Circulatory Responses to Exercise*

Are We Misreading Fick?

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The Fick equation holds that oxygen uptake (V\textsubscript{O\textsubscript{2}}) is the product of cardiac output and arterial venous oxygen difference. Factors limiting V\textsubscript{O\textsubscript{2}} (i.e., maximal V\textsubscript{O\textsubscript{2}}) with exercise have therefore been traditionally sought within the determinants of cardiac function. However, such an approach ignores a large body of research evidence indicating that peripheral factors, particularly arteriolar dilatation and skeletal muscle pump function, control circulatory responses to exercise rather than central cardiac mechanisms. Efforts to understand the limiting factors for physiologic aerobic fitness are thus more appropriately directed toward characterizing these peripheral determinants of blood flow.

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Abbreviations: AV = arteriovenous; LVED = left ventricular end-diastolic dimension; Q = cardiac output; V\textsubscript{O\textsubscript{2}} = oxygen uptake; V\textsubscript{O\textsubscript{2}max} = maximal oxygen uptake

The cardiovascular system is challenged by a bout of sustained exercise to not only increase blood flow but also to match blood flow closely with the increased metabolic needs of contracting skeletal muscles. The failure to do so would result in a breakdown of aerobic metabolism, excessively high core temperature, the accumulation of metabolic wastes, and the lack of an energy substrate, in effect, a total inability to sustain muscular activity. That this does not, in fact, occur (except in extremes of exercise intensity or environmental conditions) is testimony to the remarkable effectiveness of this circulatory response.

It follows that an understanding of the mechanisms that define the cardiovascular response to exercise should be expected to provide insights into the factors that limit endurance performance. In 1870, the German physiologist Adolph Fick provided a mathematical means of conceptualizing this issue, arguing (without experimental proof) that cardiac output (Q) is equivalent to the oxygen consumed by aerobic metabolism in the body (i.e., oxygen uptake [V\textsubscript{O\textsubscript{2}}]) divided by the oxygen extracted from the circulating blood, or the arterial venous oxygen difference. Exercise physiologists, being interested in the determinants of V\textsubscript{O\textsubscript{2}} (particularly at maximal exercise), have rearranged this equation to indicate that the limiting factors which define utilization of oxygen during exercise must reside within the determinants of Q and/or muscle oxygen extraction. As a consequence, research efforts for at least the past 50 years have focused on identifying aspects of cardiac function which might be responsible for limiting aerobic fitness. Such factors, it has been assumed, would account for interindividual differences in maximal V\textsubscript{O\textsubscript{2}} (V\textsubscript{O\textsubscript{2}max}) and would explain the superior levels of aerobic fitness that are characteristic of highly trained endurance athletes. This search has produced a number of such potential central factors, including diastolic filling properties, myocardial hypertrophy from increased circulating levels of catecholamines and anabolic agents such as angiotensin II, and training-induced diastolic stretch of myocardial fibers.

It is the premise of this review that such an interpretation of the Fick equation is misleading and inconsistent with empiric observations of the normal cardiovascular responses to exercise. These data indicate that, in the healthy individual, noncardiac...
mechanisms, mainly peripheral arteriolar dilatation and contractile function of the skeletal muscles, dictate circulatory flow during exercise. It is reasonable to expect, then, that such factors might serve to limit Vo2max rather than cardiac function. What Fick really proposed was that Vo2 is the product of the rate of circulatory flow and cellular oxygen extraction. Restricting the focus to the heart as the determinant of blood circulation during exercise may not be appropriate and could cloud our understanding of the physiologic basis of aerobic fitness.

**Historical Perspective**

The traditional attention to cardiac limitations to Vo2max is surprising given that physiologists have long been generally in agreement that peripheral, not central, factors are responsible for initiating and controlling the circulatory responses to exercise. According to the “law of the heart” described by Patterson and Starling in 1914, stretching of the myocardium produced an increase in muscle contraction and a consequent enhanced stroke volume. It was considered at that time that during exercise, then, augmented venous return to the heart from peripheral vasodilatation and skeletal muscle pump function increased left ventricular diastolic filling, with resulting increases in myocardial contractility and stroke volume. Studies in both dogs and humans in the 1950s demonstrated, however, that this was incorrect, since stroke volume in supine subjects remained stable with increasing exercise intensity, while left ventricular volume was essentially unchanged.

These observations were consistent with the contention by Guyton in 1967 that “the primary cause of augmented cardiac output is believed to be the local vasodilatation in the skeletal muscle.” He proposed that blood flow in tissues was autoregulated via a local increase in vascular conductance in response to metabolic requirements. “The heart,” he concluded, “has relatively little effect on the normal regulation of cardiac output.”

Guyton based this opinion largely on the work of Donald and Shepherd, who described no alteration in the expected rise in Q with exercise in denervated dogs lacking sympathetic stimulation of the heart. Guyton et al observed in animal studies that “an increase in efficacy of the heart as a pump cannot by itself increase the cardiac output more than a few percent, unless some simultaneous effect takes place in the peripheral circulatory system at the same time to translocate blood from the peripheral vessels to the heart.”

Bevegard and Shepherd agreed with this concept. In their classic 1967 review article, they stated that “the heart serves as a force-feed pump designed to discharge whatever volume it receives by increasing its rate or its stroke volume. Unless there is dilatation of resistance vessels in some systemic vascular bed, mediated by local, humoral, or nervous mechanisms, an increased rate will not result in an increase in cardiac output.”

Another peripheral factor, the pumping action of skeletal muscle, has long been recognized for its role in augmenting circulatory flow with exercise (see Rowland for a review). Evidence for this function has been derived largely from studies revealing shifts of blood volume and pressure away from the lower extremities during exercise. In 1996, Rowell et al concluded that “the muscle pump is a major determinant of venous return and ventricular filling pressure during exercise [and] can be viewed as a second heart on the venous return position of the circuit, having capacity to generate blood flow rivaling that of the left ventricle.”

In summary, a compelling body of evidence that has been compiled over the past 50 years supports a primary role of peripheral mechanisms, particularly arteriolar dilatation and skeletal muscle pump function, in the control of circulatory responses to exercise. These data suggest a responsive rather than a responsible role of the heart.

**Empiric Findings**

More recent studies have utilized techniques such as Doppler and two-dimensional echocardiography, acetylene and carbon dioxide rebreathing, and thoracic bioimpedance, methods that can provide information regarding circulatory changes at high work intensities. The following observations from these studies in healthy humans have, for the most part, supported earlier interpretations of the normal cardiovascular dynamics during exercise.

**While Heart Rate and Q Rise Linearly With Increasing Work Intensity, Stroke Volume Remains Essentially Stable**

Studies in human subjects have confirmed earlier observations, particularly by Rushmer and Smith in instrumented dogs, that little or no change occurs in stroke volume with increasing intensity during supine exercise. There have been exceptions (e.g., Daley et al reported a 19% mean increase in stroke volume during progressive supine cycling), and even in reports in which the mean stroke volume is stable, considerable interindividual variability has been observed. Overall, however, physiologically important changes in stroke volume are not characteristic of the circulatory response to supine exercise.
Stroke volume does predictably increase at the onset of exercise performed in the sitting or upright position.\textsuperscript{20–22} Values have consistently been demonstrated to rise by approximately 30 to 40\% by the time that work intensity reaches about 50\% of $V_{O_{2}}$\max. At intensities above this level, stroke volume plateaus and remains stable to the point of subject exhaustion.

It is reasonable to conclude that this increase in stroke volume during upright exercise reflects the mobilization of blood pooled by gravity in the dependent lower extremities. When an adult subject assumes the upright position, blood volume in the legs increases by as much as 500 to 1,000 mL, and the resulting decrease in central blood volume causes Q and stroke volume to fall by 20 to 40\%. With the onset of upright exercise, contractions of the skeletal muscles in the legs mobilize this dependent blood, central volume increase, and stroke volume and Q rise.\textsuperscript{23}

Once this process is completed, stroke volume remains stable with increasing workload, just as it does with supine exercise, and values are similar during supine and upright exercise at high work intensities.\textsuperscript{16,18,19} By this interpretation, then, the rise of 30 to 40\% in stroke volume that is observed at the onset of upright exercise should be interpreted as simply a "refilling phenomenon" (ie, a mobilization of dependent blood volume in the legs) and not part of the fundamental process by which circulatory flow increases during exercise.

**Left Ventricular End-Diastolic Dimension Remains Stable or Declines Gradually as Exercise Intensity Increases**

The size of the left ventricle in human subjects during sustained, progressive exercise was shown to be stable in early studies using radiographs in humans\textsuperscript{6} and the most typical pattern in more recent investigations with two-dimensional ultrason sound has been a small, gradual decline.\textsuperscript{21,24,25} (The only exception to this has been a small rise in ventricular diastolic dimension at the beginning of upright exercise, which is considered to reflect the transient increase in cardiac filling from blood mobilized from the lower extremities.) In effect, then, left ventricular preload does not change or may even diminish slightly as work intensity increases during an short-term bout of progressive exercise.

One is faced with the need to explain how left ventricular diastolic size can remain stable during an exercise session in which systemic venous return increases fourfold. By the only reasonable explanation, the rise in heart rate must match the increase in venous return to maintain a constant stable volume crossing the mitral valve with each beat. The result of this heart rate response is a constant (or slightly diminishing) end-diastolic size and little change in atrial pressure.

The Bainbridge reflex, in which heart rate rises in response to an increased right atrial pressure, is an ideal mechanism with which to explain the close matching of heart rate to venous return. While its existence has been clouded by controversy,\textsuperscript{26,27} this reflex has been clearly demonstrated in both humans and subhuman primates.\textsuperscript{28} Its role with exercise was proposed by Bainbridge\textsuperscript{29} almost a century ago:

> "If these conclusions are correct, the heart is provided a reflex mechanism whereby, when the venous filling is increased, the circulation can be maintained by the more rapid transference of blood from the venous to the arterial system and the risk of excessive dilatation and failure of the heart is lessened. This mechanism must play a part in the quickening of the heart during muscular exercise, which is accompanied by increased venous inflow to the heart and by a rise in venous pressure."

In this statement, Bainbridge\textsuperscript{29} also provides a clue as to why the heart rate ‘‘defends’’ left ventricular diastolic size during exercise. There are both physical and physiologic reasons why preventing ventricular chamber enlargement is advantageous for the heart.\textsuperscript{30} Most importantly, as expressed by the laws of LaPlace, an increased ventricular radius results in an increase in wall tension. Dilatation of the ventricle during exercise would cause a decrease in mechanical efficiency by increasing the workload of individual muscle fibers.

**The Contractile Force of the Heart Becomes Accentuated as Work Rate Increases During Exercise**

With increasing work intensity, the heart empties more completely during each beat, a phenomenon that is most obviously observed with two-dimensional echocardiography. While end-diastolic size (ie, the left ventricular end-diastolic dimension [LVED]) gradually decreases, a more dramatic decline is seen in the left ventricular end-systolic dimension (LVES). As a result, the left ventricular shortening fraction (ie, \([\text{LVED} - \text{LVES}] / \text{LVED} \times 100\)) rises during progressive exercise, typically from about 30 to 50\%.\textsuperscript{21,24,25} Similar changes are observed in other indexes of ventricular contractility (eg, ejection fraction and peak aortic velocity).

If, as exercise intensity increases, the left ventricular diastolic size is stable, how can the stroke volume remain unchanged if the ventricular chamber is emptying more completely with each beat? The answer must be that the increase in contractile force must serve to eject the same volume of blood in
a shorter ejection period as the heart rate rises. Supporting this concept, we found a 20% increase in shortening fraction between the first workload and peak exercise in subjects, while their mean systolic ejection time fell by 24% (and stroke volume remained stable). Increases in myocardial contractile force during progressive exercise, then, appear to maintain rather than increase stroke volume.

The Influence on Peripheral Vascular Resistance

The Onset of Exercise Is Accompanied by a Dramatic Fall in Peripheral Vascular Resistance, Which Continues To Decline in a Curvilinear Fashion as Work Intensity Increases

Typical findings were observed in a study of 10 boys in whom the mean (± SD) systemic vascular resistance fell precipitously at the onset of cycle exercise from 13.9 ± 4.4 Wood units at preexercise to 8.0 ± 1.5 Wood units at the first 25-W workload. Only minimal decreases were subsequently observed as exercise intensity rose (at 50 W, 6.8 ± 1.1 Wood units; at 75 W, 6.0 ± 1.5 Wood units). This fall in peripheral vascular resistance results from arteriolar dilatation in the exercising muscle and is reflected in minimal changes in mean systemic arterial BP (typically about 20 mm Hg) that occur in a maximal exercise test, while Q rises about fourfold.

Based on these empiric observations, it is apparent that what the left ventricle "sees" with exercise is not substantially different from that seen in the resting state. The filling volume is the same, and the amount of blood ejected per beat does not change. What is altered is that during exercise the blood must be ejected more often and at a faster rate per beat. The physiologic challenge for the heart during exercise is to beat more frequently and with greater force, the result being a stable ventricular filling volume (preload) and stroke volume.

This scenario is consistent with a central cardiac pump functioning in a responsive fashion to peripheral factors that define the amount of systemic venous return. In the next section, experimental evidence will be reviewed that supports this construct.

Experimental Models

The principal dilemma in attempting to understand the control of circulatory responses to exercise lies in sorting out the primary movers of blood flow from secondary, or responsive, variables. The many factors that contribute to circulatory flow are often interreactive, making it difficult to distinguish dependent from independent influences. Insights may be gained, however, from a number of models, both experimental and in the disease-state, that allow the roles of specific factors to be isolated.

The Artificially Paced Heart

Early studies in animal preparations indicated that isolated increases in heart rate do not cause a rise in Q, and subsequent pacing studies in intact animals and humans have borne this out. When Sugimoto et al paced the atria of anesthetized dogs from 160 to 250 beats/min, no increase in Q was observed. Ross et al studied 17 patients aged 6 to 41 years who were free of cardiac dysfunction. With atrial pacing up to 190 beats/min, no change was seen in Q, while stroke volume fell precipitously to less than half the prepacing values. Sonnenblick et al described similar findings with pacing to 111 beats/min in older individuals (no change in Q and a 37% reduction in stroke volume) along with a fall in LVED.

These data indicate that a rise in heart rate alone will not increase circulatory flow. An increase in systemic venous return to raise cardiac filling pressure is a necessary factor for augmenting blood circulation.

Factors Decreasing Peripheral Vascular Resistance

Isoproterenol, a catecholamine with both chronotropic and inotropic actions, also serves as a potent dilator of peripheral arterioles. Whalen et al showed that an isoproterenol infusion that increases heart rate by 25% results in a 32% decline in peripheral vascular resistance along with a 34% rise in Q. Similar findings have been demonstrated by others. These observations indicate that Q will rise when increases in heart rate and contractility are combined with significant reductions in peripheral vascular resistance.

An experimental, surgically induced, or naturally occurring arteriovenous (AV) fistula offers an even better model for examining the role of diminished peripheral resistance on blood circulation, since these fistulas cause blood to bypass the high-resistance systemic arterioles but have no direct cardiac effects. It has been well-recognized that the shunting of blood through an AV fistula will produce an increase in Q, and the size of the fistula correlates directly with the fall in peripheral resistance and the magnitude of rise in circulatory flow. This follows from the flow equation (pressure equals the product of flow times resistance), in which an increase in flow can be expected with a fall in resistance as long as the heart maintains pressure from the myocardial contractile force.

The influence on peripheral vascular resistance and, secondarily, blood circulation of an AV fistula is not far removed from the conditions of dynamic exercise. Binak et al demonstrated this in a study of seven subjects with traumatic AV fistulas of the lower
extremity who underwent exercise testing with and without the shunt occluded (by a BP cuff). At rest, mean Q rose from 3.9 to 7.9 L/min when the fistula was opened, while peripheral resistance fell from an average of 1,183 to 639 dyne s cm\(^{-5}\). Exercise with the fistula occluded resulted in a rise in Q from 3.9 to 4.9 L/min and a fall in peripheral resistance from 1,183 to 918 dyne s cm\(^{-5}\). These models support the concept that peripheral vasodilatation and fall in vascular resistance play a key central role in the increases in circulatory flow that are observed with exercise.

The Denervated Heart

Cardiac responses to exercise (eg, increased heart rate and contractility) depend on sympathetic stimulation. An assessment of circulatory responses to exercise in subjects with diminished sympathetic activity, then, should provide clues as to the role played by central factors in these hemodynamic responses. In this case, if peripheral factors are primary, systemic venous return should increase normally, and, since heart rate would not rise appropriately, left ventricular filling and LVd would increase. This would result in an exaggerated rise of stroke volume, causing a normal rise in Q according to the Starling principle. On the other hand, if central cardiac factors are primary, heart rate and contractility responses would be dampened (with a diminished rise in Q), with a fall in atrial pressures, stroke volume, and ventricular diastolic dimension.

As noted previously, the first scenario was precisely that demonstrated by Donald and Shepherd\(^9\) in 1964 in dogs after undergoing isolated cardiac sympathectomy. Compared to normal dogs, the exercise heart rate was markedly depressed. With increasing exercise intensity, stroke volume did not change in the control animals but rose by 80% in the denervated dogs. As a result, the rise in Q was not different in the two groups of animals, nor was the relationship of Q to \(\dot{V}O_2\).

Many of these features are observed in humans following heart transplantation, in which the transplanted heart lacks autonomic innervation. The heart rate at rest is approximately 30% higher in transplant patients than in control subjects (because of a lack of parasympathetic input), with a commensurate decrease in stroke volume but normal Q.\(^{45-49}\) With increasing exercise intensity, the heart rate response is markedly retarded, while the stroke volume increases are greater than those observed in healthy subjects. For instance, Verani et al\(^{49}\) demonstrated a 32% rise in heart rate in response to moderate-intensity supine exercise in heart transplant recipients compared to a 93% increase in healthy subjects. At the same time, stroke volume rose by 43% in the transplant patients, with no significant increase in healthy subjects.

Maximal Q values are lower in transplant patients, but the rate of rise of Q with respect to metabolic demands appears to be normal.\(^{48-50}\) Clark et al\(^{48}\) reported a slope of the \(\dot{V}O_2\)-Q regression of 0.00598, “almost identical to that reported in normal subjects.”

Right atrial pressure during exercise in transplant recipients rises to levels that are two to three times that at rest, in contrast to healthy subjects, in which little change is typically seen.\(^{47}\) Left ventricular end-diastolic pressure and size also rise with exercise following cardiac transplantation compared to those in healthy subjects. LVd increases by 14 to 20%.\(^{47,49}\) While end-diastolic pressure nearly doubles,\(^{48-50}\) The findings in both animals and humans with cardiac denervation thus support a primary role for peripheral, sympathetic-independent factors in controlling the circulatory responses to exercise.

Factors Diminishing Sympathetic Neurologic Influence: Exercise Under \(\beta\)-Blockade and in Patients With Anorexia Nervosa

Given the above set of findings, it would be expected that circulatory responses to exercise similar to those in heart transplant recipients also would be observed in patients with other conditions in which the sympathetic neural influence is diminished. Such is the case, as indicated by hemodynamic responses in subjects receiving \(\beta\)-blocker medications as well as in patients with anorexia nervosa, which is a condition of undernutrition that is characterized by diminished sympathetic tone.

Most studies have indicated that at a given level of submaximal work, \(\beta\)-adrenergic blockade by agents such as propranolol cause a reduction in heart rate, an increase in stroke volume, or little or no decrease in Q.\(^{51,52}\) Wilmore et al\(^{51}\) demonstrated a 42% lower heart rate during submaximal exercise when subjects received propranolol compared to placebo, with a 29% increase in stroke volume and no difference in Q. In a similar study involving patients with systemic hypertension, Reybrouck et al\(^{52}\) found that at a \(\dot{V}O_2\) of 0.5 L/min/m\(^2\), the heart rate with atenolol administration was 80 beats/min, compared to 120 beats/min without atenolol administration. The stroke volume while the patient was receiving medication was 56 mL/m with a \(\dot{V}O_2\) of 4.5 L/min/m\(^2\), while the values without medication were 45 mL/m\(^2\) and 5.4 L/min/m, respectively.

It should be noted that comparisons of findings with \(\beta\)-blockade and after heart transplantation are...
only valid for sympathetic tone. Transplant patients are also lacking parasympathetic influence, which is normal with β-blockade.

In patients with anorexia nervosa, who have a depressed sympathetic tone, a similar pattern has been observed. In a study of 16-year-old girls with moderately severe undernutrition, the heart rate during exercise was 16 to 22% lower than that in healthy control subjects, while stroke volume was 13% higher.53 No significant differences were observed in cardiac index at rest and during exercise in the two groups.

In both of these situations, the failure of sympathetic-driven increases in heart rate to match systemic venous return causes stroke volume to rise by a Starling mechanism (ie, augmented diastolic filling, resulting in larger end-diastolic volume, enhanced contractile force, and, consequently, greater stroke volume). This is consistent with the concept that peripheral rather than central cardiac factors control the circulation with exercise.

**Implications**

This information from historical studies, contemporary empirical findings, and experimental and disease conditions consistently implicates a peripheral basis rather a central basis for increasing circulatory flow with exercise. Most particularly, graded arteriolar dilatation and pumping action of the skeletal muscle appear to be critical not only for facilitating these responses, but also for controlling and presumably limiting them. It follows that misleading conclusions might be drawn if, instead, central cardiac factors are sought to explain hemodynamic alterations with exercise.

An illustration of this pitfall surrounds studies of the circulatory response to sustained exercise in thermoneutral or warm ambient conditions. These reports consistently demonstrate a fall in stroke volume and a rise in heart rate (so-called “cardiovascular drift”), associated with increases in core temperature.54 The depressed stroke volume has been conventionally explained by a decrease in systemic venous return and cardiac filling as blood volume decreases from dehydration and/or increased demands for cutaneous blood flow (for thermoregulation). The increase in heart rate has been interpreted as a compensatory mechanism to maintain Q as stroke volume falls.

This traditional “cardiocentric” viewpoint, however, is not consistent with the recognized circulatory responses to exercise that have been outlined above in this discussion. More likely, from these data, the rise in heart rate is the primary cardiovascular response to sustained exercise (a result of augmented sympathetic drive), with a secondary reduction in stroke volume based on a shorter cardiac filling time. In this scenario, systemic venous return is largely maintained by peripheral mechanisms, and diminished circulatory flow cannot be interpreted as being causal.

Fritzsche et al55 demonstrated that the latter explanation, in fact, is the correct one. They found that β-blockade during such exercise prevented the expected rise in heart rate and that stroke volume did not change. At the same time, cutaneous blood flow rose normally, and no differences in Q were seen compared to those in control subjects. These findings suggest, then, that the accepted explanation for “drift” (ie, cardiovascular insult from a fall in central blood volume) is incorrect.

A perceptual perspective also suggests that the limiting factors of circulatory response during exercise (which define maximal Q and, consequently, VO2max) should be sought in the determinants of factors such as arteriolar dilatation and skeletal muscle pump capacity rather than in cardiac chronotropic, inotropic, or diastolic function. The technical difficulties in studying these peripheral actions have limited such insights. Still, a number of pieces of information support the idea that these factors differentiate circulatory capacity in relationship to aerobic fitness.

Highly trained endurance athletes have a superior level of functioning of the skeletal muscle pump compared to unfit individuals. They can sustain muscle contractile force for more extended periods of time (presumably related to higher levels of cellular aerobic enzymatic activity).56 Moreover, greater pump filling (ie, preload) based on increased vascularity57 as well as augmented blood volume58 result in a larger pump stroke volume.

There also exists evidence that arteriolar vasodilatory mechanisms may be more active in trained individuals. Studies in both animals59 and humans60,61 have indicated that this enhanced vasodilatation may be mediated by an increase in endothelial nitric oxide production with exercise. For instance, Green et al62 demonstrated that the dominant arms of tennis players had greater vasodilatory capacity than the nontrained arm.

It should be recognized that the foregoing discussion reflects cardiovascular adjustments to exercise in healthy individuals. Malfunction in any of the myriad of components responsible for circulatory flow and oxygen delivery will limit the blood supply to the contracting muscles (thereby inhibiting the supply of oxygen, the energy substrate, and hormonal stimuli), quite apart from the central and peripheral factors that normally define the limits of
this circulatory response. Identifying the malfunctioning components of the system helps to differentiate normal vs pathologic limitations to exercise.

In summary, compelling evidence from many sources indicates that controlling mechanisms for circulatory responses and limitations with exercise should be sought in peripheral rather than central cardiac sites. The expression of the Fick equation in terms of Q rather than circulatory flow is misleading and may lead to spurious conclusions. Much remains to be learned regarding the determinants of factors such as arteriolar dilatation and skeletal muscle pump function. But this type of information is likely to provide important insights into the physiologic limits, and adaptability through training, of the circulatory responses to exercise.

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