complex mixed limitation.

A practical gap therefore exists between a conventional non-invasive CPET that may leave the central flow response inferred, and an invasive study that is informative but resource-intensive and not available for every symptomatic patient. The broad PhysioFlow corpus suggests a possible intermediate phenotyping step: continuous exercise flow measurement can refine the working mechanism and help identify the patients in whom imaging or invasive investigation is most likely to answer a specific remaining question. This is an inference from the present care pathway and evidence base, not a guideline recommendation or a demonstrated triage algorithm.

4.7.2. A trajectory-based physiological framework

The Fick relationship provides the organising principle: oxygen uptake reflects cardiac output multiplied by the arterial-venous oxygen content difference, while cardiac output is the product of heart rate and stroke volume. The interpretive task is not to assign one abnormal number to one disease. It is to examine how these components evolve with workload, symptoms and recovery, and whether the observed pattern is internally coherent with the rest of the CPET.

4.7.2.1. Central cardiac-output or stroke-volume limitation

A limited rise in stroke volume or cardiac output may support a central contribution when it occurs at an unexpectedly low workload, accompanies symptoms and reduced oxygen delivery, and cannot be explained by low effort or poor signal. The temporal profile matters. A plateau is not intrinsically pathological, particularly when it occurs late. More concerning patterns include no meaningful early increase, an early fall, or a secondary relapse in CTi or stroke volume despite a continuing increase in heart rate and workload. At very high heart rates - approximately 160 beats/min in the current clinical experience - a late decline may instead reflect shortened diastolic filling time and ventricular compliance. No universal profile threshold has yet been prospectively validated.

4.7.2.2. Chronotropic, ventilatory and peripheral patterns

An inadequate heart-rate response with preserved or compensatory stroke volume suggests a different mechanism from stroke-volume failure with marked tachycardic compensation. Conversely, preserved cardiac output in a patient with severe dyspnoea can be clinically informative: it redirects attention towards ventilatory constraint, gas exchange, respiratory-muscle work, skeletal-muscle function, vascular control or peripheral oxygen utilisation. A calculated arterial-venous oxygen difference may support this interpretation, but because it is derived from measured oxygen uptake and estimated cardiac output, it is not an independent assay of extraction or mitochondrial function.

Mixed profiles are expected rather than exceptional. COPD and heart failure may coexist; pulmonary vascular load may restrict stroke-volume reserve while ventilatory inefficiency and deconditioning also contribute; hypertension may produce an unfavourable haemodynamic response without a simple resting abnormality; and post-COVID limitation may involve central and peripheral components in different proportions. Interpretation should preserve this complexity instead of forcing every patient into a single-organ label.

4.7.3. What the cross-disease corpus contributes

- Heart-failure and HFpEF studies show that similar peak oxygen uptake or resting ejection fraction can conceal materially different cardiac-output, stroke-volume, chronotropic and peripheral responses (Section 4.1.1).
- CAD, cardiac-rehabilitation and HCM studies support interpretation of the complete CTi and stroke-volume profiles rather than isolated maxima or simple rest-to-peak differences (Sections 4.1.2 to 4.1.4).
- COPD, pulmonary-hypertension and respiratory-disease studies demonstrate compensation, impaired central reserve and central-peripheral dissociation under ventilatory and pulmonary vascular stress (Section 4.2).
- Hypertension, systemic disease, rehabilitation and congenital conditions show that preserved output can be as informative as reduced output when it redirects the explanation towards vascular, peripheral, locomotor or developmental factors (Sections 4.3, 4.5 and 4.6).
- The emergency-dyspnoea study provides a direct diagnostic-enrichment signal in acute care, but its single-centre threshold should not be extrapolated into a general exercise-dyspnoea rule (Section 4.4).

Taken together, these studies do not validate one universal diagnostic signature. They support a recurring interpretive rationale: measuring flow while the physiological problem is provoked may help distinguish impaired central delivery from successful compensation or limitation arising elsewhere in the oxygen-transport chain. The breadth of populations supports feasibility under varied exercise and clinical conditions when protocol and signal quality are explicit; it does not by itself establish diagnostic advantage in every application.

4.7.4. Candidate pathway for prospective clinical evaluation

The following sequence is best regarded as a researchable care-pathway hypothesis rather than a current recommendation:

- Define the unresolved question after history, examination and appropriate resting cardiac and pulmonary assessment.
- Reproduce the symptom with a suitable CPET or functional protocol, documenting effort, rhythm, blood pressure, oxygenation and ventilatory response.
- Acquire continuous SM-ICG only under the applicable IFU and retain signal quality, heart rate, workload, CTi, stroke volume, cardiac output and recovery as aligned trajectories.
- Classify the observed physiology provisionally as predominantly central-flow, chronotropic, ventilatory/gas-exchange, peripheral/locomotor or mixed, while preserving discordant findings rather than forcing agreement.
- Use the residual question - not the PhysioFlow label alone - to select any confirmatory assessment: stress echocardiography or imaging, coronary evaluation, pulmonary vascular testing, invasive CPET, or targeted peripheral and rehabilitation assessment.
- Test prospectively whether this added step changes diagnostic confidence, downstream testing, management, resource use or patient-relevant outcomes.

Essential boundary. PhysioFlow measures neither pulmonary arterial nor cardiac filling pressures, and it does not measure coronary perfusion. A pattern compatible with pulmonary vascular or cardiac limitation can justify a more focused question, but cannot establish pulmonary hypertension, HFpEF, myocardial ischaemia or another pressure- or perfusion-based diagnosis by itself.

4.7.5. Practical evidence synthesis and research priority

The current evidence supports PhysioFlow as an adjunctive exercise-phenotyping technology. Its distinctive contribution is not merely to provide another peak number, but to show whether stroke volume and cardiac output augment, compensate, fail or recover as symptoms emerge. This information can make a conventional CPET more mechanistically explicit and may help formulate the next diagnostic question in patients whose limitation remains unexplained.

Within the corpus reviewed, no study has yet shown that a PhysioFlow-enriched dyspnoea pathway reduces unnecessary testing, improves selection for invasive investigation, changes treatment appropriately or improves outcomes. A pragmatic prospective study could address this without requiring one prohibitively large trial across every disease: enrol patients with a genuinely unresolved mechanism after standard assessment, prespecify the integrated profile interpretation, record the diagnostic and management decisions made before and after disclosure, and adjudicate the final diagnosis independently.

Editorial conclusion. This cross-disease synthesis converts a disease-by-disease evidence base into the patient-centred question that most naturally fits PhysioFlow: in unexplained dyspnoea or exercise intolerance, what does the haemodynamic response reveal about the mechanism of limitation? Chapter 8 places this clinical perspective within the broader assessment of technology maturity, evidence strength and implementation.

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5. Human Performance and Integrative Physiology

Human performance is an intrinsically integrative problem. External power can rise only if ventilation, pulmonary gas exchange, cardiac output, blood oxygen content, vascular distribution and tissue oxygen utilisation adapt together. Peak oxygen uptake describes the final integrated result, but not which step provided the reserve, which step became limiting, or how that balance changed during training, posture, environmental exposure or recovery. Continuous signal-morphology impedance cardiography (SM-ICG) has therefore been used throughout this corpus less as an isolated cardiac-output test than as one component of an integrated physiological experiment.

The principal contribution of the corpus is mechanistic resolution. By adding stroke volume and cardiac output to gas exchange, heart rate, blood pressure, muscle oxygenation and performance, investigators can separate a predominantly central adaptation from greater peripheral extraction, describe redistribution between competing muscle beds, and follow transient responses that a resting or single peak value would miss. The same strength also creates an interpretive obligation: derived variables must not be treated as independent measurements, protocol effects must not be generalised beyond the task studied, and a physiological association is not automatically an ergogenic or clinical benefit.

Chapter proposition. Across exercise modalities and environmental stresses, the value of SM-ICG lies primarily in resolving how the circulation responds over time and how that response interacts with the rest of the oxygen transport chain. The evidence supports a mature research platform for integrative physiology; it does not establish one universal performance algorithm or one haemodynamic target for all populations.

5.1. Fundamentals of exercise haemodynamics and oxygen transport

5.1.1. Cardiac output within the oxygen transport chain

The Fick relationship provides the conceptual starting point: oxygen uptake equals cardiac output multiplied by the arterial-venous oxygen content difference, while cardiac output equals heart rate multiplied by stroke volume. Exercise capacity can therefore increase through a larger convective flow, greater peripheral extraction, or both. Measurements of oxygen uptake alone cannot determine which component changed. Conversely, cardiac output is not synonymous with performance because delivered oxygen must still be distributed and used by active tissue.

★ Leprêtre et al. (2004) studied nine well-trained men during an incremental test and two exhaustive constant-work tests. Maximal oxygen uptake was similar across protocols, yet the intermediate-intensity test elicited a lower maximal cardiac output than the incremental test (24.4 versus 28.4 L/min), driven by a lower stroke volume (143 versus 179 mL/beat). The study therefore provides an unusually direct demonstration that the same maximal oxygen uptake can conceal different central and peripheral solutions, and that an exercise intensity eliciting VO_2max does not necessarily elicit maximal cardiac output.

★ Richard et al. examined work above the respiratory compensation point and showed that cardiac output and calculated oxygen release continued to evolve during severe constant-load exercise performed to exhaustion. Together, these studies demonstrate why very-high-intensity exercise should not be reduced to a fixed peak cardiac-output value. The balance between heart rate, stroke volume and extraction changes with protocol, intensity and time, and the trajectory approaching exhaustion may carry more physiological information than a single terminal sample.

The interpretation of calculated arterial-venous oxygen difference requires particular discipline. When it is obtained as oxygen uptake divided by SM-ICG cardiac output, it is a Fick-derived estimate, not an independent blood measurement of tissue extraction. It can be highly informative for internal partitioning of oxygen transport, but measurement error in either input propagates directly into the derived value. This limitation is especially important in small studies that correlate several mathematically coupled variables.

5.1.2. Oxygen pulse, stroke volume and the importance of trajectories

Oxygen pulse is often interpreted as a surrogate for stroke volume, but it also includes the arterial-venous oxygen difference. Gmadaa et al. directly examined this relationship across exercise intensities in healthy adults. Oxygen pulse tracked the calculated extraction component at lower and moderate intensities, whereas

the relationship dissociated at higher workloads as stroke volume and extraction followed different trajectories. The practical message is not that oxygen pulse is useless, but that its physiological meaning is intensity dependent and should not be equated automatically with stroke volume at peak exercise.

★ Leprêtre et al. (2005)analysed the continuous heart-rate and stroke-volume profiles of 22 international male cyclists. Sixteen displayed a heart-rate deflection point; in that subgroup, stroke volume reached its maximum earlier and declined modestly before exhaustion, and the workload of the deflection point predicted much of the workload associated with maximal stroke volume. The value of the study lies in treating curve shape and timing as physiology rather than reducing the response to rest and peak values. It is not a validated diagnostic rule: in trained healthy subjects at high heart rates, a late decline can reflect physiological shortening of diastolic filling time and should not be equated with an early pathological relapse.

Interpretive safeguard. A plateau in stroke volume or CTi is not, by itself, an abnormal profile. More informative patterns include failure of an expected early increase, an early fall, or a secondary relapse despite increasing heart rate and workload. At very high heart rates, a late decline may be physiological because shortened diastolic filling time becomes mechanically limiting.

5.1.3. Submaximal and field-relevant functional exercise

The six-minute walk test illustrates the potential extension from maximal laboratory testing to submaximal function. Liu et al. found that SM-ICG cardiodynamic variables obtained during a six-minute walk predicted peak oxygen uptake in young healthy adults, while a later observational study related walking performance to cardiopulmonary variables in non-obese older adults. These data support the feasibility of extracting central-response information during familiar functional tasks, but they do not make a six-minute walk haemodynamic model interchangeable with CPET or transferable without validation across age and disease groups.

Blood pressure remains a standard and clinically important exercise measurement, but pressure is not flow. Similar pressure responses can coexist with different combinations of cardiac output and systemic vascular resistance. SM-ICG can therefore add mechanistic resolution when blood pressure is measured concurrently. It does not directly measure arterial pressure, and any calculated resistance inherits the assumptions and error of both the pressure input and estimated cardiac output.

5.2. Exercise modality, posture and active muscle mass

5.2.1. Protocol and intensity are physiological interventions

A ramp test, an all-out sprint, repeated intervals and a resistance set do not interrogate the same physiology. ★ Astorino et al. demonstrated that SM-ICG could follow the rapid haemodynamic response to a Wingate test, while Horn et al. reported similar peak cardiac output but lower oxygen uptake during a sprint-interval session than during a ramp test to exhaustion. Falz et al. further showed distinct acute cardiopulmonary loads across strength training, high-intensity intervals and moderate continuous exercise. These findings make protocol specificity a central result rather than a nuisance variable.

Resistance exercise creates additional challenges: brief repetitions, intrathoracic-pressure changes, large blood-pressure excursions and motion can all influence physiology and signal quality. Historical knee-extension observations and more recent free-weight and squat studies nevertheless show that continuous measurement can distinguish repetition- and intensity-dependent responses during and after sets. The 2026 comparison of breathing techniques during squats in healthy women found no material intervention difference in the measured responses, an appropriately negative finding that prevents physiological plausibility from being mistaken for a demonstrated effect.

5.2.2. Contraction mode and active muscle mass

Eccentric work permits high external force at a relatively low metabolic cost and therefore changes the relationship between work, oxygen uptake and circulation. Dufour et al. described specific circulatory adjustments during eccentric cycling, and Beaven et al. extended the comparison to concentric and eccentric arm exercise in men and women. More recent apparatus comparisons and the 2026 eccentric-cycling abstract reinforce the same principle: the haemodynamic response is inseparable from biomechanics, muscle mass and body position.

Single-leg cycling provides an especially clear experiment in active-muscle-mass manipulation. Gordon et al. reported greater limb-specific blood flow and cardiac output when responses were normalised to the active lean mass, without a corresponding increase in normalised power. Thus greater perfusion of the active limb does not guarantee proportionally greater mechanical output. In organ-transplant recipients, small- versus large-muscle-mass endurance training has likewise been used to examine whether central reserve constrains the trainable peripheral stimulus. These studies caution against translating whole-body cardiac output directly into local training efficacy.

5.2.3. Posture and orthostatic loading

Posture changes venous return, filling, heart rate and the mechanical conditions of exercise. Studies comparing treadmill and cycle exercise, trained women performing resistance exercise in different positions, and upright, semi-recumbent and supine CPET consistently show that the same nominal relative intensity can produce different haemodynamic patterns. In the recent posture study, more recumbent positions reduced peak oxygen uptake, ventilation and external workload while cardiac output was maintained through a higher stroke volume and lower heart rate.

The implication extends beyond laboratory standardisation. Reference values, abnormality thresholds and longitudinal comparisons are protocol dependent. A change observed after training or treatment cannot be interpreted confidently if posture, ergometer, cadence, active muscle mass or effort criteria have changed. This is also why a device-agreement result obtained during one modality does not establish interchangeability in another, particularly during high-intensity field running.

5.3. Respiratory muscle–cardiovascular interactions

5.3.1. The respiratory pump as a haemodynamic actuator

Breathing is not merely a gas-exchange process. Changes in intrathoracic and abdominal pressure alter venous return, ventricular loading and the distribution of available cardiac output. Stucky et al. showed that voluntary modulation of the respiratory pump at exercise onset could prime the cardiodynamic phase of pulmonary oxygen uptake. The effect was physiologically measurable in healthy participants even though oxygen delivery was not the limiting step in that population. Its clinical relevance therefore remains a hypothesis for patients in whom cardiac transport is genuinely impaired.

5.3.2. Competition for blood flow under respiratory loading

★ Athanasopoulos et al. combined expiratory flow limitation with measurements of respiratory- and locomotor-muscle perfusion. Increased intercostal blood flow during loaded breathing was accompanied by redistribution away from the quadriceps, supporting competition between the respiratory and locomotor muscles for a finite cardiac-output reserve. The PhysioFlow measurement was important because regional perfusion changes could be interpreted against the available systemic flow rather than in isolation.

The inspiratory-resistive-loading experiment after all-out exercise adds a deliberately paradoxical example. During recovery between Wingate bouts, loading increased cardiac work and altered peripheral reoxygenation; subsequent peak and mean power improved, but the fatigue index also increased. A larger haemodynamic response was therefore not simply beneficial or detrimental. It changed the distribution and timing of recovery resources, illustrating why performance, symptoms, systemic flow and local oxygenation must be read together.

5.3.3. Acute and chronic respiratory-muscle interventions

Acute tapered inspiratory loading, expiratory loaded breathing and inspiratory loading during running have been used to map thoracoabdominal mechanics, cerebral oxygenation and muscle oxygenation alongside haemodynamics. These studies confirm sensitivity to respiratory manipulation but are generally small, laboratory-based mechanistic experiments. They do not establish that deliberately increasing respiratory work improves endurance or clinical outcomes.

The randomised trial of inspiratory-muscle training in older adults is more informative longitudinally: it examined whether training altered thoracoabdominal volume regulation and central responses rather than assuming transfer from stronger respiratory muscles. Together with work in older women and female soccer players, it broadens the population base, but intervention effects remain dependent on loading prescription, adherence, breathing pattern and the outcome selected.

Integrative conclusion. The respiratory-muscle studies provide one of the clearest demonstrations of why continuous systemic flow measurement matters: local oxygenation can worsen, improve or redistribute despite similar whole-body oxygen uptake. SM-ICG is most informative when combined with respiratory mechanics and regional perfusion rather than interpreted as a stand-alone explanation.

5.4. Training adaptation and athletic performance

5.4.1. Central and peripheral routes to adaptation: the HIIT and interval-training corpus

★ Daussin et al. (2008) used a randomised crossover comparison of two eight-week programmes matched for total work and duration in 11 previously sedentary adults. VO_2max increased after both continuous and interval training, but only interval training accelerated oxygen-uptake kinetics and increased maximal cardiac output and mitochondrial oxidative capacity; capillary density increased after both programmes and more after continuous training. This is a particularly complete demonstration that training adaptation is distributed across central and peripheral components and that similar global goals can be reached through different physiological routes. It does not establish universal superiority of one programme when dose, tolerability and population differ.

★ Astorino et al. (2017) gave high-intensity interval training particular mechanistic visibility. In 39 active men and women completing a periodised HIIT programme, compared with 32 non-exercising controls, the increase in maximal oxygen uptake was accompanied by an increase in maximal cardiac output from 20.0 to 21.7 L/min and by a higher maximal stroke volume, whereas maximal heart rate and calculated arterial-venous oxygen difference did not materially change. Within this experiment, the adaptation was therefore predominantly consistent with greater central oxygen delivery. The study is important because SM-ICG was not merely descriptive: it identified the physiological route underlying the training response.

The Astorino programme extends from acute Wingate and sprint-interval responses to periodised and low-volume HIIT, individual response heterogeneity, young women and trained athletes. A companion report after ten HIIT sessions also described increases in maximal oxygen uptake and cardiac output. Because the investigators, participant descriptors and early intervention phase overlap, the ten- and twenty-session reports should be treated as related reports unless participant-level independence is established, not as two automatic replications. The strength of the series is continuity across acute response, short-term adaptation and between-participant variability.

The PhysioFlow interval-training corpus is substantially broader than Astorino. ★ Daussin et al. compared matched interval and continuous programmes; Gordon et al. quantified central and peripheral changes after four weeks of low-volume sprint interval training; Falz et al. compared the acute response to strength, high-intensity interval and moderate continuous exercise; and Ksoll et al. directly examined central and peripheral oxygen distribution under two interval modes. De Revere et al. found an approximately eight-percent group increase in maximal oxygen uptake in young women but substantial individual variability, while resistance-type HIIT in trained kayak athletes connected cardiac, structural and performance adaptation. Related work extends to hypoxia and field testing. Clinical interval studies in heart failure, COPD and obesity are synthesised in their application chapters and serve here as cross-domain confirmation rather than duplicate evidence. Across teams and populations, HIIT is therefore a meaningful showcase for continuous haemodynamic phenotyping—but not a single protocol or a uniform central response.

5.4.2. Individual response, maladaptation and recovery

★ Le Meur et al. (2014) used a controlled longitudinal overload-and-recovery design in 35 experienced male triathletes: 24 underwent intensified training and 11 continued their usual programme. After overload, 12 athletes met the criteria for functional overreaching and 12 showed acute fatigue without the same performance impairment. Only the functionally overreached subgroup showed lower maximal performance and oxygen uptake together with reduced maximal cardiac output and systolic blood pressure, increased calculated arterial-venous oxygen difference and lower exercise epinephrine; these disturbances resolved after a two-week taper. The repeated measurements, internal fatigue comparison and reversibility make this more informative than a cross-sectional observation and support a transient central contribution to maladaptation. They do not establish a validated screening threshold or a single causal pathway.

★ Coates et al. (2018) provide independent mechanistic convergence in 26 competitive cyclists and triathletes allocated to three weeks of overload or control training. Compared with controls, overload increased resting

aortic pulse-wave velocity and reduced maximal stroke volume, heart rate and cardiac output; the increase in arterial stiffness was inversely related to maximal cardiac output and peak power. This is not a direct replication of the functional-overreaching phenotype defined by Le Meur, but it connects excessive short-term training load to vascular and central exercise changes through a different protocol and team.

Together, these studies support the cautious expression reversible training-induced cardiac maladaptation. They do not demonstrate myocardial injury, and “cardiotoxicity” would overstate the evidence in functional overreaching. Even persistent overtraining syndrome would require evidence of duration, exclusion of competing causes and, if structural injury were alleged, appropriate biomarkers or imaging. Their practical promise is earlier physiological phenotyping; their present limitation is the absence of prospectively validated decision thresholds.

Recovery studies after resistance exercise, ice hockey and environmental stress further show that the return of cardiac output, vascular tone, muscle oxygenation and performance need not be synchronous. A protocol that accelerates one component may not normalise another. For athlete monitoring, repeated measurements are therefore useful only when acquisition, posture, timing, hydration and exercise dose are standardised and when normal within-athlete variability has been established.

5.4.3. What can and cannot be inferred for performance practice

The corpus supports SM-ICG as a research and phenotyping tool for explaining why performance or maximal oxygen uptake changed. It provides substantially less evidence that haemodynamic monitoring itself improves training decisions. Few studies prospectively allocated training from a prespecified haemodynamic phenotype, compared that strategy with standard coaching, and demonstrated superior performance or fewer adverse outcomes. Mouthguards, sport-specific intervals and other ergogenic strategies should therefore be judged on their randomised performance results, not on the mere availability of detailed cardiac data.

5.5. Population-specific exercise physiology

5.5.1. Sex and female-specific physiology

The historical exercise-physiology literature is disproportionately male. PhysioFlow studies in women have begun to address stroke volume in relation to blood volume and cardiac dimensions, autonomic and haemodynamic responses to isometric work, short-term interval training, arm exercise and resistance exercise in different postures. They show both shared principles and sex- or body-composition-related differences in the route by which oxygen delivery is achieved. They should not be treated as a single homogeneous female response.

Two focused examples appropriately constrain interpretation. Breast support did not materially alter cardiac function during jogging in the small study designed to test it. Likewise, the 2026 menstrual-cycle abstract found no significant phase-related difference in resting or submaximal exercise cardiac output, stroke volume or heart rate in 13 healthy women. The latter remains preliminary because of its small sample and limited hormonal confirmation. Null findings are important here: they discourage unsupported adjustment of haemodynamic interpretation by presumed cycle phase or equipment effect.

5.5.2. Age, development and functional reserve

Studies in older active men and non-obese older adults show that preserved daily function can coexist with age-related changes in central and peripheral exercise responses. Six-minute walk haemodynamics may help describe functional reserve, but age-specific reference distributions and longitudinal responsiveness are still limited. Training and respiratory-muscle interventions in older women also suggest that central cardiodynamic adaptation remains modifiable, although supplementation and training effects must be separated analytically.

Historical studies in adolescent boys and children combined measured oxygen uptake with SM-ICG cardiac output to estimate maximal arterial-venous oxygen difference or composite performance indices. They anticipated the integrative approach used in later work but involve small samples and mathematically derived endpoints. Growth, maturation, body size and training history complicate comparisons, making paediatric interpretation more than a scaled-down adult model.

5.5.3. Disability and other special populations

Elite paracyclists with the same official functional classification displayed meaningful within-class variation in cardiorespiratory responses. This is strategically important: functional classification and external performance do not fully specify central reserve. Studies in spinal-cord injury and wheelchair athletes also demonstrate that upper-body exercise, autonomic impairment and reduced active muscle mass change both the expected haemodynamic response and the methodological conditions. Accuracy evidence in wheelchair rugby players belongs to Chapter 3; its application implication belongs here.

Organ-transplant recipients, adults born very preterm and other special populations extend the use of SM-ICG beyond conventional athletic cohorts. These studies are best interpreted as physiological experiments on constrained reserve rather than as evidence for a generic normative threshold. Their value lies in revealing which component compensates and which fails when the integrated system is challenged.

5.6. Immersion, diving and hydrostatic stress

Immersion redistributes blood centrally, changes preload and neurohumoral regulation, and can alter post-exposure vascular control. The early post-immersion dehydration work showed that similar body-mass loss did not imply similar haemodynamic recovery after dry and immersed conditions; natriuretic-peptide responses were proposed to hinder the expected vasomotor adjustment. The key insight is methodological as well as physiological: hydration status, immersion depth, water temperature, posture and the timing of post-immersion measurement must be reported explicitly.

Breath-hold and diving-reflex studies used continuous SM-ICG to follow the rapid combination of bradycardia, stroke-volume adjustment and peripheral vasoconstriction. Work in trained divers explored the oxygen-conserving potential of this response, while historical abstracts and an academic thesis examined normal and atypical patterns during static apnoea. These sources provide coherent mechanistic signals, but evidence strength varies markedly: a peer-reviewed kinetic study, an abstract and a thesis must not be weighted as interchangeable confirmation.

Dryland versus immersed cycling belongs in the same conceptual framework because hydrostatic pressure changes central blood volume before exercise begins. It should not be grouped only by sport. The physiological response reflects the interaction of immersion, posture, contraction mode and thermal stress, and each component may modify stroke volume and vascular resistance independently.

5.7. Hypoxia, altitude, aviation and spaceflight

5.7.1. Acute and chronic hypoxia

Hypoxia reduces arterial oxygen content and forces compensatory changes in ventilation, heart rate, cardiac output and extraction. Studies in endurance athletes, trained and untrained participants, women, adults born preterm and high-altitude populations show that the contribution of convective flow depends on the severity and duration of hypoxia as well as baseline phenotype. A compensatory increase in peak cardiac output can occur without preserving one-legged performance, demonstrating that greater flow cannot fully offset reduced oxygen content or local diffusive constraints.

★ Simonson et al. (2015), with Peter D. Wagner among the co-authors, studied 21 Tibetan men living at approximately 4,200 m across a wide haemoglobin range. Lower haemoglobin concentration was associated with higher mass-specific maximal oxygen uptake, cardiac output and estimated muscle oxygen diffusing capacity; a model combining cardiac output, muscle diffusing capacity and arterial carbon dioxide pressure explained most of the between-participant variance in maximal oxygen uptake. The study is conceptually important because it challenges a simple “more haemoglobin is better” account of chronic altitude adaptation and integrates convective and diffusive determinants in an exceptional population. Its cross-sectional design cannot establish the causal direction of those relationships.

Studies of periodic breathing, ventilatory oscillations and expiratory-flow limitation broaden the picture beyond cardiac compensation. They show that ventilatory control and pulmonary mechanics interact with the central response. Calculated oxygen extraction is again a partitioning tool, not an independent tissue measurement, and comparisons across altitude studies must account for inspired oxygen, exposure time, acclimatisation and arterial saturation.

5.7.2. Pharmacological modification under hypoxia

★ Hsu et al. (2006) used a randomised, double-blind, placebo-controlled, counterbalanced crossover design in 10 trained men. Sildenafil produced no meaningful advantage at sea level, but during acute simulated altitude it increased arterial oxygen saturation, stroke volume and cardiac output and reduced the time for a six-kilometre trial by approximately 15%. A post hoc separation suggested pronounced responders and little change in non-responders, while 50- and 100-mg doses did not differ clearly. The physiological and performance changes are coherent and strongly context dependent, but the small sample, acute model and post hoc responder analysis prevent routine-use or broad population conclusions.

Recombinant erythropoietin studies likewise indicate that an increase in oxygen-carrying capacity has different performance consequences depending on the severity of arterial hypoxaemia. These experiments are valuable for testing the oxygen-transport model, not for endorsing prohibited or medically unnecessary performance enhancement.

5.7.3. Operational hypoxia, aviation and simulated spaceflight

A simulated high-altitude airdrop scenario demonstrated the operational relevance of continuous cardiorespiratory monitoring during abrupt oxygen-system failure. Anti-G straining abstracts and simulated-spaceflight studies extend the use case to altered acceleration, unloading and combined cognitive-physiological stress. These are heterogeneous operational models rather than a single validation domain. Their common contribution is the ability to track rapidly changing central responses when conventional steady-state assumptions are least appropriate.

> Boundary between Sections 5.6 and 5.7. Breath-hold diving produces hypoxaemia, but its dominant experimental framework is the diving response and hydrostatic or apnoeic stress; those studies are therefore synthesised in Section 5.6. Section 5.7 focuses on reduced inspired oxygen, altitude and operational hypoxia. This prevents one record from being counted twice as separate evidence.

5.8. Heat, cold and extreme environmental physiology

Thermal stress changes skin blood flow, plasma volume, cardiovascular drift and the competition between thermoregulation and locomotor demand. Cold-water immersion studies after exercise produced distinct central and peripheral recovery patterns: haemodynamic recovery and restoration of muscle strength did not necessarily proceed in parallel. A later trial found that a single dose of nattokinase accelerated skin-temperature recovery after cold-water immersion, but local thermal recovery should not be interpreted automatically as improved systemic haemodynamics or exercise performance.

In heat, prolonged rowing and high-intensity intervals with face coverings have been used to assess how cardiovascular strain is redistributed. Mask studies are particularly vulnerable to broad generalisation because mask type, fit, ambient temperature, humidity, exercise intensity and familiarisation differ. Heated-environment and muscle-temperature studies further show that local blood-flow–oxygen-consumption coupling can change even when whole-body indices appear relatively preserved.

These experiments demonstrate the advantage of simultaneous thermal, haemodynamic and performance measurements. They do not yet establish universal safety thresholds or individual heat- and cold-tolerance algorithms. Hydration, plasma-volume change and recovery timing remain major confounders and should be treated as measured covariates rather than narrative explanations.

5.9. Dietary, pharmacological and ergogenic interventions

Dietary nitrate, blackcurrant anthocyanins, grape-seed polyphenols, Calanus oil and nattokinase have all been studied with SM-ICG as part of a broader physiological outcome set. Histamine H2 blockade and combined H1/H2 blockade provide a pharmacological counterpart. Collectively, the studies show that exercise blood pressure, vascular resistance, cardiac output and local oxygenation can respond differently to the same intervention. They therefore discourage interpretation based on a single favourable surrogate.

The chronic dietary-nitrate study examined whether supplementation altered the haemodynamic response to dynamic exercise, while the blackcurrant programme includes a randomised crossover study in Southeast Asian men and newer work in women and an elite female endurance athlete. The 2026 additions broaden

representation but include a case study, which is hypothesis-generating by design. Calanus-oil supplementation combined with exercise training in older women improved central cardiodynamic measures, but a combined intervention cannot isolate the contribution of the supplement unless the design supports that comparison.

Histamine-receptor blockade studies show why pharmacological effects should be interpreted systemically. Augmented blood-pressure responses can occur through changes in vascular control without a parallel performance benefit, and combined receptor blockade may alter the balance of flow and resistance. Sildenafil and erythropoietin are discussed primarily in the hypoxia section because their physiological meaning depends on oxygen availability. Cross-reference is preferable to counting them again as a separate ergogenic evidence base.

Evidence standard for intervention claims. A credible ergogenic conclusion requires a randomised and adequately powered design, a prespecified performance endpoint, appropriate blinding where possible, and a haemodynamic mechanism consistent with the performance result. A change in cardiac output, stroke volume or vascular resistance alone is not proof of meaningful benefit.

Overall evidence synthesis and practical implications

The Human Performance and Integrative Physiology corpus is broad, unusually varied and mechanistically coherent. It spans maximal and submaximal exercise, resistance and endurance work, posture, respiratory loading, training, ageing, sex-specific questions, disability, immersion, hypoxia, temperature and ergogenic interventions. Across these settings, SM-ICG has repeatedly been used in conditions where continuous, scalable cardiac-output measurement creates information that oxygen uptake, heart rate or blood pressure alone cannot provide.

The strongest conclusion is not that one haemodynamic variable predicts performance universally. It is that physiological adaptation is route specific. The same change in maximal oxygen uptake can reflect different mixtures of flow and extraction; the same cardiac output can support different local blood-flow distributions; and the same peak value can be reached through different trajectories. This makes continuous profiling particularly valuable for mechanism, protocol comparison and individual-response research.

The selected core studies illustrates this convergence without pretending that every question is settled: ★ Leprêtre et al. clarified the exercise-intensity dependence of cardiac output and stroke-volume trajectories; ★ Athanasopoulos et al. demonstrated redistribution between respiratory and locomotor muscles; ★ Daussin et al. separated central and peripheral training routes; ★ Astorino et al. identified greater central oxygen delivery after HIIT; ★ Le Meur et al. and ★ Coates et al. converged on reversible central maladaptation with overload; ★ Simonson et al. integrated convective and diffusive adaptation at high altitude; and ★ Hsu et al. showed a pharmacological effect that emerged under hypoxia but not normoxia. Their collective value lies in the range of demanding physiological tests and the mechanistic role of continuous flow measurement, not in converting heterogeneous experiments into a single universal performance claim.

The evidence is nevertheless dominated by small experimental samples, many of them young and healthy, with heterogeneous devices, protocols, averaging, reporting and derived endpoints. Abstracts and historical communications enrich the record but cannot carry the same weight as fully reported peer-reviewed trials. The field has demonstrated feasibility and scientific utility more convincingly than decision utility: it remains to be shown prospectively that haemodynamic phenotyping improves training prescription, athlete management, safety or outcomes compared with existing practice.

- Use the full time-aligned response—workload, heart rate, CTi, stroke volume, cardiac output, blood pressure, gas exchange and recovery—rather than a single rest-to-peak delta.
- Keep the protocol fixed when comparing sessions; posture, exercise mode, active muscle mass, cadence, temperature and hydration are part of the physiological exposure.
- Treat calculated arterial-venous oxygen difference and systemic vascular resistance as derived constructs whose uncertainty depends on their input measurements.
- Interpret preserved cardiac output as useful information: it may redirect attention towards peripheral extraction, local perfusion, ventilatory work, biomechanics or motivation.
- Require independent performance or patient-relevant outcomes before converting a mechanistic haemodynamic change into an ergogenic or clinical claim.
- For future trials, prespecify individual-response criteria and demonstrate that phenotype-guided decisions outperform standard training or testing strategies.

Editorial conclusion. PhysioFlow emerges as an integrative physiological platform whose value extends beyond an isolated cardiac-output number. Its most defensible strength is the ability to reveal how central flow participates in adaptation under diverse and demanding stresses. The next evidentiary step is not simply another small demonstration of sensitivity, but prospective testing of whether the added mechanistic information improves a decision.

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★ = *landmark/core publication. Flags at the end of an entry indicate first- and last-author affiliation countries where available; a single flag is shown when identical.*

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6. Research and Experimental Applications

Research use is broader than clinical use. A haemodynamic platform may serve as the reference signal for a new sensor, an input to an algorithm, a continuous monitor during an experimental intervention, or a means of observing cardiovascular adaptation in an animal model. Each role asks a different question. Agreement with PhysioFlow tests concordance with PhysioFlow; it does not, by itself, establish absolute accuracy. A physiological change detected during an intervention establishes responsiveness only to the extent permitted by the design. Feasibility in an animal model cannot be translated directly into human clinical validity.

This chapter therefore evaluates what PhysioFlow enabled the investigators to observe and what the study design can legitimately support. The recurring strength is continuous, non-invasive access to central haemodynamics in settings where an invasive reference would be impractical or disproportionate. The recurring limitation is reference uncertainty: several studies use PhysioFlow as the comparator or assume that a derived output is suitable for modelling without an independent measurement of the same physiological quantity.

Chapter proposition. The experimental literature supports PhysioFlow as a versatile physiological research platform and, in selected studies, as a pragmatic comparator. It should not be described as a universal gold standard. The evidentiary claim must match the role the device actually played in each experiment.

6.1. Methodological, algorithmic and signal-processing studies

6.1.1. PhysioFlow as comparator: useful benchmark, limited inference

Stalter et al. evaluated estimated continuous cardiac output derived from pulse-wave transit time (EsCCO) against simultaneous PhysioFlow measurements during incremental and constant-load cycling in eight healthy adults. Across 74 paired observations, the correlation was 0.88 and the mean difference was 0.04 L/min, but the standard deviation of the difference was 1.49 L/min, producing limits of agreement of approximately −3.00 to +2.94 L/min. Above cardiac outputs of 15 L/min, the EsCCO signal was lost in almost half of measurements. The study therefore identified a relevant high-flow limitation of the method being tested.

The study is sometimes tempting to cite as validation of PhysioFlow because PhysioFlow served as the reference. That would reverse the direction of inference. Stalter et al. tested EsCCO against the selected comparator and provided evidence of agreement—and disagreement—between the two technologies. Without an independent criterion method, the observations cannot determine the absolute accuracy of either system. A balanced interpretation is nevertheless meaningful: investigators considered SM-ICG sufficiently established and operational during exercise to benchmark an emerging continuous technology, while the wide individual differences caution against interchangeability.

Interpretive rule. When PhysioFlow is the reference, report agreement with PhysioFlow. Reserve claims of accuracy for studies with an appropriate independent criterion method, adequate synchronisation and a protocol representative of the intended use.

6.1.2. Seismocardiography and recovery-phase estimation

Deoisres et al. used chest accelerometry and participant-specific random-forest regression to estimate heart rate, stroke volume, cardiac output and cardiac index during a submaximal cycle protocol in 60 healthy adults distributed across body-mass-index categories. PhysioFlow provided the target values. Reported mean absolute percentage errors were below 8% overall, but performance depended strongly on the recording condition. The most favourable results occurred during post-exercise recovery, with median coefficients of determination of approximately 0.75 for heart rate and cardiac output and 0.42 for stroke volume; active cycling was less favourable. The models appeared relatively insensitive to the BMI range studied.

This is a constructive proof of concept for lightweight monitoring during recovery or other relatively low-motion conditions. It is not an independent validation of the estimated variables, because the model learns the PhysioFlow output rather than an invasive or direct-flow reference. Participant-specific training also limits conclusions about performance in a previously unseen individual. The next step would require subject-level external validation, prespecified performance metrics, comparison with a criterion method where feasible, and explicit analysis of failure during motion rather than only summary error among retained signals.

6.1.3. Artificial intelligence and mathematically coupled inputs

Chang et al. combined measurements from a Terumo blood-pressure monitor and a PhysioFlow PF07 Enduro with an artificial neural network to predict cardiac index. The authors reported 97.78% classification accuracy using three physiological inputs and used data augmentation to expand the analytical dataset. The work illustrates how continuous haemodynamic outputs can be integrated into a multimodal decision or prediction architecture.

The central methodological issue is independence of the target. Cardiac index is cardiac output divided by body surface area, and cardiac output is heart rate multiplied by stroke volume. If the feature set includes PhysioFlow-derived heart rate, stroke volume, stroke-volume index or cardiac output, high prediction performance may partly reproduce an algebraic relationship already present in the inputs rather than discover a transportable biological model. Synthetic augmentation increases the number of analytical observations but does not create new independent participants or new physiological states.

Accordingly, the reported classification performance should be treated as internal algorithm development. A clinically persuasive model would require a target measured independently of its predictors, separation of participants—not rows—between training and testing, external validation in a new cohort, calibration and continuous-error reporting, and demonstration that the model adds information beyond the simple defining equation. These safeguards are especially important when derived physiological variables are used in machine learning.

6.1.4. Head-up tilt as a methodological case study

Cheung et al. compared simultaneous PhysioFlow and USCOM 1A Doppler measurements during a fixed head-up-tilt sequence in 20 healthy trained athletes. Both systems detected the expected directional response to orthostatic loading, but they differed materially in absolute stroke volume and in the magnitude of the relative change. The authors reported an implausible PhysioFlow cardiac-output response at 70° and questioned suitability in this setting. The subsequent exchange among Myers, Leprêtre and Phillips focused on whether USCOM could legitimately function as the validating standard, on technical assumptions during rapid postural change, and on the reach of conclusions beyond the protocol studied.

The exchange is valuable precisely because it does not produce a simple winner. Discordance between two non-invasive technologies does not identify which estimate is closer to true flow. Comparator choice, acquisition timing, operator dependence, posture-related signal behaviour and the absence of an independent criterion method remain plausible contributors. The primary validation analysis belongs in Chapter 3; here, the correspondence is retained as a case study in how reference assumptions shape methodological conclusions. The three commentaries are part of one scientific debate, not three additional validation studies.

Practical synthesis—method development. PhysioFlow can provide a continuous and experimentally practical target for new sensing and analytical approaches. The resulting evidence supports concordance with the PhysioFlow signal within the tested conditions. Independent physiological validity, generalisation to new individuals and robustness under motion require separate demonstration.

6.2. Human experimental and proof-of-concept applications

6.2.1. Electroconvulsive therapy

Haynes and Foust used PhysioFlow during electroconvulsive therapy under general anaesthesia, recording baseline, immediately before electrical stimulation, and one and five minutes after the seizure. The conference abstract describes nine patients and 11 treatments, although the reported sex counts sum to seven. Cardiac index decreased gradually until one minute and then increased, while heart rate and stroke volume were described as broadly stable; the authors interpreted the postictal pattern in the context of propofol anaesthesia.

The study shows that non-invasive haemodynamic observation was technically possible during a short and unusual intervention. It does not establish the complete ECT response or monitoring reliability. The sample was very small, multiple treatments may have come from the same participants, an internal numerical inconsistency is present, medication and anaesthesia are major determinants, and the sparse sampling schedule may miss the immediate sympathetic peak. No comparator was used. The report is best retained as historical proof of concept and as a prompt for a modern, time-resolved study rather than as evidence for routine ECT monitoring.

6.2.2. Short-term beta-blockade during maximal exercise

Fikenzer et al. studied five young adults during two maximal bicycle ramp tests, first without treatment and then after three days of bisoprolol 5 mg/day. PhysioFlow was used to examine the cardiac-output response across workload and recovery. The authors reported no material effect on cardiac output, maximal workload or maximal oxygen uptake despite beta-blockade.

The null result should not be interpreted as physiological equivalence. The study had only five participants, no randomised placebo condition, no blinding or washout, a fixed test order and a brief exposure. Familiarisation, day-to-day variation and compensatory stroke-volume responses could all influence the result. Its value is exploratory: continuous measurement allowed examination of how a chronotropic intervention might be accommodated within the integrated response. A controlled crossover design with verified drug effect and adequate power would be needed to establish the finding.

6.2.3. Methodological correspondence around an exploratory intervention

Bour's response to the pilot study by Drigny et al. is retained because it documents scientific scrutiny of a six-patient, uncontrolled interval-training study in adults with obesity. The primary article combined body composition, insulin sensitivity, exercise capacity, cognition and cerebral oxygenation after four months of training and is discussed in the relevant clinical section. The response is correspondence rather than a new experiment and should not be counted as independent support for PhysioFlow or for the intervention.

More broadly, this record illustrates the purpose of the chapter boundary. A small intervention study may be clinically motivated yet remain primarily hypothesis-generating when it lacks a control group, contains numerous outcomes and cannot isolate which component of the intervention caused the observed change. PhysioFlow can strengthen mechanistic description in such a study, but the presence of a haemodynamic measurement does not repair the causal limitations of the design.

Practical synthesis—human proof of concept. These studies demonstrate experimental reach, not a mature application. They justify better designed follow-up work when the physiological question is compelling; they do not establish monitoring standards, therapeutic equivalence or improved decisions.

6.3. Preclinical and veterinary applications

6.3.1. Pharmacological responsiveness in conscious beagles

Payseur et al. assessed whether PhysioFlow could detect expected cardiac-output responses to tool compounds in conscious beagles. Dobutamine increased cardiac output, acepromazine decreased it and minoxidil produced no significant change under the tested conditions. The directional responses to positive inotropy and sedation/vasodilation support biological sensitivity and suggest a low-burden approach for repeated cardiovascular observations in preclinical pharmacology.

The inference remains relative rather than absolute. Expected effects from the literature and current standards are not equivalent to a simultaneous invasive reference in the same animal. The study supports detection of pharmacological change in a conscious canine model; it does not establish interchangeability with thermodilution or measured-variable Fick, nor does it define performance in other breeds, sizes or disease states.

6.3.2. Neonatal asphyxia and resuscitation in piglets

Berisha et al. evaluated neonatal impedance cardiography in 15 asphyxiated piglets during induced asystole, cardiopulmonary resuscitation and the period after return of spontaneous circulation. Approximately half of registrations met the study's good-quality criterion, and recording quality varied markedly between animals. When available, the haemodynamic trajectories were physiologically plausible across the experimental transition.

This is an appropriately labelled feasibility study. It explores whether a non-invasive signal can be obtained in a very small body during profound circulatory instability; it does not validate cardiac output because no independent comparison was performed. Small body surface area, thoracic anatomy, possible shunting and the controlled sedated laboratory setting all limit translation to human neonates. The variable acquisition success is itself a substantive result and should be reported alongside the interpretable traces.

6.3.3. Chronic atrioventricular block as a remodelling model

Van Bavel and colleagues used repeated treadmill exercise before and after induction of complete atrioventricular block in dogs to examine how structural and functional remodelling supports activity despite chronic bradycardia. The 2021 conference abstract and the 2023 full article arise from the same programme and should be treated as companion records. The full study indicates that cardiac output remained lower after atrioventricular block and strongly dependent on heart rate, while adaptation over time allowed tolerance of moderate treadmill work.

PhysioFlow contributed continuous haemodynamic phenotyping within a longitudinal disease model. The scientific contribution concerns compensation and remodelling, not validation of the device. Repeated within-animal observations are a strength for trajectory analysis, but species-specific conduction, remodelling and exercise behaviour preclude direct clinical thresholds for humans.

6.3.4. Veterinary interventional monitoring

Kim et al. first described two dogs undergoing interventional heartworm extraction. Cardiac output rose after removal in both clinical narratives, including a 115% increase in one dog, suggesting immediate haemodynamic relief that was not necessarily apparent from routine pressure measurements alone. The case report established clinical feasibility but, by design, could not separate procedure effect from anaesthesia, ventilation, fluid administration or spontaneous variation.

A subsequent pilot study extended real-time monitoring to dogs with heartworm disease and gastric dilatation undergoing heartworm extraction or gastric decompression, with healthy controls for context. Cardiac index increased significantly after intervention—by approximately 14.7% in the heartworm group and 28.5% in the gastric-dilatation group—while mean arterial pressure did not show an equivalent uniform change. The finding is clinically coherent and illustrates why flow may complement pressure during relief of mechanical obstruction.

The veterinary evidence remains preliminary. Samples were small, treatment and anaesthesia were not standardised as experimental exposures, and no simultaneous criterion cardiac-output method was used. The defensible conclusion is that continuous SM-ICG detected plausible peri-interventional trajectories and may offer useful adjunctive information. Prospective veterinary studies should define acquisition success, repeatability, agreement with an independent reference and whether the added signal changes management or outcomes.

6.3.5. Translational boundaries

Across beagles, piglets and canine disease models, PhysioFlow has been used without the burden of repeated catheterisation and has captured directional responses to drugs, resuscitation, chronic remodelling and relief of obstruction. This breadth is relevant to research maturity: the platform can operate in unusually demanding experiments and can provide repeated within-subject trajectories.

Translation requires restraint. Electrode geometry, thoracic dimensions, skin and coat preparation, conscious versus anaesthetised state, ventilation, shunts and disease-specific anatomy may all affect signal generation. An animal experiment can establish feasibility and biological responsiveness in that model. It cannot substitute for human validation, and even veterinary routine use requires species- and application-specific evidence.

Overall evidence synthesis and research priorities

Chapter 6 shows a technology functioning as research infrastructure rather than only as a device under evaluation. PhysioFlow has supplied target signals for seismocardiography and artificial-intelligence models, served as a comparator for EsCCO, captured short human experimental responses, and supported longitudinal and interventional animal studies. This diversity is a credible marker of usability and scientific reach.

The same diversity does not create one cumulative validation claim. Several studies test the new method against PhysioFlow rather than PhysioFlow against a criterion method; some observe only directionally plausible change; and some are abstracts, case reports or companion publications. Their proper contribution is to show where continuous non-invasive haemodynamics can make an experiment possible or richer, while defining the validation that remains necessary for the proposed downstream use.

- State explicitly whether PhysioFlow is the device under test, the comparator, an algorithmic input or an observational research instrument.

- Use an independent target when validating new sensors or prediction models; avoid judging a derived variable from inputs that reproduce its defining equation.
- Split machine-learning data by participant or animal and validate externally; data augmentation does not replace independent biological observations.
- Report acquisition failures and excluded segments as primary feasibility outcomes, particularly during motion, resuscitation and small-animal recording.
- Distinguish repeated measurements, treatments and companion publications from independent sample size and independent replication.
- For translational and veterinary studies, pair trajectory sensitivity with application-specific repeatability, an appropriate comparator and a decision-relevant endpoint.

Editorial conclusion. The research corpus supports PhysioFlow as a mature, flexible platform for continuous physiological experimentation. Its strongest contribution is enabling time-resolved haemodynamic questions that would otherwise be difficult to study at scale. The next methodological advance is disciplined independence: independent references, independent subjects and independent validation of whether the added signal improves an inference or a decision.

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★ = *landmark/core publication. Flags at the end of an entry indicate first- and last-author affiliation countries where available; a single flag is shown when identical.*

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7. Vascular and Impedance-Derived Investigations

Most PhysioFlow publications use the transthoracic impedance waveform to estimate stroke volume and cardiac output. A smaller body of work asks a different question: whether the morphology and timing of impedance changes can also describe vascular mechanics or reveal physiological information not contained in a single flow estimate. eORTA is the most developed example. It should therefore be evaluated on its own construct, reference methods and intended use, rather than treated as a secondary cardiac-output variable.

This distinction also clarifies the chapter boundary. Studies in which PhysioFlow measures cardiac output while arterial stiffness is measured by a separate device belong to the relevant clinical or physiological chapter. Studies that interrogate a PhysioFlow-derived local aortic stiffness signal belong here. A final group uses the raw impedance waveform or PhysioFlow as a reference for another model; those studies are retained as ancillary signal applications and interpreted according to that more limited role.

Chapter proposition. eORTA is a technically original, patented and partially validated extension of the PhysioFlow signal. The available evidence supports biological plausibility, association with established vascular measures and responsiveness in selected experiments. It does not yet establish a routine clinical test, normative thresholds, prognostic value or decision impact.

7.1. eORTA and local aortic stiffness

7.1.1. Measurement concept and intellectual-property context

The eORTA concept emerged from a reinterpretation of bioelectrical impedance changes produced by pulsatile blood flow in a conducting artery. The proposed approach was local rather than regional: instead of estimating the transit velocity of a pressure wave over a measured arterial path, it used the impedance signal at an anatomical site to derive an index related to arterial-wall behaviour. The later formulation separated two components—a local resistance term associated with flow-related drag and a local distensibility term—which were combined into the AoStiff index.

This is not merely another implementation of carotid–femoral pulse-wave velocity (cfPWV). Local and regional measurements interrogate overlapping but non-identical vascular properties, and the arterial tree is mechanically heterogeneous. Correlation with cfPWV is therefore relevant evidence of construct convergence, but it cannot demonstrate numerical interchangeability. The specific attraction of eORTA is the possibility of obtaining local information—and potentially separating resistance and distensibility—from the same impedance platform used for haemodynamic monitoring.

The method generated a patent family originating from ESAIP, the University of Angers and Angers University Hospital, with Mathieu Collette, Anne Humeau and Georges Lefthériotis named as inventors. According to the manufacturer's history, Manatec subsequently acquired the relevant patent rights. That acquisition gives the research strategic importance for the PhysioFlow programme, but patent ownership is not itself evidence of analytical validity, clinical utility or current regulatory scope.

7.1.2. A coherent development pathway

Study	Role in the pathway	Main contribution	Main constraint
Collette 2008	Signal groundwork	Time and spatial invariance of limb impedance features in 15 healthy participants at rest.	Peripheral recordings; small resting sample; no stiffness criterion.
Collette 2009	Model and initial index	Physical model, simulated and experimental signals; Ira related to cfPWV in 20 participants (R^2=0.77).	Correlation, not agreement; early single-centre derivation.
Collette 2011, MBEC	Component validation	AoStiff vs cfPWV in 120; AoRes and AoDist compared with MRI-derived drag and distensibility in 8.	MRI evidence is compelling but based on only eight participants.

Study	Role in the pathway	Main contribution	Main constraint
Collette 2011, Hypertens Res	Local–regional comparison	In 118 patients, impedance wave velocity vs cfPWV r=0.88 and local AoStiff vs cfPWV r=0.75; GTN subgroup n=52.	Association does not establish interchangeability or universal pressure independence.
Hallab 2013	Clinical association	PhysioFlow AoStiff was higher in patients with carotid plaques within a 77-patient vascular-risk cohort.	Cross-sectional; plaque group was older; no adjusted diagnostic or outcome model.

The 2008 study was not an eORTA validation study, but it established that selected impedance-signal features recorded from limbs were sufficiently stable across five-minute intervals and sufficiently similar between limbs to support further signal interpretation. The 2009 paper then supplied the key conceptual step: a physical model relating impedance variation to the kinetic energy of blood flow and an initial local stiffness index, Ira. In 20 participants at rest, Ira was associated with the cfPWV reference (R^2=0.77; p<0.0001). This was a promising derivation result, not a definitive validation dataset.

The 2011 Medical & Biological Engineering & Computing paper substantially strengthened the chain. AoStiff correlated with cfPWV in 120 participants (r=0.79; p<0.0001). In a separate eight-person MRI subset, the proposed resistance component correlated with MRI-derived drag forces (r=0.95) and the distensibility component with MRI-derived aortic distensibility (r=0.93). The magnitude of these correlations is notable because each component was compared with a conceptually aligned measurement. The very small MRI sample, however, leaves substantial uncertainty around precision, spectrum effects and transportability.

A companion 2011 study enrolled 118 consecutive patients and compared both impedance-derived regional wave velocity and local AoStiff with tonometric cfPWV. Correlations were strong for the regional impedance measure (r=0.88) and moderate-to-strong for local AoStiff (r=0.75). In 52 participants given glyceryl trinitrate, mean arterial pressure fell by approximately 4% while local AoStiff and regional impedance wave velocity did not change significantly. This pharmacological perturbation supports the claim that the signal was not simply tracking a small acute pressure change produced by peripheral vasodilation. It should not be generalized into complete independence from pressure under all haemodynamic conditions.

Why this series matters. The value of the eORTA literature lies in its internal continuity: signal behaviour, physical model, component-level comparison, local–regional convergence and an acute perturbation test address different parts of the same construct. No single paper completes validation, but together they constitute a credible development programme that deserves more than a passing mention.

7.1.3. Clinical association and independent experimental use

Hallab et al. provided a first clinical association rather than a validation study. Among 77 patients undergoing vascular screening, the 25 patients with carotid plaques had higher PhysioFlow AoStiff than the 52 without plaques (10.4±0.7 versus 8.2±0.5 m/s; p<0.02). They were also approximately ten years older and had greater carotid intima–media thickness. The finding is biologically coherent and connects eORTA with vascular phenotype, but the design does not show independent discrimination after age and risk-factor adjustment, establish a diagnostic threshold, or predict events.

Three studies from an independent exercise-physiology group then used the PhysioFlow aortic-stiffness output as an experimental variable. Naylor et al. studied 20 recreationally active men—10 with normal blood pressure and 10 with high-normal blood pressure—before and after combined histamine H1/H2 receptor blockade at rest and during progressive cycling. AoStiff was higher in the high-normal group, and the study used the combined haemodynamic and vascular response to examine impaired histaminergic vasodilation. This is important external adoption of the output, although it does not independently validate how accurately AoStiff represents local wall mechanics.

Dillon et al. used crossover supplementation designs in 20 men. After a single grape-seed-extract dose, blood pressure changed but AoStiff did not, showing within that protocol that the variable did not automatically move whenever pressure changed. After seven days of supplementation in overweight or obese men, resting AoStiff was lower after grape-seed extract than after placebo (10.2±1.0 versus 13.0±1.9 arbitrary units; p=0.002), while mean arterial pressure was modestly lower at rest and during submaximal cycling. The chronic result supports

short-term responsiveness but does not prove mediation, durable vascular remodelling or clinical benefit. Small samples, short exposure and multiple endpoints warrant restraint.

Balanced interpretation. Independent investigators used eORTA in plausible human experiments and obtained both positive and null responses. That pattern is more informative than uniformly favourable results would be: it suggests a signal capable of differential behaviour, while leaving criterion validity and clinical meaning to be established.

7.1.4. Evidence maturity: underdeveloped, not disproven

The fairest description is neither “validated clinical product” nor “abandoned curiosity”. eORTA is a coherent patented method with encouraging construct evidence and limited external use that was not carried through the later stages expected for a deployable vascular biomarker. The absence of those stages is a development gap; it is not negative evidence against the underlying signal.

The most consequential omissions are reproducibility across days, operators, centres and device generations; prespecified agreement analyses against local criterion measurements; reference ranges across age, sex and body habitus; robustness during exercise and larger pressure changes; external replication; and prospective association with decisions or outcomes. The early studies mostly report correlations. Correlation can establish convergent behaviour but cannot determine bias, limits of agreement or interchangeability.

Because the intellectual property was acquired by Manatec, a disciplined re-evaluation may have strategic value. A credible programme would first verify the current implementation and lock the algorithm and acquisition conditions; then test repeatability and controlled responsiveness; reproduce the local component comparisons with modern MRI or another appropriate local reference; and only then move to multicentre reference ranges and a clearly defined clinical question. This sequence would determine whether eORTA is a useful PhysioFlow extension without asking an initial study to prove clinical outcomes prematurely.

Editorial position. eORTA merits prominent treatment because it combines a distinctive signal concept, a coherent peer-reviewed development series and company-owned strategic potential. Its present limitation is incomplete translation, not lack of an evidentiary foundation.

7.2. Ancillary impedance signals and vascular models

7.2.1. Impedance morphology during head-up tilt

Bellard et al. illustrate how the transthoracic impedance waveform can be informative independently of absolute cardiac-output estimation. In 68 patients with recurrent unexplained syncope, 38 developed symptoms during a 70° head-up-tilt test and 30 did not. A change of more than 40 ms in the slow ejection-time component T2 during the first 5–10 minutes predicted a positive test with 68% sensitivity and 70% specificity. Combining early impedance and peripheral haemodynamic changes increased specificity to 97% and positive predictive value to 93% in the same cohort.

This is a clinically interesting within-cohort signal-discovery study, not an externally validated diagnostic rule. The composite was developed and evaluated in one sample, the isolated sensitivity was modest, and the physiological origin of T2 remained incompletely resolved. Its enduring contribution is conceptual: useful information may reside in time-resolved impedance morphology even when the primary question is not the absolute value of cardiac output.

7.2.2. PhysioFlow as a reference for peripheral-waveform modelling

Wołos et al. developed a personalised arterial-tree and left-ventricular elastance model from radial pressure waveforms in 35 haemodialysis patients and 14 healthy controls. PhysioFlow stroke volume served as the comparison target. Model-estimated and PhysioFlow stroke volume were moderately correlated in both groups (r=0.58 and r=0.57, respectively), and the authors reported systematic underestimation by the model.

The study is relevant to vascular and integrative modelling, but its direction of inference must remain clear. It tests a new peripheral-waveform model against PhysioFlow; it does not validate PhysioFlow against an independent criterion. The publicly available model and dataset strengthen transparency. Future work should compare both approaches with an external flow reference and test whether estimated vascular parameters add decision-relevant information in dialysis.

7.3. Overall evidence synthesis and next steps

The eORTA programme progressed from signal analysis to physical modelling, reference convergence, component-level MRI comparison, pharmacological testing and selected clinical or experimental applications. That pathway forms a coherent development sequence for an ancillary device output and contributes a distinct vascular dimension to the overall evidence synthesis.

The evidence nevertheless stops before clinical deployment. The strongest current statement is that local aortic stiffness derived from bioimpedance is a plausible construct with preliminary construct-validity evidence: its behaviour converges with established vascular measures and can respond differentially to experimental interventions. Claims of diagnosis, prognosis, treatment selection or outcome improvement would be premature.

- Preserve eORTA as a distinct PhysioFlow innovation rather than dispersing its papers across generic physiology categories.
- Separate local AoStiff from regional cfPWV and avoid treating correlation as interchangeability.
- Confirm the exact current software implementation, units and acquisition requirements before making contemporary product claims.
- Prioritise repeatability, external criterion comparison and reference ranges before a large outcomes study.
- Use ancillary waveform studies to show scientific reach, while keeping their inference separate from cardiac-output validation.

Editorial conclusion. The eORTA corpus does not yet justify routine clinical adoption, but it does justify renewed attention. It represents a scientifically grounded, strategically relevant asset whose translational development appears incomplete rather than scientifically exhausted. The 2011 component and local–regional comparison studies are central to this development sequence, while their scope remains distinct from clinical outcome validation.

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★ = *landmark/core publication. Flags at the end of an entry indicate first- and last-author affiliation countries where available; a single flag is shown when identical.*

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8. Overall Evidence Synthesis

No single publication can carry the entire clinical case for a measurement platform. Validation studies address agreement or repeatability under defined conditions; application studies ask whether the measurement reveals relevant physiology; prognostic studies ask whether it adds information about future risk; and implementation studies ask whether clinicians can use that information at scale. PhysioFlow is unusual not because every one of these questions has been answered definitively in every specialty, but because the same platform has been used across a broad range of demanding human settings while producing largely coherent haemodynamic information.

This chapter therefore avoids two equally misleading conclusions. The first would be promotional: that the number of publications alone proves universal accuracy, diagnostic utility or improved outcomes. The second would be excessively sceptical: that the absence of one decisive multicentre outcomes trial leaves twenty-five years of validation, physiological and clinical evidence merely “preliminary”. A fair synthesis must judge the maturity of each application separately and apply the same standard to PhysioFlow that is applied to established neighbouring technologies.

8.1. The scale and composition of the evidence base

8.1.1. Documentary footprint

The publication matrix contains 328 unique documentary records. These are not 328 independent clinical trials. They comprise 262 records classified as articles and 49 abstract-related records, with the remainder including comments or replies, academic works, reports, protocols and other documentary material. Abstracts, full articles and companion analyses may describe the same or overlapping cohorts. Two records concerning other devices (BioZ and pOpmetre) are retained for traceability and excluded from the PhysioFlow result-orientation analysis.

Documentary category	Publication matrix count	Interpretation
Records labelled Article	262	Largest component; includes validation, clinical application, physiology and methodological studies.
Abstract-related records	49	Important for historical completeness and signal discovery; lower weight when no full report is available.
Other documentary records	17	Comments/replies, academic works, protocols, reports and other non-standard records.
Total unique records	328	Documentary footprint, not a count of independent studies or unique participants.
Landmark flags in the source register	29	Agreed cross-chapter navigation markers; not formal quality grades.

The matrix remains deliberately live. Some publications identify PhysioFlow only in the methods, some use generic terms such as impedance cardiography, and some device identifications require author confirmation. The present count is therefore a documented minimum corpus rather than a claim of perfect bibliographic exhaustiveness.

8.1.2. Approximate number of human enrolments

A first reconciliation of sample sizes in the 2024 Clinical Studies Reference Guide, the subsequent matrix additions and the chapter-level audits supports an order-of-magnitude estimate of approximately 9,000 human participant enrolments. A prudent current range is 8,000–10,000. The range is more defensible than a single exact number because not every documentary record reports an extractable sample size, and several publication families reuse or enlarge earlier cohorts.

The estimate counts reported enrolments rather than unique individuals. Where an abstract and full article clearly refer to the same study, or where a later report appears to enlarge an earlier cohort, the larger

identifiable cohort is used once. Animal work and the non-PhysioFlow BioZ record are excluded. Residual overlap may still inflate the total; conversely, missing sample sizes and currently unavailable reports make undercounting likely. The number should therefore be communicated as “approximately nine thousand reported human enrolments across the documented corpus”, not as a regulatory-grade count of unique patients.

Recommended external wording. The current evidence map includes 328 unique documentary records and approximately 9,000 reported human participant enrolments. Because cohorts overlap and some sample sizes remain unverified, the participant figure is an order-of-magnitude estimate rather than an exact unique-patient count.

8.1.3. Favourable, neutral and adverse findings

Study orientation must be defined from the measurement question, not from whether an intervention worked. A trial in which treatment does not change cardiac output is not negative evidence against PhysioFlow if the patient may genuinely have remained unchanged. Likewise, a study can be clinically negative for its primary hypothesis while still demonstrating technically successful, physiologically coherent haemodynamic measurement.

Orientation	Operational definition	Records, n (%)
Supportive/favourable	PhysioFlow agrees sufficiently with a credible external reference, reproduces an established response, or provides coherent and useful physiological, clinical or prognostic information.	281 (89.5%)
Neutral	No device-relevant discrepancy is demonstrated; a null intervention, absent group difference or stable PhysioFlow value may reflect a genuinely unchanged physiological state.	18 (5.7%)
Mixed/non-conclusive	Some results are supportive and others discordant, or protocol, comparator, software generation, IFU compliance or data availability prevents confident attribution.	12 (3.8%)
Adverse	A material PhysioFlow result conflicts with a credible external truth or firmly established physiological standard, without an adequate methodological explanation.	3 (1.0%)

The publication matrix audit classifies 314 documentary records as evaluable for device-relevant orientation: 281 favourable (89.5%), 18 neutral (5.7%), 12 mixed/non-conclusive (3.8%) and 3 adverse (1.0%). The remaining 14 records comprise 12 classified as contextual and two concerning other devices; they are excluded from these percentages. Thus, 328 is the full register count and 314 is the denominator for result orientation. These are all-record documentary proportions—not independent-study success rates or estimates of measurement accuracy. Within the narrower 40-record validation/reliability subset, 26 records are favourable, 11 mixed/non-conclusive and 3 adverse. The three adverse records arise from two research programmes: two related reports from one legacy paediatric Taylor programme and the separate Kemps heart-failure comparison. This distinction prevents the broad application literature from diluting discordance in the measurement-performance subset and prevents related publications from being counted as independent failures.

8.2. What the validation literature establishes

8.2.1. Absolute values: broadly comparable performance under defined conditions

Taken as a whole, the validation literature shows that inferiority is not generally observed, with a small number of clearly identified exceptions. Foundational measured-variable Fick studies, several thermodilution, imaging and rebreathing comparisons, and later clinical validations report acceptable agreement or clinically coherent absolute values under defined conditions. Agreement remains context dependent, and no method should be assumed numerically interchangeable with every comparator in every population. Findings are most consistent with contemporary system versions and documented adherence to the IFU. Because most comparative studies were not designed as formal non-inferiority trials, this is a qualitative synthesis of consistency, agreement and clinical coherence—not statistical proof of non-inferiority.

This distinction matters because cardiac output has no error-free practical reference method. Measured-variable Fick depends on accurate oxygen-consumption and blood oxygen-content measurements; thermodilution is

sensitive to technique, rhythm and valvular conditions; rebreathing is constrained by ventilation and gas mixing; and echocardiography or magnetic resonance introduces its own acquisition and modelling assumptions. Disagreement between two methods does not, by itself, identify which method is wrong. Bland–Altman results, percentage error, simultaneity and the clinical consequence of the observed difference must all be considered.

Critchley and Critchley's widely used approximately 30% percentage-error criterion was derived from the combined precision expected when a test method is compared with an imperfect reference. It is a methodological convention based on the 95% limits of agreement relative to mean cardiac output, not a natural law or proof that every value meeting the criterion is clinically interchangeable. The same caution should be applied symmetrically to PhysioFlow and to established comparators.

Defensible metrological claim. Across appropriate comparisons, PhysioFlow generally provides cardiac-output values comparable to reference or established methods, with few clearly identified exceptions. Agreement remains context dependent and does not justify universal interchangeability. Results are most consistent with contemporary systems, measurement quality and IFU-compliant acquisition; most studies were not formal non-inferiority trials.

8.2.2. Repeatability and sensitivity to change

Repeatability and dynamic sensitivity are among the most consistent strengths of the corpus. Early exercise studies demonstrated stable repeated responses. Electrode-repositioning work found limited bias under controlled conditions. In healthy adults, McCarthy et al. directly compared duplicate measurements with nitrous-oxide rebreathing and found lower measurement error and generally higher reliability for PhysioFlow across rest, moderate exercise and high intensity. That study evaluates precision rather than absolute accuracy, but precision is exactly what serial physiology and response assessment require.

Sensitivity is supported not by one comparison, but by the repeated detection of directionally coherent responses to exercise intensity, posture, preload manipulation, ventilation, hypoxia, pharmacological intervention, training, rehabilitation and recovery. These findings show that the signal is not merely stable: it changes when cardiovascular physiology is expected to change and sometimes remains stable when the experimental manipulation does not plausibly alter forward flow. Responsiveness is not a substitute for criterion validity, but it is an essential and clinically relevant dimension of measurement performance.

★ Filaire et al. add an important modern exercise comparison with inert-gas rebreathing. Their results support concomitant agreement in response while again showing that the two methods should not simply be substituted for one another numerically. The combined message from McCarthy and Filaire is stronger than either paper alone: PhysioFlow can offer high repeatability and useful dynamic agreement even when different non-invasive methods retain method-specific absolute values.

8.2.3. IFU compliance is part of validity, not an afterthought

The PhysioFlow evidence cannot be interpreted independently of acquisition quality. Particular attention is required for skin preparation, approved electrodes manufactured less than one year before use and taken from a pouch opened on the day of testing, correct electrode positioning, lead integrity, signal-quality criteria, appropriate calibration or autocalibration, and correct demographic inputs. Hardware and software generation, and any steady-state requirements of the comparator, must also be considered when interpreting a comparison. Every physiological measurement method has conditions under which its estimates are valid.

Studies with uncertain IFU compliance, non-commercial software, obsolete amplification, expired or inappropriate electrodes, non-simultaneous comparison or insufficient individual data should remain visible. Their results may identify real vulnerabilities. They should not, however, be treated as unqualified tests of the current commercial system. Conversely, manufacturer explanations must be labelled as such and should not replace independent data or reanalysis.

The 2025 reproducibility study by ★ Schoch et al. illustrates this boundary. Its between-visit variability is important and argues against over-interpreting small changes in one individual. At the same time, the analysis combined instrument, biological and exercise-response variability; IFU-related concerns were not fully resolved; and individual data were not made available for independent reanalysis. The same research group subsequently used PhysioFlow with an explicit signal-quality threshold in HFpEF. This later application does not retrospectively validate the earlier reproducibility estimate, but it does show that the investigators considered carefully quality-controlled PhysioFlow data usable for physiopathological analysis.

8.3. Multidisciplinary convergence and transportability

The breadth of the PhysioFlow literature is not decorative. A device that produces plausible values only in one laboratory or one healthy population has limited external validity. PhysioFlow has instead been used in cardiology, pulmonary medicine, internal and systemic disease, perioperative and critical care, paediatrics, rehabilitation, elite and recreational exercise, altitude and hypoxia, environmental physiology, pharmacology, signal processing and vascular research. The populations range from healthy children and trained athletes to patients with severe cardiac, pulmonary or systemic disease.

Domain	Recurring measurement role	What the domain contributes
Cardiology	Exercise reserve, haemodynamic phenotyping, prognosis and rehabilitation response.	Large prognostic cohorts and clinically interpretable dynamic profiles; application-specific decision rules remain uneven.
Pulmonary medicine	Separation of ventilatory, central-flow and peripheral-extraction limitations.	Evidence in COPD, pulmonary hypertension, cystic fibrosis and mixed dyspnoea under technically demanding conditions.
Systemic medicine	Integrated oxygen transport in hypertension, metabolic disease, cancer, pregnancy and post-infectious states.	Shows that a null or preserved cardiac-output response can correctly redirect interpretation toward peripheral or non-cardiac mechanisms.
Critical/perioperative care	Continuous observation of rapid haemodynamic change.	Feasibility and response tracking; limited evidence for stand-alone alarms or outcome-guided protocols.
Paediatrics/congenital disease	Exercise adaptation and reserve across heterogeneous anatomy.	Later studies support haemodynamic assessment in selected paediatric and congenital populations. Early Taylor findings require interpretation in light of their methodological limitations and legacy technology (Chapter 3).
Human performance	Training, fatigue, HIIT, hypoxia, altitude and recovery.	Repeated-measures and crossover designs demonstrate sensitivity, reversibility and integrative physiological value.
Research/vascular signals	Method development, reference platform and ancillary waveform analysis.	Extends the platform beyond a single cardiac-output number while keeping exploratory constructs distinct from established use.

Taken together, the breadth, repetition and physiological coherence of these findings mean that PhysioFlow should no longer be approached as an untested measurement platform. The corpus supports the feasibility of acquiring interpretable dynamic haemodynamic information across demanding and diverse settings. The questions that remain concern defined boundaries: measurement performance in a specified population and protocol, the interpretation of a particular profile, and the validity of a threshold or decision pathway. Conversely, a claim of general invalidity must account for the full multidisciplinary corpus, contemporary device generations and acquisition conditions, rather than rely selectively on a few discordant or legacy comparisons. This is a requirement for balanced evidence appraisal, not a reversal of the scientific burden of proof: physiological coherence alone does not demonstrate absolute accuracy or clinical outcome benefit.

8.4. Clinical maturity must be assessed application by application

A monitor is not a treatment. Requiring PhysioFlow itself to improve mortality without specifying how its information changes management confuses measurement validity with the efficacy of a clinical strategy. The relevant hierarchy is therefore: can the platform measure; can it detect meaningful change; does it add physiological or prognostic information; can a decision rule be defined; and does using that rule improve care, efficiency or outcomes? Different PhysioFlow applications occupy different positions on that pathway.

8.4.1. Clinical vigilance and patient safety

The safety relevance of continuous exercise haemodynamics is primarily informational. An unexpected deterioration in the response—particularly an early or disproportionate fall in CTi or stroke volume while workload and heart rate continue to rise—may reveal physiological discordance before conventional endpoints become unequivocally abnormal. Such a finding should not be dismissed solely because the ECG, symptoms or peak values appear otherwise reassuring. It is not a diagnosis, proof of ischaemia or a universal criterion for terminating exercise. A late plateau is not necessarily abnormal, and a decline at very high heart rates may reflect shortened diastolic filling rather than pathological loss of reserve.

Within the overall clinical context, a clearly abnormal or discordant trajectory may nevertheless warrant greater caution during the test, closer observation of recovery, a more conservative initial exercise prescription or targeted additional assessment. The appropriate action depends on signal quality, timing, symptoms, rhythm, blood pressure, gas exchange, prior disease and the purpose of testing. This is a principle of clinical vigilance, not a claim that PhysioFlow provides an autonomous safety alarm or replaces established exercise-test supervision and stopping criteria.

8.4.2. Actionability, cognitive burden and medico-legal balance

Additional information can reduce uncertainty, but it can also create cognitive and medico-legal burden when an abnormal signal has no agreed interpretation or next step. Clinicians may feel exposed both by not acting on an unexplained finding and by overreacting through defensive investigation. The value of haemodynamic monitoring therefore depends on interpretability and actionability, not on displaying more variables. PhysioFlow should be framed around a limited number of quality-controlled trajectories and an explicit escalation logic rather than as an additional stream of isolated numbers.

A practical framework is graded rather than binary: an expected profile requires no PhysioFlow-specific escalation; a borderline or uncertain profile calls for interpretation in context and, where appropriate, repeat assessment or observation; a clearly abnormal or discordant profile should not be trivialised and should prompt review of the test, recovery and broader clinical picture. An unexplained abnormal signal may warrant contextual clinical review, but it does not mandate automatic imaging, catheterisation or treatment. This distinction also reduces the risk of false reassurance, unnecessary investigation and avoidable patient anxiety. Communication should acknowledge uncertainty and explain proportionate next steps rather than convert every deviation into a disease label.

Application or measurement role	Current evidence position	Appropriate conclusion
Continuous non-invasive haemodynamics at rest and during exercise	Established platform capability within documented acquisition and signal-quality conditions.	Appropriate for physiological assessment and monitoring when interpreted in context.
Within-person response and trending	One of the strongest and most recurrent evidence domains.	Often more defensible than assuming numerical interchangeability with another method.
Integrated exercise phenotyping	Strong multidisciplinary support.	Useful for separating central flow, chronotropic, ventilatory and peripheral-extraction contributions.
Prognostic enrichment	Substantial in heart-failure referral cohorts; suggestive in selected other populations.	Can complement established CPET variables; thresholds should remain population specific.
Adjunctive diagnosis or rehabilitation profiling	Promising but heterogeneous.	Supports targeted implementation and prospective validation of defined profiles, including CTi/SV morphology.
Stand-alone disease diagnosis or universal replacement of invasive methods	Not established.	Should not be claimed without application-specific evidence and, where relevant, pressure measurements.

Application or measurement role	Current evidence position	Appropriate conclusion
PhysioFlow-guided improvement in hard outcomes	Sparse and strategy dependent.	A worthwhile implementation question, not a prerequisite for accepting the underlying measurement platform.
eORTA and ancillary vascular outputs	Coherent but incompletely translated development pathway.	Scientifically credible exploratory assets requiring contemporary construct and implementation work.

Clinical-readiness position. The accumulated literature is sufficient to support PhysioFlow as a mature measurement and physiological-phenotyping platform. It is not sufficient to treat every derived variable as a stand-alone diagnostic test or to apply one decision threshold across diseases. Those two statements are compatible and should appear together.

8.5. Evidence standards and the bias of adoption

Established technologies benefit from an adoption advantage. Clinicians know their limitations, have learned how to work around them, and often judge new methods against an idealised version of the incumbent rather than against its observed precision, operator dependence and outcome evidence. PhysioFlow should not face a higher evidential hurdle because it is newer or less embedded, but neither should it receive a lower standard merely because existing methods are imperfect.

The pulmonary-artery catheter is an instructive comparator. The meta-analysis by Shah et al. (2005), covering 13 randomised trials and 5,051 critically ill patients, found neither mortality benefit nor shorter hospital stay from pulmonary-artery-catheter use, despite the catheter's central historical role. This did not make the measured pressures and flows physiologically meaningless; it showed that information improves outcomes only when linked to an effective interpretation and treatment strategy. The same logic should govern outcome demands placed on non-invasive monitoring.

The reference methods are also less absolute than their labels suggest. Hamilton et al. (2025) found that direct Fick and thermodilution led to different haemodynamic classifications in 18 of 152 patients with pulmonary hypertension (11.8%). During exercise, Siuba et al. (2026), from the Cleveland Clinic team including Tonelli, also examined how the choice between thermodilution and direct Fick affects exercise pulmonary-hypertension classification. These comparisons show that disagreement between accepted invasive methods can affect clinical interpretation. Such evidence does not excuse a poor PhysioFlow comparison; it supports assessing the uncertainty of both methods rather than assigning all disagreement to the non-invasive device.

A symmetrical evidence standard would compare technologies across the same dimensions: acquisition risk and burden; absolute agreement; repeatability; operator and patient dependence; response sensitivity; physiological construct validity; clinical discrimination; availability during exercise; scalability; and evidence that a defined use changes decisions or outcomes. PhysioFlow is particularly strong in non-invasive continuity, exercise feasibility and integrative response measurement. It is less mature in externally validated application-specific decision pathways. That is a balanced comparison, not an appeal to lower standards.

8.6. The limitations that remain material

- The corpus is heterogeneous: protocols, populations, device generations, comparators and reported variables differ substantially.
- Many application studies are small, single-centre or mechanistic; abstracts contribute useful historical signals but cannot carry the same weight as complete peer-reviewed reports.
- Publication and selection bias are plausible. A favourable literature cannot be assumed to include every unsuccessful acquisition or unpublished null analysis.
- IFU compliance and signal-quality reporting are inconsistent. Some adverse or ambiguous studies cannot be attributed cleanly to device performance, comparator error, protocol, software generation or biological variability.
- Several research groups have produced multiple reports from overlapping cohorts. Publication count must not be confused with independent replication or unique-patient count.

- The evidence is strongest for measurement, trending and physiological phenotyping. It is less complete for stand-alone diagnosis, prescriptive thresholds, clinician decision impact and improved hard outcomes.
- The clinical and medico-legal consequences of additional information depend on actionability. Poorly contextualised signals may create false reassurance, defensive over-investigation or patient anxiety; future implementation work should therefore test interpretation pathways as well as measurement performance.
- Orientation coding is complete at documentary-record level in the publication matrix, but publication families, overlapping cohorts and exact participant totals still require ongoing reconciliation.

These limitations narrow claims; they do not reset the evidence base to zero. They identify where confidence should be conditional and where the next study can be most informative.

8.7. What further evidence should—and should not—do

The default conclusion should no longer be a generic call for “more studies”. Repeating small feasibility exercises without a defined decision consequence would add little. The technology does not need to be re-proven from first principles in every new population. New work should close a named boundary or test a clinical action.

- Maintain the living documentary audit: reconcile publication families, extract missing sample sizes, document new device confirmations and review orientation when fuller data become available.
- Use a concise IFU-compliance and signal-quality checklist in every future report, including device and software generation, electrode status, skin preparation, calibration, data-retention rules and the proportion of analysable recordings.
- Prioritise transparent data sharing and independent reanalysis, especially when conclusions—favourable or adverse—depend on individual limits of agreement, unexpected findings or disputed acquisition conditions.
- For CTi and stroke-volume morphology, test prespecified profiles in independent cohorts rather than relying only on peak values or simple rest-to-peak deltas.
- Choose a small number of high-value clinical gaps in which continuous non-invasive exercise haemodynamics could plausibly change classification, rehabilitation planning or diagnostic sequencing, then test decision impact prospectively.
- Evaluate implementation and economic consequences alongside accuracy: test completion, avoided procedures, time to explanation, clinician cognitive burden, patient understanding, scalability and the consequences of false reassurance or false escalation.
- For eORTA, first confirm the present implementation and modern construct validity before pursuing outcome claims.

Research priority. The next decisive PhysioFlow studies should not ask again whether a signal can be obtained. They should ask whether a prespecified, IFU-compliant haemodynamic interpretation improves a defined clinical decision, in a population where the present pathway leaves an acknowledged gap.

8.8. Final synthesis

For assessment of exercise reserve and the timing of changes in CTi or stroke-volume trajectories, a standardised incremental exercise test is particularly informative because haemodynamics can be related continuously to increasing workload and heart rate. A plateau after an appropriate initial rise can be physiological; little initial augmentation followed by a plateau at an unusually low workload suggests limited haemodynamic adaptation and warrants contextual interpretation. A subsequent decline despite increasing workload and heart rate is a distinct pattern, although a late decline at very high heart rates may reflect shortened filling time. An insufficient fall in vascular resistance is one possible contributor to limited adaptation, but cannot be inferred from the profile alone. These are interpretative principles, not universally validated diagnostic thresholds; constant-load exercise and recovery remain useful for other physiological questions.

- PhysioFlow is supported by a broad, twenty-five-year, multidisciplinary body of evidence rather than by one pivotal paper.
- The publication matrix contains 328 unique documentary records, including 262 records classified as articles and 49 abstract-related records.
- The documented literature represents approximately 9,000 reported human participant enrolments, with a prudent current range of 8,000–10,000 and explicit overlap caveats.
- Across comparative studies, inferiority is not generally observed; acceptable or clinically coherent absolute values are reported in most defined settings, particularly with contemporary systems and documented IFU-

compliant acquisition. The few discordant results remain visible, and universal numerical interchangeability should not be assumed.

- Across controlled studies, useful repeatability, dynamic sensitivity and physiological coherence recur as strengths, while the magnitude of individual change that can be interpreted depends on protocol, population, signal quality and measurement error.
- The repeated, multidisciplinary findings support a mature measurement platform, not a technology awaiting its first validation. They justify assessing remaining uncertainties application by application, while requiring general criticisms to account for the whole corpus and the conditions under which measurements were obtained.
- Across all 314 evaluable records in the publication matrix, 89.5% are favourable, 5.7% neutral, 3.8% mixed/non-conclusive and 1.0% adverse. These documentary-record proportions are not independent-study success rates or validation accuracy estimates; the narrower validation/reliability subset contains 26 favourable, 11 mixed/non-conclusive and 3 adverse records.
- The absence of a single universal outcomes trial should not be confused with absence of validation. Measurement platforms create value through the decisions built around them.
- The safety contribution of additional haemodynamic information depends on disciplined interpretation: a clearly abnormal trajectory may warrant caution and review, while uncertain findings should not trigger automatic escalation. Actionability is the bridge between more information and safer care.
- A fair comparison must correct for adoption bias and apply symmetric evidential standards to PhysioFlow and incumbent technologies.
- The future programme should move from repeated proof of feasibility toward independent profile validation, transparent quality reporting and targeted decision-impact studies.

Overall editorial conclusion. The PhysioFlow corpus is not a substitute for application-specific clinical judgement, but it is far too extensive and internally coherent to be dismissed as preliminary. Taken as a whole, it supports a mature, reproducible and responsive non-invasive haemodynamic platform whose principal remaining challenge is translation into selected clinical pathways—not foundational technological credibility.

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★ = *landmark/core publication. Flags at the end of an entry indicate first- and last-author affiliation countries where available; a single flag is shown when identical.*

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