Editorial Comments

The Peripheral Circulation and Lactic Acid Metabolism in Heart, or Cardiovascular, Failure

Karlman Wasserman, MD, PhD

Cellular Respiration and Cardiovascular Function

The most immediate task of the circulation is to provide oxygen to the cells of the body and to remove CO₂. Other than to satisfy the tissue oxygen requirements, cardiac output probably does not need to be at the level at which it normally functions. At rest, on average, about one fourth of the oxygen is removed from the circulation by the body. Myocardial and skeletal muscle have relatively low blood flow relative to metabolic rate, whereas kidney has a very high blood flow. Thus, the arterial-venous Po₂ differences across the vascular beds of the body are quite variable.

The unique aspect of the skeletal muscle circulation is its great ability to lower vascular resistance and to allow blood flow to increase. This process is essential if the increased O₂ supply required to generate adequate high-energy phosphate for muscle contraction is to be accommodated. An inadequate O₂ supply constitutes circulatory failure. Fac

See p 769

tors determining the oxygen flow into the muscle mitochondria (OₘO₂) are defined by Fick’s law of diffusion: QₘO₂ = K(PₘO₂ - PₚO₂)(A/L), where K is a constant describing the diffusibility and solubility of O₂ in body fluids, (PₘO₂ - PₚO₂) is the partial pressure gradient between the capillary (the O₂ source) and the mitochondria (the site of oxygen consumption for energy production), A is the surface area for diffusion, and L is the path length from the oxygen source to the mitochondria.

For O₂ to diffuse from the capillary to the mitochondria, a partial pressure gradient must be present. The capillary to mitochondrial Po₂ gradient (PₚO₂ - PₘO₂) must be higher, the greater the distance between the capillary red cell and the mitochondria. The Po₂ at the end of a capillary (muscle venous Po₂) (i.e., after the muscle has removed the oxygen required for muscle energy) depends on the blood flow and the rate of oxygen consumption. Thus, the cardiovascular system must keep the capillary Po₂ high enough for O₂ to diffuse at a rate sufficient to satisfy the muscle O₂ requirement. Although circulatory failure will occur with defects in cardiac function, the degree to which the circulation will fail also depends on how the blood flow is distributed to the various vascular beds. A more effective blood flow distribution to the exercising muscles for a given cardiac output will result in more available O₂ for muscle work and less lactic acidosis locally and systemically.

For walking exercise, muscle blood flow must increase to about 20 times that at rest for the muscles to function totally aerobically. The supply of O₂ to the muscles performing work depends not only on the heart output but also on the peripheral circulation. Two patients with identical cardiac lesions will have different symptoms during exercise if the peripheral circulation of one adapts to the exercise better than that of the other. Further, a review of Fick’s law of diffusion readily shows that anemia and tissue edema impair the ability of the heart to deliver oxygen to the exercising tissues. When these conditions complicate heart failure, a higher cardiac output is required, and this is reflected in a relative tachycardia, which may be detrimental in the presence of myocardial ischemia.

Supply and Demand Balance and Heart Failure

Cardiac output increases linearly with O₂ consumption in normal subjects with a slope of approximately six. Six liters of blood with normal hemoglobin and normal hemoglobin concentration contain only 1.21 O₂. Thus, a task requiring an O₂ consumption increase of 1 l/min (e.g., brisk walking) that is accompanied by an increase in cardiac output of 6 l/min leaves only 0.21 O₂ in muscle venous blood. This will result in a venous O₂ saturation of 18% (P₀₂ of about 10 mm Hg) in the blood draining the muscle, assuming the entire increase in cardiac
output perfused the exercising muscle. From this analysis, it is clear that the circulation to exercising muscles barely meets the O₂ requirements in performing exercise even in normal subjects. Impaired O₂ transport to meet the oxygen requirements in performing work, because of a primary cardiac defect, increased pulmonary vascular resistance, or peripheral vascular disease, should be accompanied by muscle tissue hypoxia and increased muscle lactate output at inappropriately low work rates.

Inadequate Cellular Respiration Produces H⁺ and Lactate and Consumes Glycogen

In this issue of Circulation, Sullivan et al. studied the rate of muscle lactate production, blood flow, and O₂ consumption of the exercising lower extremity of patients with heart disease and of normal subjects. They observed an increased rate of muscle lactate production and a reduced rate of muscle oxygen utilization in the patients with heart failure. The disproportionate increase in lactate relative to pyruvate reflects a change in the cellular redox state in muscles experiencing inadequate O₂ delivery and O₂ consumption.

The findings of Sullivan et al. fit with the classic hypothesis that the major increase in lactate during exercise is due to increased production rather than decreased removal and that production is more pronounced when muscle O₂ supply is compromised. Also, anaerobiosis, as reflected by increased lactate production and decreased O₂ uptake, is evident well below maximally tolerated exercise levels. Reduced oxygen uptake in the leg obviously relates to the reduced oxygen delivery rather than to less oxygen extraction because venous O₂ content is decreased, not increased.

The consequence of increased cellular lactate, as reflected in the increased lactate in the venous effluent from the exercising leg, is an equal molar increase in hydrogen ion. The latter must be immediately buffered in the cell because lactic acid is almost totally dissociated by the cell’s pH. Because HCO⁻₃ is a volatile anion (an anion that evaporates into the gaseous phase), it is the primary buffer in the cell. Also, because HCO⁻₃ is a volatile anion, the new osmoles of lactate are counterbalanced by a decrease in HCO⁻₃ osmoles as it buffers H⁺ (each millimole of lactic acid neutralized by a nonvolatile anion will increase the cellular osmotic pressure by 17 torr). Thus, it can be assumed that the muscle cells producing lactic acid have a reduced pH but are only slightly hyperosmotic at moderately heavy work rates. During a very heavy work rate, when lactate increases in the cell to concentrations beyond the buffering capacity of the cellular HCO⁻₃, cellular osmolality must increase and swelling must occur.

Anaerobic glycolysis induced by exercise is accompanied by a depletion of muscle glycogen that is more rapid (12–18 times) than when exercise is performed aerobically because breakdown of glucose to lactic acid results in only 6% of the energy produced per glucosyl unit of glycogen compared with the complete oxidation of glucose to CO₂ + H₂O. Prior studies, in rats and humans, in which arterial perfusate oxygen tension was reduced to the exercising muscle, have shown increased lactate production and glucose turnover. In summary, at least four changes can occur in the contracting muscle cells consequent to the inadequate muscle oxygen supply in heart failure: 1) lowered cellular redox state, 2) metabolic acidosis, 3) rapid glycogen utilization, and 4) increased cell osmolality and swelling. These are all possible contributors to the patient’s symptoms of fatigue and dyspnea.

Peripheral Vascular Control in Heart Failure

A major finding of Sullivan et al. is that blood flow to the other organs of the body, on average, remains unchanged during exercise. Because perfusion pressure is increased to the same degree in both groups and the cardiac output response is reduced, muscle vascular resistance during exercise is high in patients with heart failure compared with normal subjects. Sullivan et al. suggest that a reflex regulation of blood pressure may prevent the muscle circulation from dilating normally to prevent the inadequate cardiac output increases from resulting in hypotension. Because many local vasodilators and conditions, including ADP, H⁺, and low P₂O₂, must be more prominent in the exercising muscles of the patient with heart failure, the normal, humorally mediated vasodilation due to exercise must be overridden by the baroreflex regulation of arterial blood pressure.

The homeostatic mechanisms regulating nonmuscle blood flow during exercise are probably a reflection of the necessity to maintain the supply of blood with an adequate P₂O₂ for normal metabolism of these organs. Thus, in order that these organs not fail during exercise, their blood flow is maintained. Because blood flow to the nonmuscle organs is maintained while arterial pressure increases, an increase in vascular resistance should occur in these organs. In contrast, because of the increased O₂ consumption of the exercising muscles, their blood flow should increase in proportion to the increased oxygen requirement. This requires a selective and controlled vasodilation of the muscle bed. But if primary disease of the heart limits cardiac output and therefore muscle blood flow increase, muscle metabolism must be supplemented by anaerobic metabolism. Because of their high glycogen content, muscles can sustain anaerobic metabolism much longer than other organs, and partially anaerobic exercise can be sustained for short periods, of which the duration is inversely related to the lactate rise.

Does Vasodilator Treatment of Heart Failure Divert Blood Flow From Muscles?

The increased blood pressure during exercise is obviously important in obtaining optimal perfusion
pressure, but equally important is the increase in vascular resistance to organs other than exercising muscles and the simultaneous vasodilation of the vascular beds of exercising muscles. Thus, the use of vasodilators in treatment of heart failure may have both negative and positive aspects. The positive aspect is a lowering of the afterload of the heart, thereby allowing cardiac output to increase. On the other hand, nonselective vasodilation may block selective peripheral vasoconstriction that is important to divert the increase in cardiac output to tissues of high metabolic rate and to match increased metabolic rate with increased blood flow. Therefore, although cardiac output may be increased, the increase may not be effective in improving exercise tolerance if physiologic control of vascular tone is lost. The ideal afterload-reducing drug is one that does not interfere with the normal selective changes that occur in vascular resistance in response to exercise.

How should we measure the ability of vasodilator drugs to improve exercise tolerance? Because therapy that blocks the normal rise in blood pressure during exercise (needed to perfuse the exercising muscle at high work rates) may prevent selective blood flow increase to the exercising muscle, maximal (peak) oxygen uptake may not be increased with these drugs, although submaximal exercise parameters, such as the anaerobic threshold, might be improved. This remains to be addressed by investigators seeking therapeutic measures for treating patients with heart failure.

As is evident from the study of Sullivan et al., cardiac output increases with a shallow slope relative to work rate in patients with heart failure. Consequently, muscle blood flow is inadequate at relatively low work rates, and early onset of lactic acidosis is a predictable consequence. The formation of lactic acid stresses the patient by its increased stimulus to breathing. The latter results from the increased CO₂ formed when lactic acid is buffered and from the reduced pH resulting from the HCO₃⁻ fall. However, the formation of lactic acid in the muscle also shifts the oxyhemoglobin dissociation curve to the right. This has the beneficial effect of allowing O₂ to unload from hemoglobin at a higher P0₂, thus favoring mass diffusion of O₂ into the cells, delaying anaerobic fatigue, and increasing oxygen extraction in these oxygen-deprived acidotic vascular beds. Unfortunately, this situation cannot be sustained, possibly because the accumulation of hydrogen ion also adversely affects cellular metabolism and muscle contraction. In addition, depleting glycogen stores constrains the use of the more efficient substrate for exercise (oxidation of glycogen results in about 10% more high-energy phosphate than the same rate of oxidation of fatty acids).

**Cardiovascular, Not Heart, Failure!**

Thus, although the primary defect in heart disease could be attributed to the failure of the heart to supply the tissues, in particular the working skeletal muscles, with adequate oxygen under conditions of increased stress, the symptoms are not solely dependent on the behavior of the heart. The response of the peripheral circulation to the reduced cardiac output determines the relative effectiveness of the cardiac output. The steep increases in epinephrine and norepinephrine concentrations at levels of work above which lactic acidosis develops might be viewed as compensatory for the low cardiac output state.

Heart failure occurs when the peripheral circulation does not or cannot adequately adjust to an inadequate cardiac output (O₂ delivery) to keep pace with the metabolic requirements. Because the heart muscle provides the energy to propel the blood into the elastic, innervated, and humorally regulated blood vessels, the symptoms caused by a given cardiac lesion must be influenced by the state of the blood vessels supplying tissues. Also, the O₂ flow should be adequate to maintain the critical (minimal) P0₂ for that organ. Of importance, cardiac contraction is not the sole factor maintaining the adequacy of oxygen flow to the mitochondria of metabolically active tissues. Because of the obvious interplay between the heart and the peripheral circulation, a term better than “cardiac” failure is “cardiovascular” or “circulatory” failure.

**References**


(Circulation 1989;80:1084–1086)
The peripheral circulation and lactic acid metabolism in heart, or cardiovascular, failure.

K Wasserman

Circulation. 1989;80:1084-1086
doi: 10.1161/01.CIR.80.4.1084

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/80/4/1084.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/