Structural and Functional Determinants of Oxygen Transport in Exercise: The Role of Total Hemoglobin Mass

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ABSTRACT

Cardiac hemodynamics during exercise depend on both structural and functional adaptations of the oxygen transport system. This narrative review summarizes the knowledge on total hemoglobin mass (tHbmass) as a structural determinant of convective oxygen transport, and cardiac output and hemodynamic responses as key functional determinants, with attention to sex-related differences and clinical translation. We describe carbon monoxide rebreathing as the preferred method for quantifying tHbmass, outline typical values in untrained and endurance-trained men and women, and discuss the contributions of genetics, training, altitude exposure, and blood manipulation to inter-individual variation. The association between tHbmass and maximal oxygen uptake, its sport-specific distribution, and emerging clinical applications in the differential diagnosis of anemia and risk stratification are highlighted. We then review the regulation of cardiac output and arteriovenous oxygen difference during dynamic exercise, compare invasive and noninvasive techniques for their assessment, and summarize consistent sex differences in stroke volume, cardiac output, blood volume, and oxygen-carrying capacity. Across both domains, major gaps remain, particularly in the paucity of data in women and elite athletes studied at or near their physiological limits. Integrative assessments combining tHbmass, blood volume, and exercise hemodynamics may improve the understanding of both normal performance and cardiovascular pathology.

KEYWORDS

cardiac output; total hemoglobin mass; exercise; woman; elite athlete; man; oxygen transport systems

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INTRODUCTION

The total hemoglobin mass (tHbmass) represents the total amount of hemoglobin in circulation and is a key determinant of blood oxygen-carrying capacity. Unlike hemoglobin concentration (Hb), which can be influenced by plasma volume changes, tHbmass directly reflects the oxygen transport potential and correlates strongly with maximal oxygen uptake (VO_2max) and endurance performance (12, 13). An increase of 1 g in tHbmass is estimated to raise VO_2max by ~4 $mL \cdot min^{-1}$ (12). Elite endurance athletes have substantially higher tHbmass than untrained individuals – on average about 35% greater – enabling superior aerobic performance (10, 14). This expansion can be even more pronounced (by an additional ~14%) in athletes native to high altitude (e.g. ~2600 m) (15, 16). In contrast, hemoglobin concentration alone often fails to distinguish athletic adaptations, as endurance athletes typically expand plasma volume such that (Hb) remains within the normal range despite elevated tHbmass (10). Indeed, numerous studies have confirmed a strong relationship between VO_2max and tHbmass or blood volume, whereas (Hb) is a poor predictor of aerobic capacity (12). These observations underscore the importance of tHbmass as a more physiologically relevant marker of oxygen transport in sports hemodynamics. This chapter reviews the methods used to measure tHbmass, the physiological underpinnings and variability of tHbmass, and its applications in athletic and clinical contexts, following a systematic and evidence-based approach.

MEASUREMENT TECHNIQUES

Determining tHbmass requires measuring the total circulating hemoglobin, which can be achieved through dilution techniques. Historically accepted gold standards involved the infusion of tracers (e.g. radioisotope-labeled erythrocytes for red cell volume and albumin for plasma volume) (17). However, tracer methods are costly and invasive, making them impractical for routine use. In sports and clinical research, the carbon monoxide rebreathing method has become the preferred technique for measuring tHbmass, owing to its accuracy comparable to radioactive methods and minimal health risk (15, 18, 19). The principle, introduced by Haldane in 1900, is to inhale a small dose of carbon monoxide (CO) mixed with oxygen and rebreathe it in a closed circuit for a short period. CO has a high affinity for hemoglobin; thus, a known quantity of CO binds to a proportion of the circulating Hb. By measuring the increase in carboxy hemoglobin (%HbCO) in the blood before and after rebreathing, the total Hb Mass can be calculated using the dilution principle. In essence, the absorbed CO dose and the change in %HbCO allow computation of tHbmass, given the known CO–Hb binding capacity and molecular weight of hemoglobin (15, 18). This method has been refined over decades and is now highly reliable when proper protocols are followed. It has been validated against isotope dilution with a very high correlation and has been shown to detect even small changes in blood volume (17, 20). Because only a few milliliters of blood are sampled and CO doses are low, the procedure is safe and well-tolerated, enabling widespread application in both athletes and patients (15, 19).

PROTOCOL AND ADVANCES

Traditional CO rebreathing protocols require approximately 10 min of rebreathing a $CO–O_2$ gas mixture and multiple blood samples. Newer optimized protocols have dramatically shortened this procedure. Schmidt and Prommer introduced a 2-minute CO bolus rebreathing method that yields tHbmass values equivalent to the longer protocol(18). In this optimized method, a bolus of CO (usually ~1.0–1.5 $mL \cdot kg^{-1}$ body weight of CO gas) is inhaled and rebreathed for only 2–3 minutes, which accelerates CO uptake and distribution. Blood is obtained a few minutes before and after rebreathing to measure %HbCO. The shortened protocol was shown to produce virtually identical tHbmass results to the 10-minute method, with a typical error of ~1.7% and narrow limits of agreement (18). Importantly, such precision is sufficient to detect physiologically relevant changes; for example, a ~1.5–2.0% increase in tHbmass can be reliably identified above technical error (15, 16). The optimized CO rebreathing test has a minimal impact on the subject's well-being, aside from a transient slight reduction in maximal exercise capacity immediately after the test due to a small residual CO load. Overall, recent methodological advances have made tHbmass measurement faster and more feasible for routine and repeated testing (15).

BIOLOGICAL SIGNIFICANCE

tHbmass fundamentally determines the oxygen transport capacity of blood. Cross-sectional studies have demonstrated that top-endurance athletes possess markedly greater tHbmass relative to body size than non-athletes, often in the range of ~13–16 g of hemoglobin per kg body weight ($g \cdot kg^{-1}$) for elite males, compared to ~9–11 $g \cdot kg^{-1}$ in untrained men. (Females generally have ~1–2 $g \cdot kg^{-1}$ lower values than males of similar training status owing to lower testosterone and higher iron losses.) For instance, highly trained male endurance athletes average ~13.5 $g \cdot kg^{-1}$, whereas untrained males are ~10 $g \cdot kg^{-1}$. This difference of ~35–50% in tHbmass between elites and untrained individuals is a major contributor to the superior VO_2max of athletes (7, 8, 13, 21). Such a large tHbmass expansion cannot be explained by hemoconcentration; in fact, endurance training triggers plasma volume expansion that keeps (Hb) within the normal range, masking the true increase in oxygen-carrying capacity (10, 13). Thus, measuring tHbmass provides deeper insights into an individual's aerobic potential that hemoglobin concentration alone would miss.

TRAINABILITY AND ALTITUDE

There is an ongoing debate on the extent to which tHbmass can be augmented by training versus genetic

determination. Long-term athletic training at sea level appears to have only a modest effect on tHbmass once initial adaptations are complete (22). In well-trained adults, tHbmass tends to plateau, suggesting a genetic ceiling for everyone (22, 23). A controlled cross-sectional analysis found that 16-year-old competitive endurance athletes had significantly lower tHbmass (~12.4 $g \cdot kg^{-1}$) than 21-year-old athletes (~14.2 $g \cdot kg^{-1}$), but there was no further increase by age 28 despite continued elite training (24). These findings imply that substantial gains in tHbmass occur during late adolescence with intensive training, but additional years of high-level training do not further boost tHbmass in adulthood. As a result, high tHbmass in elite adult athletes is likely to reflect both training during developmental years and innate predisposition. Endogenous erythropoietin stimulation from hypoxic exposure is one of the few potent stimuli that increase tHbmass beyond normal training effects. Altitude exposure (e.g., living high at 2000–2500 m for >14 h/day while training low) typically elicits a 4–8% increase in tHbmass over ~3–4 weeks (15, 22). A meta-analysis-like synthesis in this area suggests an average ~6.5% tHbmass gain after ~3 weeks above 2500 m. This boost, while meaningful, often does not completely bridge the gap to athletes who grew up at altitude in American Ands (who inherently have ~14% higher tHbmass) (15, 16). Contrary to this finding, Kenyan elite runners have similar tHbmass to European low landers, brining different root causes of the dominance of Eastern African runners in endurance running events (25). However, altitude training or simulated hypoxia remains a widely used strategy for stimulating erythropoiesis in athletes. Conversely, under normoxic conditions, true increases in tHbmass are slow and limited, and one study concluded that prolonged sea-level endurance training yields only minor changes in tHbmass, reinforcing that exceptionally high tHbmass in elite athletes is largely genetic or reliant on hypoxic exposure (22). Notably, exogenous erythropoietin (EPO) doping or blood transfusions can artificially elevate tHbmass well beyond an athlete's natural baseline, significantly enhancing oxygen delivery (16). This has implications for both the performance and anti-doping efforts, as discussed below.

ACCURACY AND PRECISION

Achieving high precision in tHbmass measurement is critical, especially for tracking small changes (e.g., due to training or doping). The typical analytical error (coefficient of variation) of modern CO rebreathing is approximately 1–2% when standardized protocols are used (18, 20). Rigorous attention to methodological details can further reduce the errors. For example, using a multi-wavelength co-oximeter to measure %HbCO, researchers recommend taking multiple replicate measurements on the blood sample (e.g., ≥5) and ensuring that the administered CO dose raises %HbCO by at least 5–6% above the baseline (26). Under these conditions, the technical error becomes very low, and a change above ~1.5% in tHbmass can be regarded as real (exceeding the typical error) (20). The CO rebreathing method itself is highly accurate if there are no errors in dosing or sampling, and any deviation in the results is more likely due to technical issues (e.g., leaks in the system, errors in CO volume, or spectrophotometer variability) than to the method principle. Comparisons between CO rebreathing and direct RBC mass measurements showed virtually no systematic bias (17). Thus, when proper calibration, dosing, and replicates are in place, tHbmass can be measured reproducibly for both individual monitoring and research purposes.

REFERENCE VALUES

A robust body of data now defines normal tHbmass ranges. Table 1 summarizes the classification ranges for tHbmass (normalized to body weight) in healthy men and women from untrained status to elite endurance athletes. These values, derived from a large dataset of ~1000 measurements, illustrate the spectrum of tHbmass in relation to athletic proficiency (21).

Tab. 1 Classification of total hemoglobin mass (tHbmass) relative to body weight in endurance athletes vs. untrained populations. Values are typical ranges; "highest recorded" denotes the extreme high values documented in the authors' dataset (21).

Category	Male tHbmass ($g \cdot kg^{-1}$)	Female tHbmass ($g \cdot kg^{-1}$)
Untrained (normal)	9.5–10.5	8.5–9.5
Recreational athlete	10.5–12.0	9.5–10.5
Regional-level athlete	12.0–13.5	10.5–11.5
National elite	13.5–15.0	11.5–12.5
International elite	14.5–6.5	12.0–13.5
Highest recorded	~20.1	~14.5

These ranges show that even within endurance sports, substantial variation exists. For example, an international-class male endurance athlete often has around 15 $g \cdot kg^{-1}$, whereas an untrained man is around 10 $g \cdot kg^{-1}$. Women's values are roughly 1–2 $g \cdot kg^{-1}$ lower in each category. Notably, tHbmass is strongly linked to fat-free mass as well – expressing tHbmass per lean mass can reduce differences between groups, since endurance athletes tend to have less body fat (8, 13). Nonetheless, the absolute tHbmass is a decisive factor for aerobic power. These reference data are useful in both sports science (to gauge if an athlete's tHbmass is commensurate with their competition level) and in identifying aberrant values that might indicate blood manipulation (16).

ATHLETIC APPLICATIONS

In high-performance sports, tHbmass measurements are used to monitor the effects of training interventions or altitude camps. It is thought to be suitable for potential blood doping; however, different approaches have been adopted by the World Antidoping Agency for various reasons (27, 28). A practical application is tracking an athlete's tHbmass before and after an altitude training camp. For instance, a 3-week camp at a moderate altitude might

increase tHbmass by several percent, and measuring this change can confirm whether the athlete responded as expected (15). In one analysis, only 56–69% of athletes showed a meaningful tHbmass increase after altitude exposure, partly due to individual variability in erythropoietic response (29). Understanding such responses can help coaches personalize altitude training strategies. tHbmass data are also valuable for anti-doping programs. The Athlete Biological Passport (ABP) currently monitors indirect markers [hematocrit (Hb), reticulocytes], but tHbmass has been proposed as a more direct indicator of blood manipulation. Research has shown that using tHbmass in testing could enhance the detection of blood doping, since an artificial boost (via EPO or transfusion) would elevate tHbmass outside an athlete's individual baseline range (16). Apart from doping control, another application is talent identification and athlete development. Since a large tHbmass is advantageous for endurance performance, some have speculated that measuring tHbmass in youth athletes could help predict future potential (23). However, as Steiner and Wehrlin observed, 16-year-old athletes had not reached adult tHbmass levels and there was high overlap with non-athletes, suggesting caution in using tHbmass alone as a talent predictor. However, exceptionally high tHbmass values in mature athletes are often indicative of an extreme endurance phenotype or specific adaptation (e.g., altitude), and such data can inform the training focus or the need for medical evaluation if values are anomalously high (24).

In terms of sport-specific variation, endurance disciplines generally show the highest tHbmass. A 2013 study of athletes across different sports found that elite endurance athletes (long distance runners, cyclists, triathletes, cross-country skiers, etc.) all had similarly high relative tHbmass (~13 $g \cdot kg^{-1}$ in males, ~10–11 $g \cdot kg^{-1}$ in females), whereas power-oriented athletes had significantly lower values. For example, elite male judo athletes were measured at ~11.2 ± 0.7 $g \cdot kg^{-1}$, comparable to untrained men, despite their highly competitive level (13). Such findings indicate that a high tHbmass is not a prerequisite for success in purely anaerobic or mixed sports such as judo, and training in those sports does not stimulate large hematological adaptations. On the other hand, sports with a major aerobic component consistently show elevated tHbmass; even among endurance athletes, subtle differences can exist (e.g., professional road cyclists tend to have slightly higher mean tHbmass than swimmers or triathletes) (7, 8). This sport specificity reflects the differing demands and training stimulus; sustained endurance training and high cardiac outputs appear necessary to maximize erythropoiesis and blood volume. Thus, tHbmass measurement allows objective comparison of hematological fitness across sports and can aid in identifying whether an athlete's blood profile is in line with their sport's demands.

CLINICAL APPLICATIONS

Beyond athletics, tHbmass assessment has emerging clinical relevance, particularly in the evaluation of anemia and cardiorespiratory fitness. Traditional anemia diagnosis relies on hemoglobin concentration; however, this can be misleading in conditions where the plasma volume is abnormal. Measuring total hemoglobin directly can distinguish between true anemia (reduced total Hb) and "dilutional" anemia (normal total Hb with expanded plasma volume) (30). Otto et al. demonstrated this in patients with chronic heart failure and liver disease. Despite low hemoglobin concentrations, many of these patients had near normal tHbmass; their low (Hb) was largely due to excess plasma volume. In heart failure patients, tHbmass and (Hb) were poorly correlated, whereas plasma volume explained the variance in (Hb) much better (10). Some individuals with identical tHbmasses were classified as "anemic" or not anemic solely based on fluid volume differences, meaning that conventional labs can lead to misdiagnosis and potentially inappropriate therapy. For example, a patient with a normal total Hb level could appear anemic if they are hypervolemic, potentially prompting unnecessary investigations or iron/EPO therapy, when the real issue is fluid management. By measuring tHbmass (via a quick CO rebreathing test), clinicians can gain clarity: if tHbmass is normal, efforts can focus on reducing plasma volume overload rather than stimulating erythropoiesis. Given that the CO rebreathing method is now simple, safe, and inexpensive, the authors have advocated for its routine use in hospital settings to improve anemia assessment (10).

Another clinical application is in preoperative evaluation and critical care. The total Hb mass has been found to correlate with objective exercise capacity. In pre-surgical patients undergoing cardiopulmonary exercise testing (CPET), tHbmass was significantly associated with peak oxygen consumption, whereas conventional (Hb) did not (10). This suggests that measuring tHbmass could potentially better stratify patients' fitness and oxygen delivery reserve before major surgery, potentially aiding in risk assessment or in guiding preoperative optimization (e.g., deciding on erythropoietic therapy or blood transfusion if tHbmass is truly low). In chronic hemodialysis patients, tHbmass measurements have provided insight into anemia management. A recent study using CO rebreathing in dialysis patients found that most patients had expanded blood and plasma volumes and that their anemia was largely dilutional. Specifically, 18 of the 19 patients met the anemia criterion based on hemoglobin concentration, but when assessed by total red cell volume (a function of tHbmass), only 9 patients had a genuinely low RBC volume (true anemia). The other samples had a normal red cell mass diluted in excess plasma (30). This distinction is clinically important; treatment with erythropoiesis-stimulating agents might be unnecessary or less urgent in patients whose total RBC mass is adequate. Instead, interventions could target fluid removal to correct the hematocrit. These examples illustrate the clinical value of tHbmass measurement in differentiating anemia etiologies and tailoring treatment. As the method becomes more accessible with new devices such as Detalo Clinical (Detalo Health, Denmark) and standardized protocols are being developed, we are likely to see broader adoption in both sports medicine and clinical medicine to assess hemoglobin mass as a vital sign of oxygen transport capacity (15, 30, 31).

HEMODYNAMICS AND EXERCISE

GENERAL DESCRIPTION OF HEMODYNAMICS DURING EXERCISE

During dynamic exercise, the cardiovascular system undergoes profound adjustments to meet the increased metabolic demands of working muscles. Cardiac output increases dramatically and approximately linearly with oxygen uptake (VO_2) (32). In healthy individuals, an increase in cardiac output of approximately 5–6 L is required for each 1 L increase in VO_2 above rest. This robust linear relationship holds across age and fitness levels, with trained athletes capable of raising cardiac output up to 5–6 times resting levels, and in concert with increased oxygen extraction, achieving a 12-to 18-fold increase in oxygen delivery to tissues (33). For example, an untrained male might raise cardiac output from ~5 L/min at rest to ~20–25 L/min at maximal exercise, while simultaneously increasing the arteriovenous O_2 difference (a-v O_2 diff) threefold (e.g. from ~5 to 15 mL O_2 per 100 mL blood), enabling VO_2 to rise from ~0.3 L/min at rest to ~3.0 L/min or more at peak effort. In trained endurance athletes, cardiac output can reach 30–40 L/min, highlighting the extraordinary capacity of the heart to augment the flow during exercise (3).

The increase in cardiac output is mediated by increases in both heart rate and stroke volume. The heart rate increases linearly with the workload. Stroke volume also increases, especially from rest to moderate intensities, owing to enhanced venous return (muscle pump and venoconstriction increasing preload) and augmented myocardial contractility (sympathetic inotropy). In untrained individuals, stroke volume may plateau at approximately 40–50% of VO_2max as the filling time shortens at high heart rates (3). However, in highly trained subjects, stroke volume can continue to rise or at least be maintained up to maximal exertion, owing to cardiac remodeling and superior diastolic function. The net result is that cardiac output ($\dot{Q}$) increases approximately linearly with VO_2, maintaining a ratio of ~5–6 L blood per 1 L O_2 in normoxic exercise (33). This coupling ensures adequate oxygen transport to active muscles.

Peripheral vascular adjustments are accompanied by central cardiac response. Systemic vascular resistance decreases substantially during exercise because of metabolic vasodilation in contracting muscles. Large muscle mass exercises (running, cycling, etc.) trigger an expansive dilatation of arterioles, which can reduce total peripheral resistance to a quarter of resting values. Arterial blood pressure is usually maintained or even elevated during dynamic exercise owing to the feed-forward and reflexive cardiovascular control mechanisms that simultaneously increase cardiac output to offset the drop in resistance. The mean arterial pressure typically rises modestly (e.g., from ~90 mmHg at rest to 110–130 mmHg at peak exercise) despite the large decrease in resistance, indicating that the flow increase is proportionally even greater. The result is a finely tuned cardiovascular response: heart rate and contractility increase (raising cardiac output), vein constriction (augmenting preload), and arterioles in active muscles dilate (lowering afterload), all coordinated to deliver oxygen when needed while maintaining perfusion pressure (3).

It was historically assumed that maximal exercise is primarily "cardio-limited", meaning that the pumping capacity of the heart is the rate-limiting factor for oxygen delivery and VO_2max. Indeed, maximum cardiac output correlates strongly with VO_2max in homogeneous groups, and interventions, such as endurance training or blood doping, that enhance cardiac output generally raise VO_2max (34). However, a large body of evidence indicates that peripheral factors play a critical role in governing circulatory response and exercise capacity (35). The classic work of Guyton et al. demonstrated that the heart cannot increase output unless the peripheral vasculature "allows" it via sufficient venous return and vasodilation, and that the circulation is demand-driven by the muscles (36). Furthermore, Rowland (2005) emphasized that focusing solely on cardiac determinants "may not be appropriate and could cloud our understanding" of aerobic fitness, since peripheral arteriolar dilation and the skeletal muscle pump largely dictate the increase in flow during exercise in healthy individuals (37). In other words, the heart responds to the demands set by the muscles and is a servant to the periphery. Thus, optimal exercise hemodynamics require the integration of central and peripheral adaptations such as a strong heart, adequate blood volume and hemoglobin mass, responsive vasculature, and efficient muscle oxygen extraction. Deficits in any component can limit overall performance.

MEASUREMENT TECHNIQUES OF HEMODYNAMICS DURING EXERCISE

Accurate measurement of hemodynamic variables (particularly cardiac output) during exercise is challenging. Historically, the gold-standard methods were invasive: the Direct Fick method and indicator dilution methods (e.g., thermodilution) performed with cardiac catheters (3). Although invasive techniques can be very accurate, they are clinically and logistically difficult for exercise studies. Consequently, a variety of less-invasive and non-invasive methods have been developed. This section outlines the key techniques and discusses their accuracy and utilization in exercise testing.

INVASIVE REFERENCE METHODS

The Direct Fick method determines cardiac output ($\dot{Q}$) by measuring whole-body oxygen uptake (VO_2) and arteriovenous O_2 content difference. In practice, VO_2 is obtained via metabolic gas analysis, and blood samples are drawn from a systemic artery and mixed venous blood (via a pulmonary artery catheter) to measure O_2 content. Cardiac output was calculated as $\dot{Q} = \frac{\dot{V}O_2}{C_aO_2 - C_vO_2}$ (Fick equation). When performed carefully with measured VO_2 and blood gases, the direct Fick test is highly accurate, particularly under steady-state conditions. Its drawbacks include the need for invasive PA catheterization and technical difficulties during exercise (3).

In contrast, the thermodilution method involves injecting a cold saline bolus into the right atrium and measuring the downstream temperature change in the pulmonary

artery. CO was computed from the thermodilution curve using the conservation of energy principles (2). Thermodilution is widely used in clinical settings (e.g., intensive care) and is convenient for repeated measures at rest. However, it may be less accurate during vigorous exercise owing to factors such as injectate warming and rhythm or valvular issues. Under ideal conditions, both Fick and thermodilution have errors of the order of 5–15% (2). Even in patients, ethical considerations limit invasive hemodynamic exercise testing to special circumstances. As one group noted, "reference methods often require catheterization of the pulmonary artery, which is not only arduous but also associated with risks," motivating the search for alternatives (33).

IMPEDANCE CARDIOGRAPHY (ICG)

Impedance cardiography is a noninvasive method that has gained popularity for exercise testing because it can provide continuous beat-by-beat estimates of stroke volume and cardiac output. The technique implemented in devices such as PhysioFlow (Menatec, France) involves applying electrodes to the thorax to measure changes in electrical impedance with each cardiac cycle. Blood volume changes in the aorta during systole transiently decrease thoracic impedance. By analyzing the impedance waveform, stroke volume can be estimated using proprietary algorithms. Modern impedance cardiographs use improved signal processing (signal-morphology ICG) to better account for motion and artifacts, making them more suitable for exercise conditions (33). ICG is completely noninvasive (just surface electrodes), easy to apply, and can track dynamic changes continuously during exercise. However, accuracy and validation are long-standing concerns. Early studies of older ICG systems showed mixed results; however, newer devices (e.g., PhysioFlow) have been validated against invasive standards in various settings. An important 2015 study by Siebenmann et al. directly compared four methods (modified Fick, inert gas rebreathing, PhysioFlow impedance, and pulse contour analysis) in subjects during incremental cycling in normoxia and hypoxia. They found that all methods detected the increase in cardiac output with intensity, but the absolute values and $\dot{Q}$–VO_2 slopes differed by up to 50% between devices. In normoxia, the "true" slope (by Fick) was ~5 L/min increase in $\dot{Q}$ per 1 L/min VO_2, and the PhysioFlow gave a similar slope (~6 L/min per 1 L VO_2, within the 95% CI of Fick). This suggests that impedance cardiography may provide more consistent and physiologically plausible estimates during exercise than other noninvasive methods (33).

Despite these favorable results, one must consider that impedance cardiography requires careful application and device-specific calibration. Motion artifacts, although mitigated in newer devices, can still pose challenges during high-intensity exercise (especially running or upper-body movement). Legendre et al. (2021) utilized impedance cardiography during cardiopulmonary exercise testing in chronic heart failure and found that peak exercise cardiac output measured by ICG was the strongest hemodynamic predictor of prognosis, independent of VO_2peak (38).

INERT GAS REBREATHING

Another noninvasive approach is inert gas rebreathing (e.g., using the Innocor, Cosmed, Italy). Subjects rebreathe a small volume of a blood-soluble inert gas (such as nitrous oxide) mixed with oxygen for a few breaths. Uptake of the gas by pulmonary blood flow causes its concentration to decrease, and the cardiac output is estimated (applying the Fick principle for inert gas). Rebreathing is appealing because it measures $\dot{Q}$ from gas exchange without blood draws or catheters. It has been validated at rest and during mild exercise against direct Fick and thermodilution, often showing mean differences of <1 L/min. However, during high-intensity exercise, these assumptions can break down. Indeed, Siebenmann et al. found that the Innocor systematically read lower $\dot{Q}$ than other methods at maximal exercise, and more than one-third of the Innocor readings were implausibly low (implying negative venous O_2 content) (33). Thus, inert gas rebreathing is now considered inconvenient for exercise at near-maximal cardiac output.

PULSE CONTOUR METHODS

Pulse contour analysis continuously estimates cardiac output from the arterial pressure waveform recorded at the finger or wrist. It is noninvasive and provides beat-by-beat data. However, it often requires individual calibration (e.g., with blood pressure and demographic data) and can be sensitive to vasomotor changes (which are profound during exercise). For example, Nexfin (Bmeye, Amsterdam, Netherlands) failed to capture an increased cardiac output response during hypoxic exercise (33). The likely explanation is that changes in the vascular tone and pressure waveform shape under different conditions can confound pulse contour algorithms.

HEMODYNAMIC DIFFERENCES BETWEEN MEN AND WOMEN DURING EXERCISE

Men and women exhibit noteworthy differences in cardiovascular structure and function, which translate into distinct hemodynamic responses during exercise. On average, men achieved higher absolute cardiac outputs and VO_2max values than women, even when matched for age and training status (39). These differences are largely attributable to the body size, composition, and sex-related physiological factors.

CARDIAC OUTPUT AND STROKE VOLUME

Women generally have smaller resting and maximal stroke volumes than men. This is partly due to smaller cardiac dimensions (lower left ventricular end-diastolic volume [LVEDV] and myocardial mass) in females. Even when body size is considered, men tend to have a slightly higher stroke index (SV normalized to the body surface area) at rest and during exercise (32). For instance, in one study of young adults matched by fitness, untrained men had a maximal stroke volume ~20% greater than women (e.g., ~120 mL vs. ~100 mL), and even after normalizing to body size, a small gap remained (32, 40). As a result,

Tab. 2 Hemodynamic differences at peak exercise between men and women (32).

Parameter	Men vs Women (peak exercise)
Heart Rate (max)	~No significant difference (age-adjusted)
Stroke Volume (max)	Higher in men (even after size adjustment)
Cardiac Output (max)	Higher in men (men often >20 L/min vs women ~15–20 L/min)
Cardiac Index ($\dot{Q}$/BSA)	Slightly higher in men or similar
Ejection Fraction	Similar or slightly higher in men
Arterio-venous O_2 diff	Higher in men (women extract less O_2)
Systemic Vascular Resistance	Lower in women at equivalent work (more vasodilation)

the maximal cardiac output is usually higher in men. A typical maximal $\dot{Q}$ for a healthy, moderately fit male might be 20–25 L/min, whereas for a female with similar fitness, it might be 15–20 L/min. In a representative study, Diaz-Canestro et al. (2022) found that peak exercise cardiac output (adjusted for body mass) was ~25% lower in women than in men (women: ~13 L/min normalized vs. men: ~17 L/min normalized), corresponding to lower VO_2 Peak values (42 ± 9 vs. 50 ± 11 mL/min) (39). The primary driver of the cardiac output difference was stroke volume, since maximal heart rates were not significantly different between sexes (both typically reached ~85–90% of the age-predicted maximum, and actual max HR values were similar when matched by age). Table 2 summarizes the key hemodynamic differences during peak exercise.

The slightly lower stroke volume in women is not solely due to body size. Studies controlling for lean body mass still find women's stroke volume index to be a bit lower (41, 42), implying intrinsic cardiac or hemodynamic differences. Women's left ventricles are not only smaller, but also their blood volume is ~10–20% lower per body weight on average (7, 21). In a crossover experiment, reducing young men's blood volume and hemoglobin to female levels abolished the previously higher exercise LVEDV, SV, $\dot{Q}$, and VO_2peak of men – making them equivalent to women (39). This elegantly demonstrates that blood volume and O_2 carrying capacity are major determinants of the sex gap in hemodynamics and aerobic capacity.

OXYGEN CARRYING CAPACITY AND EXTRACTION

The arterial O_2 content in woman is ~1–2 mL/dL lower than that in men. At maximal exercise, women also tend to have slightly higher mixed-venous O_2 content (i.e., they extract slightly less of the delivered O_2). The net effect is the smaller a-v O_2 difference among women. Indeed, Bassareo and Crisafulli (2020) noted that the one parameter "unanimously" lower in females is the a-vO_2 diff, due largely to lower hemoglobin and O_2 carrying capacity (32). For example, if a man has a maximal a-vO_2 diff of 15–16 mL/100 mL, a woman with a similar fitness might reach ~13–14 mL/100 mL. This is not because women's muscles cannot extract oxygen as a percentage; rather, if a woman starts with an arterial O_2 content of ~18–19 mL/dL (due to lower Hb) and extracts 80%, her venous content may be ~3–4 mL/dL. A man starting at ~20 mL/dL and extracting 80% would go down to ~4 mL/dL; the relative extraction was similar, but the absolute difference was slightly larger for the man due to the higher starting O_2 content (4). Regardless, when normalized for arterial O_2 content, the percentage O_2 extraction is often comparable or even higher in women, which indicates that their muscles are indeed utilizing available O_2 efficiently. However, in absolute terms, a smaller O_2 content means that the maximal arteriovenous O_2 difference is usually a few mL/dL less than that in men. This compounds the effect of a lower cardiac output on VO_2max. (4, 32, 41, 42).

CARDIAC FUNCTIONAL RESERVE

Women have a smaller cardiac reserve primarily due to structure, but functionally, their ejection fraction (EF) at peak exercise is similar to that of men. In fact, some studies found that women can attain a higher EF at max (since their end-systolic volumes are very small), but others show no significant difference (32). Historically, a contentious point was whether women exhibited an earlier plateau in stroke volume than did men. Some early reports suggested that untrained women plateau at ~50% VO_2max whereas men plateau closer to 90% VO_2max, possibly because of less increase in contractility or more constraints on filling. More recent research controlling for fitness and body size indicates that both sexes can increase stroke volume through near-maximal intensities, especially if exercise is upright and tested personnel are trained. For example, Wang et al. (2019) found that even highly trained female endurance athletes did not show a stroke volume plateau before exhaustion (43). Thus, the paradigm that women have a "less robust Frank-Starling mechanism" is not conclusively supported; when appropriately scaled, women's percent increase in stroke volume from rest to max is similar to that of men, but the absolute volumes achieved are lower.

CONCLUSION

In summary, hemodynamics have been studied extensively from both structural and functional perspectives to the deep level of detailed descriptions of biological processes. However, a global picture combining both approaches is still missing, and there is almost no evidence when counting differences in both sexes. In addition, the majority of the studies were conducted on sedentary or generally

active populations. Data from elite athletes reaching human physiological limits are missing for various reasons. This is a challenging field, which might shed light on the biological principles of human physiology and possibly also pathophysiology, as we see in the early adoption of methods such as total hemoglobin mass in clinical practice.

REFERENCES

1. Ream AK. Cardiovascular hemodynamics. JAMA. 1968 May 20; 204(8): 742.
2. Endrys J. Invazivní hemodynamické metody (Thesis). Prague: Charles University, 2004. 116 pp.
3. Stouffer GA, Klein JL. Cardiovascular Hemodynamics for the Clinician. Cardiovascular Hemodynamics for the Clinician: Third Edition. Wiley, 2025. 1–464 p.
4. Proctor DN, Beck KC, Shen PH, Eickhoff TJ, Halliwill JR, Joyner MJ. Influence of age and gender on cardiac output-VO2 relationships during submaximal cycle ergometry. J Appl Physiol (1985). 1998; 84(2): 599–605.
5. Wang JS, Wu MH, Mao TY, Fu TC, Hsu CC. Effects of normoxic and hypoxic exercise regimens on cardiac, muscular, and cerebral hemodynamics suppressed by severe hypoxia in humans. J Appl Physiol. 2010; 109(1): 219–29.
6. Wagner PD. Limiting factors of exercise performance. Dtsch Z Sportmed. 2010; 61(5): 108–11.
7. Zelenkova IE, Zotkin SV, Korneev PV, Koprov SV, Grushin AA. Relationship between total hemoglobin mass and competitive performance in endurance athletes. J Sports Med Phys Fitness. 2019 Feb; 59(3): 352–6.
8. Zelenkova I, Zotkin S, Korneev P, Koprov S, Grushin A. Comprehensive overview of hemoglobin mass and blood volume in elite athletes across a wide range of different sporting disciplines. J Sports Med Phys Fitness. 2019 Feb; 59(2): 179–86.
9. Mujika I, Millet GP, Zelenkova I, Bourdillon N. Hemoglobin Mass and Blood Volume in Swimming: A Comparison Between Highly Trained, Elite, and World-Class Swimmers. Int J Sports Physiol Perform. 2023 Nov 1; 18(11): 1357–61.
10. Otto JM, Plumb JOM, Clissold E, et al. Hemoglobin concentration, total hemoglobin mass and plasma volume in patients: Implications for anemia. Haematologica. 2017 Aug 31; 102(9): 1477–85.
11. Falz R, Fikenzer S, Hoppe S, Busse M. Normal Values of Hemoglobin Mass and Blood Volume in Young, Active Women and Men. Int J Sports Med. 2019; 40(4): 236–44.
12. Schmidt W, Prommer N. Impact of alterations in total hemoglobin mass on VO2max. Exerc Sport Sci Rev. 2010; 38(2): 68–75.
13. Malczewska-Lenczowska J, Sitkowski D, Orysiak J, Pokrywka A, Szygula Z. Total haemoglobin mass, blood volume and morphological indices among athletes from different sport disciplines. Arch Med Sci. 2013; 9(5): 780–7.
14. Heinicke K, Wolfarth B, Winchenbach P, et al. Blood volume and hemoglobin mass in elite athletes of different disciplines. Int J Sports Med. 2001; 22(7): 504–12.
15. Siebenmann C, Keiser S, Robach P, Lundby C. CORP: The assessment of total hemoglobin mass by carbon monoxide rebreathing. J Appl Physiol. 2017; 123(3): 645–54.
16. Jelkmann W, Lundby C. Blood doping and its detection. Blood. 2011; 118(9): 2395–404.
17. Thomsen JK, Fogh-Andersen N, Bulow K, Devantier A. Blood and plasma volumes determined by carbon monoxide gas, 99mTc-labelled erythrocytes, 125 I-albumin and the T 1824 technique. Scand J Clin Lab Invest. 1991 Jan 29; 51(2): 185–90.
18. Schmidt W, Prommer N. The optimised CO-rebreathing method: A new tool to determine total haemoglobin mass routinely. Eur J Appl Physiol. 2005; 95(5–6): 486–95.
19. Karlsen T, Lenian I, Aamot IL, Dalen H. Safety of the CO-Rebreathing Method in Patients with Coronary Artery Disease. Med Sci Sports Exerc. 2016 Jan; 48(1): 33–8.
20. Gore CJ, Hopkins WG, Burge CM. Errors of measurement for blood volume parameters: a meta-analysis. J Appl Physiol. 2005; 99: 1745–58.
21. Schmidt W. Classification of total hemoglobin mass and blood volume. Bloodtec GmbH. 2019.
22. Schmidt W, Prommer N. Effects of various training modalities on blood volume. Scand J Med Sci Sports. 2008; 18 Suppl 1: 57–69.
23. Prommer N, Wachsmuth N, Thieme I, et al. Influence of endurance training during childhood on total hemoglobin mass. Front Physiol. 2018 Mar; 9: 1–9.
24. Steiner T, Wehrlin JP. Does hemoglobin mass increase from age 16 to 21 and 28 in elite endurance athletes? Med Sci Sports Exerc. 2011; 43(9): 1735–43.
25. Prommer N, Thoma S, Quecke L, et al. Total hemoglobin mass and blood volume of Elite Kenyan runners. Med Sci Sports Exerc. 2010; 42(4): 791–7.
26. Ulrich G, Strunz J, Frese F, Bärtsch P, Friedmann-Bette B. Dependence of hemoglobin mass estimation with the optimized CO-rebreathing method on different spectrophotometers. Scand J Med Sci Sports. 2012; 22(2): 224–31.
27. Schumacher YO, Saugy M, Pottgiesser T, Robinson N. Detection of EPO doping and blood doping: The haematological module of the Athlete Biological Passport. Drug Test Anal. 2012; 4(11): 846–53.
28. Jo-Anne Schneider A, Borry P, et al. Future opportunities for the Athlete Biological Passport. Front Sports Act Living. 2022 Nov; 4: 1–6.
29. Nummela A, Eronen T, Koponen A, Tikkanen H, Peltonen JE. Variability in hemoglobin mass response to altitude training camps. Scand J Med Sci Sports. 2021 Jan 1; 31(1): 44–51.
30. Bomholt T, Larsson S, Rix M, et al. Intravascular volumes evaluated by a carbon monoxide rebreathing method in patients undergoing chronic hemodialysis. Hemodial Int. 2020; 24(2): 252–60.
31. Ahlgrim C, Birkner P, Seiler F, et al. Applying the optimized CO rebreathing method for measuring blood volumes and hemoglobin mass in heart failure patients. Front Physiol. 2018 Nov 12; 9: 1603.
32. Bassareo PP, Crisafulli A. Gender Differences in Hemodynamic Regulation and Cardiovascular Adaptations to Dynamic Exercise. Curr Cardiol Rev. 2019 Mar 25; 16(1): 65–72.
33. Siebenmann C, Rasmussen P, Sørensen H, et al. Cardiac output during exercise: A comparison of four methods. Scand J Med Sci Sports. 2015 Feb 1; 25(1): 20–7.
34. Wagner PD. Determinants of Maximal Oxygen Transport and Utilization. Annu Rev Physiol. 1996; 58(1): 21–50.
35. Rowland TW. Circulatory responses to exercise: Are we misreading fick? Chest. 2005; 127(3): 1023–30.
36. Guyton AC. Determination of Cardiac Output by Equating Venous Return Curves with Cardiac Response Curves. Physiol Rev. 1955 Jan; 35: 122–9.
37. Rowland TW. The circulatory response to exercise: role of the peripheral pump. Int J Sports Med. 2001; 22(8): 558–65.
38. Legendre A, Moatemri F, Kovalska O, et al. Responses to exercise training in patients with heart failure. Analysis by oxygen transport steps. Int J Cardiol. 2021 May 1; 330: 120–7.
39. Diaz-Canestro C, Pentz B, Sehgal A, Montero D. Differences in Cardiac Output and Aerobic Capacity Between Sexes Are Explained by Blood Volume and Oxygen Carrying Capacity. Front Physiol. 2022 Mar 17; 13: 747903.
40. Hutchinson PL, Cureton KJ, Outz H, Wilson G. Relationship of cardiac size to maximal oxygen uptake and body size in men and women. Int J Sports Med. 1991; 12(4): 369–73.
41. Fu Q, Levine BD. Cardiovascular response to exercise in women. Med Sci Sports Exerc. 2005 Aug; 37(8): 1433–5.
42. Hossack KF, Bruce RA. Maximal cardiac function in sedentary normal men and women: comparison of age-related changes. J Appl Physiol Respir Environ Exerc Physiol. 1982; 53(4): 799–804.
43. Wang E, Solli GS, Nyberg SK, Hoff J, Helgerud J. Stroke volume does not plateau in female endurance athletes. Int J Sports Med. 2012; 33(9): 734–9.