Myocardial Oxygen Consumption: The Quest for its Determinants and Some Clinical Fallout
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Oxygen Consumption of the Heart: Newer Concepts of Its Multifactoral Determination
by E. H. Sonnenblick, J. Ross, Jr., E. Braunwald (1)

ABSTRACT

The factors that control the consumption of oxygen and utilization of energy by the heart have been of interest to cardiovascular physiologists and clinicians for many years. The determinants of myocardial oxygen consumption (MVO₂) have warranted this careful consideration since, in the presence of steady state conditions and with the obligatory aerobic nature of myocardial metabolism, MVO₂ serves as a measure of the total energy utilization of the heart. Therefore, since utilization of high energy phosphates, which constitute the immediate energy source for contraction, is not readily determined directly, advantage is taken of the close correlation between energy utilization and MVO₂, and the latter is measured experimentally. Further, under clinical conditions that place a restraint on coronary blood flow and, hence, on the availability of oxygen to the myocardium, factors that alter MVO₂ become a primary consideration.

A major advance in our understanding of the determinants of MVO₂ has come from an appreciation that cardiac muscle is subject to the same general principles of control and analysis as is skeletal muscle. Thus, the same factors that govern the conversion of chemical energy into mechanical work in skeletal muscle are important considerations in dealing with heart muscle. In the present discussion the development of an integrative concept of the determination of MVO₂ will be reviewed, and its relation to our present knowledge of muscle mechanics will be assessed briefly. Such a synthesis may offer insight into some of the apparent discrepancies and inconsistencies with which the literature on the subject abounds and may provide a more rational framework for understanding the dynamic control of MVO₂ in both physiologic and pathologic states.

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50th Anniversary Historical Article

INTRODUCTION

In this edition of the Journal, we release the twelfth in a series of reviews of influential articles that have been previously published in ACC journals, including the American Journal of Cardiology (from 1958 to 1982) and JACC (from 1983 to the present). The publication of these articles is only one aspect of the ACC’s 50th anniversary commemoration, which highlights 50 years of leadership in cardiovascular care and education. The articles are intended to encourage reflection on the remarkable progress made in cardiovascular medicine over time, as well as to acknowledge the amazing prescience of some early investigators in anticipating and, in many cases, later guiding developments in their field.

The working group responsible for selecting these articles and asking reviewers to write editorials solicited suggestions from the ACC’s clinical committees and individual members. The group achieved consensus fairly easily, including whom the group should ask to prepare the accompanying editorials. We initially drew up a list of 14 general areas to cover in this series, but later found that there are several major areas of modern cardiology, prominently molecular cardiology, in which the truly landmark articles have, alas, not yet been published in JACC. Therefore, the working group decided not to categorize by subject, but instead, to concentrate on the most important articles.

The working group, a task force of the Subcommittee for the Commemoration of the ACC 50th Anniversary, owes a great deal to Ms. May A. Roustom and the efficient and tireless staff at Heart House for facilitating this project. We also wish to thank all who suggested articles and, most important, the authors who prepared reviews for their willingness to contribute their time and wisdom.

Influential Articles in JACC Working Group
Sharon A. Hunt, M.D., F.A.C.C.
Rick A. Nishimura, M.D., F.A.C.C.
H.J.C. Swan, M.D., Ph.D., M.A.C.C.
Michael J. Wolk, M.D., F.A.C.C.
I joined the team led by Stanley J. Sarnoff in the Laboratory of Cardiovascular Physiology at the (then) National Heart Institute to investigate the hemodynamic determinants of this critical variable. The importance of \( \text{MVO}_2 \) had been appreciated since the work of Evans and Matsuko (2) in Ernest Starling’s laboratory at the beginning of the 20th century. These investigators understood that the heart is an aerobic organ and cannot (except for very brief periods) develop an oxygen debt. However, there had been surprisingly little research on this important aspect of cardiovascular physiology for four decades, and we felt that if we could “get a handle on” the determinants of \( \text{MVO}_2 \), we would gain important insights into the heart’s total metabolic activity and could then relate this to its contractile function.

Our first task was to develop a canine heart preparation in which the key hemodynamic parameters (preload, afterload and heart rate) could be accurately measured and independently controlled. In the classical heart-lung preparation, heart failure is progressive, but we needed to maintain normal cardiac function over several hours. This would avoid the confounding influence of progressive reductions of contractility and of ventricular dilation on the relation between cardiac contraction and energetics. Therefore, in our “isolated supported heart preparation,” we used a separate support dog whose circulation was in series with the isolated heart and whose lungs served to oxygenate the blood (3). The idea for this preparation had been sparked by the technique of controlled cross circulation, which allowed open-heart surgery to be performed before the perfection of the heart-lung machine.

These experiments were both complex and costly; they involved the use of a new generation of flow meters that provided simultaneous and precise measurement of cardiac output and coronary blood flow. Each experiment took a team of eight investigators, post docs and technicians about 18 h, and the manual analysis of the records produced by the first eight-channel recorder used in cardiovascular physiology took us another week or so.

From this study we learned that at any heart rate, intraventricular pressure was the most important determinant of \( \text{MVO}_2 \). The area under the left intraventricular pressure curve, which we termed the “tension-time index,” proved to be an even better correlate of \( \text{MVO}_2 \) than the peak pressure itself because this area takes account of the important effects of heart rate and the relatively modest effects of stroke volume (4). Having established the tension-time index as a major determinant of \( \text{MVO}_2 \), we went on to demonstrate that \( \text{MVO}_2 \) in turn, is the major determinant of coronary blood flow (5). Subsequently, other investigators devised techniques for calculating ventricular wall tension, an even closer correlate of \( \text{MVO}_2 \) than the tension-time index (6).

### Control of Myocardial Oxygen Consumption: Physiologic and Clinical Considerations

**by E. Braunwald (7)**

**ABSTRACT**

The basal oxygen consumption of the heart is small, approximately 20 percent of that of the contracting organ. Oxygen cost of depolarization is approximately 0.5 percent of the total oxygen consumed by the normally working heart. There is a far greater oxygen cost of “pressure work” as opposed to “flow work,” and a close relation between the area beneath the left ventricular pressure curve, that is, the tension-time index, and myocardial oxygen consumption. Also, the contractile state of the heart, as reflected in the maximal velocity of isotonic shortening, is a major determinant of myocardial oxygen consumption. Thus, velocity of contraction shares its role of important determinant of myocardial oxygen consumption with developed tension and heart rate. Although the precise costs of activation and maintenance of the active state of the myocardium have not yet been clearly defined, it is likely that they are relatively low. In studies on isolated papillary muscles, oxygen consumption was found to be a function of the tension that is developed and the velocity of shortening of the unloaded muscle. Shortening against a load requires oxygen above and beyond that required for the development of tension. Almost the entire increase in myocardial oxygen consumption produced by the administration of catecholamines results from the increased contractile activity produced rather than from a direct stimulating effect of the catecholamines on myocardial metabolism. Severe valvular regurgitation does not increase myocardial consumption significantly when myocardial tension is held constant. Congestive heart failure is associated with depression of myocardial contractility, but this cannot be attributed to any reduction of high energy phosphate stores in cardiac muscle. A technique for reducing myocardial oxygen requirements by stimulating the carotid sinus nerves is described and its application to the treatment of angina pectoris demonstrated. It is also shown that following coronary occlusion, interventions that increase myocardial oxygen consumption appear to increase the size of the infarction, whereas those that decrease myocardial oxygen consumption reduce the size of the infarction.


**Review**

A decade later, I resumed studies of this subject with new collaborators—John Ross, Edmund Sonnenblick, James Covell, Neal Coleman, Tom Graham and others. In the interim, principles of skeletal muscle mechanics had been adapted to the heart. A second set of experiments was carried out using a new canine preparation. With the dog on total cardiopulmonary bypass, a balloon was placed into the left ventricle so that it contracted isometrically; myocardial
contractility was defined as the maximal velocity of calculated contractile element shortening, the so-called Vmax (8). We demonstrated the importance of myocardial contractility as the third key determinant of MV\(\dot{O}_2\) (9,10) and then extended our work to the isolated papillary muscle, which allowed more precise measurement of myocardial shortening (11). From this work and the work of other investigators, we defined nine determinants of MV\(\dot{O}_2\)—the “big three” (systolic wall tension, contractility and heart rate) and six others (Table 1). These experiments were then extended to dogs with experimentally-produced and quantified valvular regurgitation (12).

An understanding of the determinants of MV\(\dot{O}_2\) clarified a number of previously puzzling clinical observations. For example, the reduced levels of systolic wall tension in mitral regurgitation explained the infrequency of ischemic manifestations in patients with this valvular abnormality. The rarity of angina in patients with idiopathic dilated cardiomyopathy and severe heart failure—despite the increase in left ventricular volume and, therefore, in wall tension—could be explained by the diminished myocardial contractility. A reduction of MV\(\dot{O}_2\) through slowing of heart rate and blockade of the stimulant effects of sympathetic influences on myocardial contractility was responsible for the anti-anginal actions of the beta-adrenoreceptor blockers which allowed more precise measurement of myocardial shortening (11).

As stated in the 1971 paper:

“...An understanding of the determinants of myocardial oxygen consumption is particularly relevant to patients with acute myocardial infarction... Since the blood supply to (the) ischemic segment of myocardium is markedly reduced, its survival may depend on its oxygen needs. If the oxygen requirement of the myocardium is stimulated by factors such as increased tension, or contractility, or both, the viability of the ischemic area may be reduced and the size of the infarct enlarged...”

“To test this hypothesis, branches of the left anterior descending coronary artery were ligated in the open chest dog and epicardial leads were recorded over the anterior surface of the left ventricle before and after the occlusion. Areas of ischemia, i.e., with elevations of the ST segment, were observed in the direct distribution of the occluded vessel... The augmentation of myocardial oxygen consumption produced by stimulating myocardial contractility with the administrations of positive inotropic agents such as isoproterenol caused further elevation of ST segments... Conversely, the administration of a beta adrenergic blocking drug, propranolol, which blocks the stimulating effects of adrenergic agents on the heart, would be expected to lower myocardial oxygen demands, and in these studies it was found to reduce the ST-segment elevations occurring during coronary occlusion. It was of considerable interest that changes in myocardial oxygen consumption produced at late as 3 hours after coronary occlusion altered the area of ischemic injury. (my current emphasis)...”

“Reduction of myocardial oxygen demands produced by slowing the heart rate and counteracting the augmentation of sympathetic influences may reduce oxygen demands and thereby the size of the infarction.” (my current emphasis)

These observations led to a long string of experiments in the dog and rat, conducted first with the late Peter Maroko and subsequently with James Muller and Robert Kloner, in which a variety of interventions—including myocardial reperfusion—were shown to be effective in limiting myocardial damage following coronary occlusion (16). These experiments, in turn, led to our efforts in the TIMI (Thrombolysis in Myocardial Infarction) trials to improve clinical outcome with thrombolytic therapy early in the course of myocardial infarction (17).

In 1955, when we began our work on elucidating the determinants of MV\(\dot{O}_2\), we did not appreciate its potential clinical relevance. At that time, our experiments were categorized as basic physiologic research, of little if any clinical import. Their potential clinical significance became clear only after a latent period of about 15 years (55 years if we take as the starting point the 1915 experiments of Evans and Matsuoko [2] referred to previously). It is gratifying to me that we now live in an era in which there is great encouragement for investigators to accelerate “bench to bedside” translation.
REFERENCES