

# The Metabolic Demand and Oxygen Supply of the Heart: Physiologic and Clinical Considerations

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The utilization of energy by the working heart has been studied extensively over the years. Because the conversion of chemical energy to mechanical work by the heart is highly dependent on oxygen, the oxygen required and the oxygen available for this conversion are considered to form the conceptual framework of the metabolic demand and supply of the heart, respectively. The oxygen requirement of the myocardium, as assessed by the rate of oxygen consumed ( $MVO_2$ ), is a function of the mechanical components of ventricular contraction and include: (1) the force developed and sustained by the muscular wall during its contraction; (2) the rate of force development; and (3) the frequency of generating force in the wall per unit time. The oxygen available to the mitochondria, which satisfies this requirement, is primarily determined by the oxygen delivered per unit of time (that is, coronary flow) and the oxygen extracted. Collectively, the response in flow and oxygen extraction represent the metabolic reserve of the heart.

Normally, during increments in work, coronary vascular resistance decreases permitting an increment in flow; oxygen extraction (65 to 70 percent) changes little under these circumstances. However, when the response in coronary vascular resistance is limited or at its optimal value, further increments in oxygen requirements are accompanied by an increase in oxygen extraction to 80 to 85 percent; oxygen extraction may exceed 90 percent in the presence of a reduced oxygen-carrying capacity. Stressed beyond the limits of its metabolic reserve (that is, minimum coronary vascular resistance and maximal oxygen extraction) the oxygen available to the heart becomes insufficient and, hence, an aerobic limit is reached. As a consequence, anaerobic metabolism commences, ventricular performance declines and pulsus alternans appear.

The concept of inappropriate oxygen demand relative to oxygen supply would appear to be central not only to the patient with coronary artery disease whose oxygen delivery may be compromised, but also to patients with chronic hemodynamic overload (for example, aortic stenosis) whose hypertrophied ventricle is now failing. Moreover, the implications of an aerobic limit may also explain the limits of hypertrophy.

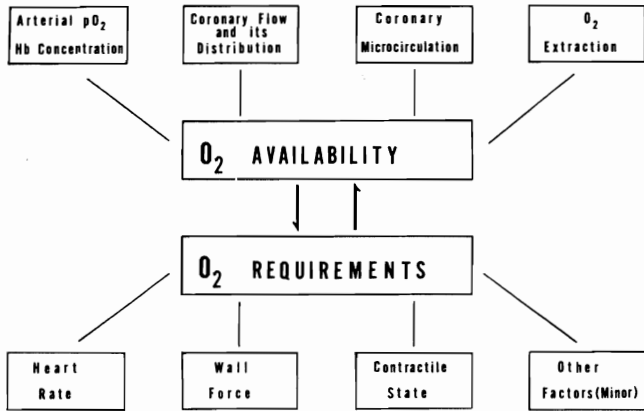
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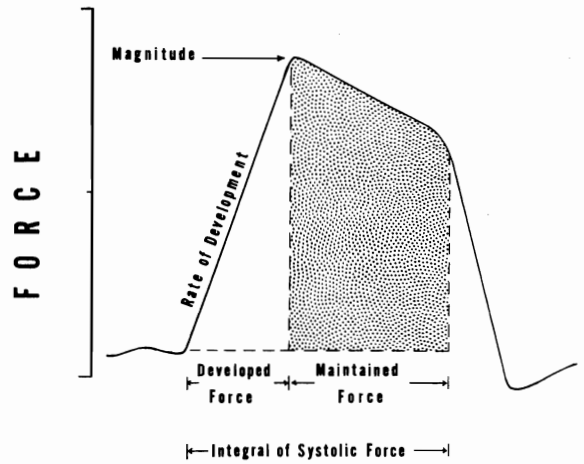
The energy requirements of the working heart have received much attention over the years. In the heart, unlike skeletal muscle, the conversion of chemical energy to mechanical work is highly dependent on oxidative reactions; an oxygen debt leads to a decline in ventricular performance. As a result the heart is considered to be an obligate aerobic organ.<sup>1,2</sup> The interrelation between oxygen requirements and oxygen availability, synonymous with the concept of metabolic demand and supply, is fundamental to any consideration of the heart's capacity for work. This is particularly the case for the ischemic heart whose oxygen availability, relative to oxygen requirements, may be compromised. In addition, it has been suggested that the metabolic demand of the mechanically

**O<sub>2</sub> Supply :**



**O<sub>2</sub> Demand :**

**FIGURE 1.** Schematic representation of the factors that regulate the demand and supply of oxygen in the heart cells and thereby reflect the heart's requirements for oxygen and its availability. Hb = hemoglobin.



**FIGURE 2.** The major determinants of myocardial oxygen consumption expressed in relation to their influence on the components of systolic wall force.

overloaded heart (for example, aortic stenosis) eventually exceeds its available energy supply and, as a result, areas of hypoxia and subsequent fibrosis develop and the ventricle fails.<sup>3,4</sup> However, the actual role of hypoxia in the genesis and progression of the failing heart remains to be elucidated.

During the past 4 years we have been interested in examining those aspects of ventricular contraction that influence myocardial oxygen consumption (that is, the demand for oxygen<sup>5,6</sup> and those factors that regulate the availability of oxygen).<sup>6,7</sup> Moreover, we wanted to determine whether a limit to oxygen availability exists and what influence exceeding such an aerobic limit would have on ventricular performance.<sup>7</sup> This report reviews the physiologic principles that relate to the metabolic demand and oxygen supply in the heart and considers their relation to the pathophysiology of the diseased heart.

**The Metabolic Demand of the Heart**

**Determinants of myocardial oxygen consumption:** As an obligate aerobic organ the consumption of oxygen by the heart reflects its energy requirements. The energy utilized in maintaining organelle systems,

the oxygen cost of electric depolarization and the activation of the contractile process have all been found to require only a minor fraction of the total energy consumed.<sup>1,2</sup> The major determinants of myocardial oxygen consumption (MVO<sub>2</sub>) (Fig. 1) include systolic wall force (as determined by chamber pressure and volume), myocardial contractile state and heart rate.<sup>1,2</sup> Hence, these components of ventricular contraction collectively represent the metabolic demand placed on the heart.

The relative contribution of each of the major determinants on MVO<sub>2</sub> has been difficult to discern because they are interrelated through wall force. For example, alterations in contractile state or heart rate will influence both MVO<sub>2</sub> and wall force. However, a uniform expression of energy utilization can be developed if the effects of a perturbation in contractile state and heart rate are related to MVO<sub>2</sub> through their influence on the following components of wall force (Fig. 2 and Table I): (1) the magnitude of developed force; (2) the interval during which force is generated and maintained per contraction (that is, the integral of systolic force); (3) the rate of force development; and (4) the frequency with which force is developed per unit of time.

**Wall force and the role of chamber pressure and volume:** An increment in ventricular chamber pressure or volume would be expected to raise both the magnitude of force, which the myocardium and its fibers must

**TABLE I**  
**Factors Regulating the Components of Wall Force**

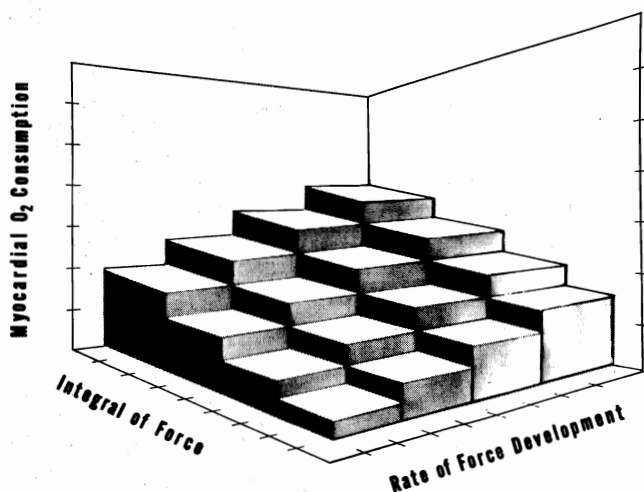
Wall Force	Chamber		Contractile State		Heart Rate	
	Increased Pressure	Increased Volume	Increase	Decrease	Increase	Decrease
1. Magnitude	+	+	+ or -	+	0	0
2. Integral	+	+	-	+	-	+
3. Rate of development	+	+	+	-	+	-
4. Frequency of development	0	0	0	0	+	-

+ = increase, - = decrease; 0 = no change.

develop, and the force that is sustained during ejection (that is, the afterload). Hence, the total integral of systolic force for any given cardiac cycle is increased.<sup>5</sup> Increments in filling volume and diastolic pressure, which collectively reflect an elevation in preload and the degree of fiber stretch, would also raise the rate with which force is developed during the isovolumic contraction period. A reduction in diastolic chamber size, however, would reduce both the integral of systolic force and the rate of force development.

**Role of myocardial contractility:** The performance or output of either ventricle as a muscular pump is a function of the shortening of its constituent muscle fibers. Fiber shortening is determined by: (1) the load resisting its shortening (that is, afterload); (2) the length of the fiber during shortening; and (3) the contractile state of the fiber. Contractile state refers to that property of cardiac muscle that is independent of afterload or shortening length. For a more detailed discussion of cardiac mechanics the interested reader is referred to our recent review.<sup>8</sup>

Alterations in myocardial contractile state exert a predominant influence on the rate of force development and may also influence the magnitude of developed force<sup>6</sup> (Table I). The direction of these responses will be related to whether a positive or negative shift in contractility has occurred and whether this was induced pharmacologically by an agent that also has chronotropic properties or an influence on the resistance vessels (that is, arterioles) of the peripheral circulation. As a case in point, epinephrine would not only raise the inherent rate of force development, but also the frequency of force development per minute (that is, heart rate). The responses in the magnitude and integral of force after administration of epinephrine would also be influenced by the degree of arteriolar constriction. Hence, the overall effect of epinephrine would be an increment in  $\dot{MVO}_2$ .



**FIGURE 3.** Three dimensional representation of the interrelations among myocardial oxygen consumption (cc/min per 100 g), the integral of systolic wall force per minute and the peak rate of force development.

**Role of heart rate:** Increments in the frequency of contraction result in an augmentation in net  $\dot{MVO}_2$  expressed as cubic centimeters of oxygen consumed per minute. Because of the force-treppe phenomenon an augmentation in contractile state and the rate of force development also occurs.<sup>6</sup> However, under the circumstances the integral of systolic force may actually decline. As a result, the net energy utilization per beat will be dependent on the magnitude of these discordant responses.<sup>6</sup> For example, if an increment in heart rate raises the rate of force development less than the accompanying decline in the integral of force then the  $\dot{MVO}_2$  per beat is actually reduced. Nevertheless, because the heart must generate and sustain a given force more frequently per unit of time with the tachycardia, the  $\dot{MVO}_2$  per minute and force integral per minute are increased.

The interrelation between  $\dot{MVO}_2$ , the integral of force per minute (that is, reflecting the magnitude and duration of force and the influence of heart rate), and the rate of force development (that is, the role of contractile state) is shown in Figure 3. An increment in any of these components of wall force requires an almost equivalent elevation in energy expenditure. Hence, we chose to conceptualize the major determinants of  $\dot{MVO}_2$  as follows:  $\dot{MVO}_2 = a\text{TFI} + b\text{dF}/\text{dt} + c$ , where TFI is the systolic force integral per minute,  $\text{dF}/\text{dt}$  is the peak rate of force development,  $c$  represents the minor determinants of oxygen consumption, and  $a$  and  $b$  are constants. Returning to the question of the relative cost of each of the major determinants, we have concluded<sup>6</sup> that for equivalent increments in force, whether achieved by raising diastolic volume or contractility, the augmentation in  $\dot{MVO}_2$  is approximately the same; increments in heart rate, however, require a much larger expenditure of energy.

**Reducing myocardial oxygen consumption:** The response in the components of force, often proceeding in opposite directions, determine the clinical response to various therapeutic interventions. For example, patients with nocturnal angina, symptomatic heart failure and cardiomegaly may experience relief of their angina after digitalization. Conversely, patients with ischemic heart disease and normal heart size have an exaggeration of their anginal symptoms with digitalis. The explanation for these diametrically opposed results resides in the net effect of digitalis on force and thereby  $\dot{MVO}_2$ . In the presence of cardiomegaly digitalis diminishes chamber size and the magnitude and integral of force; it simultaneously will also raise the rate of force development. In those patients whose angina is relieved after digitalis, the net result is a decline in  $\dot{MVO}_2$ , which is explained by the decrease in the force integral being greater than the accompanying increase in the derivative of force. However, the extent to which chamber dimension can decline in the normal-sized heart after digitalis is limited and, as a result, the increment in the rate of force development is unopposed, leading to an imbalance in oxygen demand and supply and consequently angina. These discordant responses in force and hence  $\dot{MVO}_2$  after digitalis have also been demonstrated

in the experimental animal.<sup>9</sup> A reduction in intravascular and intracardiac volume with diuretic agents would also be expected to lower the energy requirements of the enlarged and failing heart.

*Propranolol and nitrates represent the mainstay in the treatment of patients with angina.* Viewed simplistically, propranolol decreases  $\dot{M}\dot{V}O_2$  by reducing heart rate and the rate of force development. Nitrates, such as isosorbide dinitrate, are able to reduce metabolic demand by peripheral venodilatation, which attenuates the venous return and chamber dimension throughout the cardiac cycle. Hence, the magnitude and rate of force development decline with nitrates. The response in heart rate and blood pressure (that is, the double product) to propranolol and nitrates provides a useful clinical estimate of the reduction in  $\dot{M}\dot{V}O_2$ .

### Metabolic Supply of the Heart

**Concept of metabolic reserve:** The capacity of the heart for work, unlike that of skeletal muscle, is greatly dependent on aerobic conditions. The amount of oxygen available to the myocardium (Fig. 1) and its mitochondria, in particular, is determined by (1) the arterial oxygen content and hemoglobin concentration (that is, oxygen-carrying capacity); (2) coronary flow and its distribution through the microcirculatory network (that is, oxygen delivery); (3) the anatomic characteristics of the coronary microcirculation, including the relation of capillaries to myocardial fibers and the diffusion distance for oxygen; and (4) the portion of this delivered oxygen that is driven from the capillaries into the intracellular compartment and which also reflects the influence of transit time. Within the cell, the diffusion of oxygen to the mitochondria is facilitated by the reversible combination of myoglobin with oxygen and the translational diffusion of oxymyoglobin.<sup>10</sup> During acute increments in work the myoglobin content, mitochondrial oxygen tension, and capillary oxygen tension remain unchanged while coronary flow increases. *This increment in coronary flow has been attributed to two possible mechanisms that reflect the adaptation of the microcirculation to variations in metabolic demand.* The first involves a redistribution of flow from nonexchanging to exchanging vessels<sup>11</sup> in a manner analogous to the concept of ventilation:perfusion ratios in the lung. The other mechanism focuses on a recruitment in the number of perfused channels, or the density of open capillaries.<sup>12</sup> However, the relative contribution of either mechanism, remains uncertain. Oxygen extraction may also increase with an augmented work load, but to a lesser extent than the elevation in flow. In the chronically overloaded hypertrophied heart it is not clear whether a proliferation of the capillary bed occurs,<sup>3</sup> thereby preserving the normal diffusion distance for oxygen between the hypertrophied fiber and its capillary bed, or whether part of the adaptation process involves myoglobin or mitochondrial energetics. Nonetheless we have viewed the compensatory adjustments in both flow and oxygen extraction, which occur during acute or chronic elevations in work, as constituting the *metabolic reserve* of the heart.

*Capillary oxygen delivery is established by coronary blood flow, coronary arterial oxygen content, and the oxygen-carrying capacity (that is, hemoglobin concentration).* For any given hemoglobin level the amount of delivered oxygen (coronary flow  $\times$  arterial oxygen content) that is actually consumed (that is, coronary flow  $\times$  arteriovenous oxygen difference) represents the oxygen extracted or, more simply, the ratio of the arteriovenous oxygen difference to the arterial oxygen content. Unfortunately, these measurements do not actually establish the adequacy of the delivered oxygen relative to the mitochondrial oxygen content; rather, they only approximate the kinetics of intracellular molecular oxygen. However, either lactate and pyruvate, or the ratio of reduced to oxidized nicotinamide adenine dinucleotide (NADH/NAD) would reflect the proportion of reduced to oxidized substrate and thereby provide a better description of the adequacy of oxygen delivery to the intracellular compartment. Lactate and pyruvate measurements have been used for this purpose for some time. However, the measurement of NADH using a fluorescence photographic method represents a more recent technique that is now available for this purpose.<sup>13</sup> Harken et al.<sup>14</sup> discuss the relation of NADH to ventricular performance after coronary occlusion in this Seminar. Their findings suggest that myocardial oxidative reserve is negligible.

**Reserve in oxygen extraction:** For a wide variety of conditions, including exercise,<sup>15,16</sup> atrial pacing,<sup>17</sup> catecholamine infusion,<sup>18,19</sup> hyperthyroidism<sup>20</sup> and various cardiac diseases,<sup>15-19,21-24</sup> myocardial oxygen extraction has been found to range between 65 and 75 percent. It has often been presumed that oxygen extraction is invariant and that the 65 to 75 percent range represents a physiologic limit. However, this may not be the case when coronary flow is restricted. Daniell<sup>25</sup> has observed that in the open chest dog, myocardial oxygen extraction reaches a maximal value of  $84 \pm 3$  percent, with progressive reductions in total left coronary flow. Shea et al.<sup>26</sup> reported a similar plateau in oxygen extraction when left coronary flow was limited in the open chest dog. Case et al.<sup>27</sup> observed that when coronary flow was not controlled during progressive reductions in hematocrit, oxygen extraction was invariant as work was increased. However, when coronary stenosis was superimposed in two hearts during similar conditions of anemia and work, oxygen extraction increased to 85 and 91 percent, respectively.<sup>7</sup> Our findings on oxygen extraction and its maximal limit are in close agreement with these observations. Using an isolated canine heart preparation in which coronary flow and oxygen extraction could be measured continuously during progressive increments in metabolic demand, we observed that oxygen extraction will plateau at approximately 82 percent in either the normally perfused or panischemic heart. When the oxygen-carrying capacity had been reduced by producing a dilutional anemia, oxygen extraction exceeded 90 percent. Moreover, our observations in the underperfused heart indicated that myocardial ischemia and hypoxia are not synonymous. Hypoxia, as evidenced by the onset of

myocardial lactate production, does not occur until the conditions of oxygen availability are exceeded.

The fundamental issue pertaining to maximal oxygen extraction, therefore, is the relation between the demand for oxygen and the available oxygen supply. Although a large fraction of the delivered oxygen (65 to 75 percent) is utilized by the heart under a variety of circumstances, oxygen extraction is not maximal unless the coronary vascular reserve has been fully utilized (that is, optimal vasodilatation) or the oxygen-carrying capacity of blood is compromised in the coronary flow-limited heart. This reserve in oxygen extraction has been schematically represented in Figure 4.

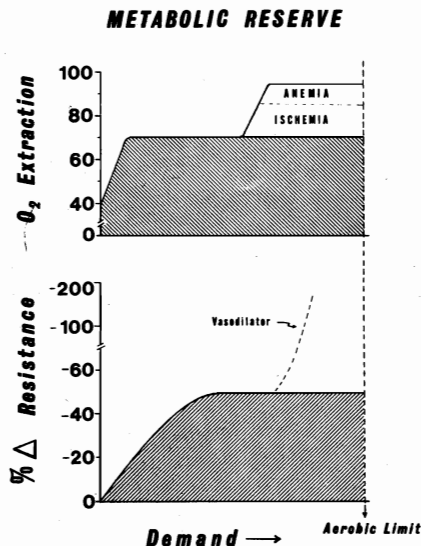
Observations in patients with coronary artery disease would appear to indicate a similar response; however, variations in regional flow and segmental obstructive coronary disease differing in severity and location preclude direct comparisons with the panischemic canine heart. Messer et al.<sup>21</sup> found that 23 of 28 patients with coronary artery disease increased their oxygen extraction during exercise from an average of 69 percent at rest to 75 percent after 7 minutes of exercise; 91 percent of patients without coronary artery disease had no change in oxygen extraction (70 ± 6 percent) during similar levels of work. In the series of Cohen et al.,<sup>22</sup> 13 of 38 patients with coronary artery disease did not experience an increase in coronary flow during the intravenous administration of isoproterenol. In 6 of these 13 patients myocardial oxygen extraction was

increased or unchanged, as opposed to the response in normal subjects, whose coronary flow increased 65 percent and oxygen extraction decreased from 72 to 66 percent during isoproterenol infusion.<sup>17</sup> Neill<sup>23</sup> found that during atrial pacing coronary arteriovenous oxygen difference remained unchanged in two patients and increased in four patients with coronary disease. Angina developed in all six of these patients.

**Coronary vascular reserve:** Utilization of the reserve in oxygen extraction represents a minor response to increments in aerobic work and demand and is brought into play only under conditions in which oxygen delivery is impaired. The coronary vascular reserve, or density of open capillaries, represents the major compensatory response to increased oxygen needs. The importance of alterations in coronary flow has been amply demonstrated during increments in oxygen demand created by exercise<sup>15,16</sup> or atrial pacing<sup>17</sup> or when the oxygen-carrying capacity<sup>7,27</sup> or arterial oxygen tension<sup>28</sup> was purposely reduced.

We examined the boundaries to the coronary vascular resistance (that is, the ratio of the pressure gradient across the coronary circulation to coronary flow), which accompanies coronary vasodilatation during marked increments in aerobic work. It was observed<sup>7</sup> that for conditions in which coronary perfusion pressure was held constant (80 mm Hg) coronary flow increased by an average amount of 45 percent (range 35 to 63 percent). Coronary vascular resistance, therefore, decreased to a similar degree. These findings are in accord with those of others in experimental animals<sup>26,27</sup> and man<sup>15,18-19</sup> in which a variety of conditions were imposed on the myocardium and thereby the coronary circulation. Hence, a substantial decline in coronary vascular resistance occurs during increments in aerobic demand, which permits an increased delivery of oxygen (Fig. 4). This decline in coronary vascular resistance represents the optimal coronary vasodilatation that results for the given metabolic demand. However, coronary flow is not maximal. We have found that flow may increase even further under these conditions when dipyridamole, a potent coronary vasodilator, is administered.<sup>7</sup> However, despite the fact that coronary flow has increased with dipyridamole, ventricular performance (that is, the developed force-length relation) was noted to decline, suggesting that a nonpreferential redistribution of regional coronary flow (that is, "a coronary steal") has been created.

This unexpected response in flow when coronary vasodilatation was at its presumed maximum suggests that the coronary vascular resistance is reduced in a heterogeneous fashion during increments in metabolic demand and that this adjustment in resistance is based on the given relation between supply and demand in various regions of the myocardium. Coronary vascular resistance, therefore, achieves an optimal, albeit not maximal level during increments in aerobic work. The explanation for the response in resistance, related to presumably heterogeneous differences in demand, remains to be elucidated.



**FIGURE 4.** The metabolic reserve of the heart may be described by the changes in oxygen extraction (percent) and the percent decrease in coronary vascular resistance that occur in response to a progressive elevation in metabolic demand. Note that oxygen extraction reaches a plateau early and does not increase again until the coronary vascular reserve has reached its optimal level. Myocardial ischemia or anemia will promote a greater extraction of oxygen. Coronary vasodilators, such as dipyridamole, may increase coronary flow beyond its optimal limits. Once oxygen extraction and coronary flow are maximal, additional increments in demand result in cell hypoxia and, thus, the aerobic limit of the heart is exceeded.

**Aerobic limit of the heart:** When the metabolic reserve of the heart is fully utilized (that is, maximal oxygen extraction and optimal vasodilatation) any further demand for oxygen cannot be satisfied. We have viewed this state as representing the aerobic limit of the heart. Beyond this aerobic limit additional increments in oxygen requirements result in metabolic demand exceeding the oxygen supply and, hence, cellular hypoxia. As a result anaerobic metabolism commences and intracellular oxidation-reduction systems shift to a more reduced state. Lactate accumulates intra- and extracellularly as reflected by a decrease or reversal in the arterial-coronary sinus lactate difference, lactate extraction and the production of lactate.<sup>29</sup> These measurements have been utilized for some time as an indication that the aerobic limit has been surpassed and also to assess the adequacy of coronary flow and oxygen availability in both human being<sup>16-18,20,22-24,30,31</sup> and experimental animal.<sup>7,26,27</sup>

Shea et al.<sup>26</sup> found a net lactate production across the myocardium when coronary flow was reduced from 160 to 35 ml/min. At this juncture of negative arteriovenous lactate difference, oxygen extraction was more than 78 percent. These investigators examined the influence of increments in pressure work when coronary flow was held constant. Here again, atrioventricular lactate difference became negative when coronary vascular resistance had reached its minimal value. In our studies<sup>7</sup> anaerobic metabolism also occurred when the metabolic demand exceeded the available supply of oxygen. This imbalance in demand and supply could be produced in either the normally perfused or panischemic heart. It is clear that left ventricular performance decreased when the aerobic limit was surpassed. Pulsus alternans appeared in the majority (more 80 percent) of hearts irrespective of the coronary perfusion pressure.<sup>7</sup> The appearance of pulsus alternans in hearts perfused at 80 mm Hg suggests that an imbalance in supply and demand might also exist in the failing, nonischemic heart and that these hearts may "outdistance" their blood supply.

### Myocardial Energy Utilization in Acquired Heart Disease

**Conditions of imbalanced supply and demand:** Fallen et al.<sup>18</sup> examined the response in coronary flow, oxygen extraction and lactate metabolism to an isoproterenol infusion in patients with aortic valvular stenosis and angina. In five patients having angina without coronary artery disease, the isoproterenol challenge was not accompanied by the expected normal rise in coronary flow. However, oxygen extraction did increase in three of these patients, and myocardial lactate production developed in all five patients. In seven patients with aortic stenosis without angina, coronary flow increased significantly (47 percent), oxygen extraction decreased and only one patient had any evidence of myocardial glycolysis, although it was uncertain whether or not this patient had normal coronary arteries. Myocardial lactate production has also been

observed in patients with aortic stenosis by Trenouth, et al.<sup>17</sup> when heart rate was raised to 120 to 140 beats/min by atrial pacing; lactate extraction became negative in 6 of these 12 patients. All six of these patients had a history of exertional angina despite the absence of coronary artery disease. The 12 patients with aortic stenosis all underwent surgical replacement of their diseased valve. Of the four patients who did not survive operation or died within 3 months of their operation, three had demonstrated negative lactate extraction (mean -31 percent) during atrial pacing.

In the series of Cohen et al.,<sup>22</sup> 38 patients with coronary artery disease had metabolic studies during an isoproterenol challenge. Thirteen of these patients did not have a significant increase in coronary flow; 6 of these 13 had either no change or an increase in oxygen extraction, whereas in 5 of these 6 patients lactate extraction declined to less than 10 percent or became negative. Neill<sup>23</sup> also examined the response in myocardial metabolism in 13 patients with coronary artery disease and angina. Here oxygen demand was raised by atrial pacing. During the tachycardia (120 to 140 beats/min), coronary arteriovenous lactate difference became negative in three patients and the oxygen difference and percent extraction increased in two of these three patients. One other patient whose lactate extraction was negative before pacing had an even further decline in the arteriovenous lactate with tachycardia. Hence, in four patients it was possible to demonstrate that the demand for oxygen exceeded the available supply. The fact that these findings could not be demonstrated in the remaining patients may merely reflect the limitations of the coronary sinus sampling site as an index of regional differences in coronary flow and demand in segmental coronary artery disease.

**Oxygen availability and heart failure:** Over the years several schools of thought have developed regarding those events that initiate failure. One theory that has received recent support emphasizes a feedback control of ventricular hypertrophy based on normalizing wall force per unit of muscle (that is, wall stress).<sup>32</sup> Hypertrophy, which may have served for many years to normalize the augmented wall force of the pressure- or volume-overloaded heart, eventually becomes incapable of compensating for the increased hemodynamic load. Hence, failure results, accompanied by a continuing cycle of progressive chamber enlargement and failure. The explanation for this inappropriate response in wall thickness, and presumably protein synthesis, is unknown. Other investigators<sup>3</sup> have theorized that the metabolic demand of the mechanically overburdened heart eventually exceeds its available energy supply. As a consequence, a defect in mechanical performance and protein synthesis ensues. It is these events that lead to progressive chamber dilation and inappropriate elevation in wall stress without concomitant hypertrophy.

Most clinical studies in patients with cardiac disease have observed a common range for coronary flow and  $MVO_2$  when expressed per 100 g of ventricle.<sup>15-18,20,23,24,30,33-36</sup> This range corresponds to that

**TABLE II**  
**Ventricular Mass and Energetics in Aortic Stenosis**

	Normal Heart	→ Compensated AS →	Decompensated AS
Peak systolic wall force (g)	2,835	8,160	13,060
End-diastolic volume (cc)	100	125	250
LV pressure (mm Hg)	80	200	200
LV mass (g)	125	450	600
Peak systolic wall stress	152	146	216
MVO <sub>2</sub> (cc/min)	10	36	48
Coronary blood flow (cc/min)	100	360	480
O <sub>2</sub> extraction (%)	75	75	80
MVO <sub>2</sub> (cc/min per 100 g)	8	8	8
Coronary blood flow (cc/min per 100 g)	80	80	80

AS = aortic valve stenosis; LV pressure = left ventricular pressure at aortic valve opening, which approximates the point of peak systolic wall force; MVO<sub>2</sub> = myocardial O<sub>2</sub> consumption; Normal heart = trivial to nonexistent aortic valve gradient.

observed in patients without significant cardiac disease. Because of the increased muscle mass with cardiac disease, total coronary flow and MVO<sub>2</sub> are substantially increased. Comparison of MVO<sub>2</sub> in patients at rest with compensated and decompensated failure has also revealed no differences even though the wall stress was shown to be greater in the patient with symptomatic failure. However, as discussed earlier in this review, when metabolic demand is raised in patients with heart failure, as occurs with pacing or isoproterenol administration, evidence of cell hypoxia results and myocardial lactate is produced despite the absence of obstructive coronary disease. This response suggests that under these circumstances metabolic demand exceeds the given metabolic supply. Considering that the total coronary flow (expressed in cc/min) may be increased three to four times above normal, commensurate with the increase in muscle mass, it is not surprising that the coronary vascular reserve may be fully utilized under these circumstances.

*The response in ventricular mass and energetics that occurs as a result of an augmented hemodynamic load may be described in the following manner (Table II):* In aortic valve stenosis, for example, the gradual nar-

rowing of the valve orifice imposes a progressive hemodynamic burden on the ventricle. Consequently, wall force and MVO<sub>2</sub> (cc/min) are increased and myocardial mass begins to increase. Once a stable phase of hypertrophy results, the energy utilization per cell (and mass) is again normal; force is now also distributed over a greater surface area of fibers and, hence, wall stress (force per cross-sectional area of muscle) returns to the expected normal range (the compensated phase).<sup>32</sup> Eventually, coronary flow, or specifically capillary vasodilatation, and oxygen extraction reach their optimal limit and exhaust the *metabolic reserve*. Under these circumstances the supply of oxygen to the heart may prove adequate only at rest. During conditions in which oxygen demand is raised, anaerobic metabolism occurs. As a result of the cell hypoxia a decline in contractile state follows and the heart fails, leading to a further increment in chamber size and, as a consequence, a progressive elevation in wall force. At this point (decompensated phase) metabolic demand, as determined by systolic force, is greater than the supply of energy and, as a result, protein synthesis and myocardial mass cannot keep pace with the existing needs. Consequently, wall stress is also increased. Oxygen utilization would likewise be raised and to a level that is dependent on the absolute increment in force. A vicious cycle of progressive increments in demand ensues, which is unaccompanied by compensatory alteration in myocardial growth.

*The correction of the disease state at this point may or may not ameliorate the demand.* The response in demand would seemingly be a function of the response in wall force. If demand is attenuated and the balance between supply and demand is restored, then the depression in contractility may be reversed. In this case, mass would also gradually regress to more normal levels. If it were possible to document routinely the metabolic reserve and an imbalance in supply and demand in the overloaded heart with such interventions as pacing or catecholamine infusion, this information might prove useful in assessing the degree of failure, the timing of operative intervention and the utility of the compensatory response in mass. However, the validation of this argument requires systematic study. Finally, the problem of oxygen availability may represent just one of many mechanisms that may be deranged in the failing heart.

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