ESSAYS ON APS CLASSIC PAPERS

Relating cardiac performance with oxygen consumption: historical observations continue to spawn scientific discovery

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This essay examines the historical significance of two APS classic papers that are freely available online:

STUDIES THAT HAVE DEFINED the relationship between cardiac mechanical activity and oxygen utilization have been key in advancing our understanding of the heart in health and disease. The isolated heart (e.g., Langendorff preparation) has been used effectively in this regard to exclude systemic neurohumoral influences and to control the effects of loading pressure and heart rate.

Two articles published in the American Journal of Physiology, one in 1957 by Sarnoff et al. (6) and one in 1967 by Neely et al. (4), are classic examples of how the relationship between cardiac performance and oxygen consumption was determined. Building upon the work of Starling and Vischer (7), Sarnoff et al. (6) used a novel blood-perfused preparation consisting of an isolated dog heart supported by a donor dog. Unlike many prior and subsequent investigations, this preparation maintained cardiac performance, allowing critical evaluation of the effect of varying heart rate, aortic pressure, and preload on oxygen consumption in the left ventricle (5). Neely et al. (4) used a modification of the rat Langendorff system that included EDTA to chelate trace metals, heparin to reduce thrombi, larger recirculation volumes, and more physiological perfusion pressures. With this preparation he was able to conduct experiments for up to 3 h without a deterioration in function, while manipulating ventricular pressure development, filling pressure, and heart rate and observing the effect on oxygen consumption and flow.

Despite the marked difference in species and heart sizes, both Sarnoff and Neely identified the importance of the tension-time index (average ejection pressure of the left ventricle multiplied by the duration of ejection) and peak systolic pressure as strong correlates of oxygen consumption, while changes in cardiac output and work were not. These results correctly predicted marked increases in oxygen utilization in the presence of ventricular dilatation, even to the point where oxygen demand outstrips supply.

These two studies were turning points in the development of a clearer understanding of the interplay between cardiac oxygen consumption and function. Interest was stimulated to make similar functional measurements in humans and intact animals. The stage was thereby set for subsequent identification of new methodologies, diagnostic tools, and therapeutic approaches used today and planned for the future. This included the development of impedance catheter measurements of left ventricular volumes and pressures in vivo, and noninvasive tissue Doppler, computed tomography (CT), and magnetic resonance imaging (MRI) quantification of regional systolic and diastolic function in humans. As confirmed by these newer techniques, the fundamental principle remains valid: namely, that wall tension is a major determinant of myocardial oxygen consumption.

Recent treatments for heart failure are also in part based on the principles defined by Sarnoff and Neely. For example, the symptom and mortality benefit of afterload reducers such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or hydralazine plus isosorbide relates to a reduction in tension-time index that parallels the lowering of ventricular developed pressure and oxygen demands of the heart. A pharmacological reduction in heart rate (e.g., β-adrenergic blockers) produces a similar improvement in oxygen consumption and a reduction in heart failure symptoms. Other applications have followed. The Batista procedure for cardiomyopathy surgically removes part of the dysfunctional and dilated ventricle. The reduction of ventricular volume thereby directly reduces tension and increases contractile efficiency based on the law of LaPlace. Although results with this procedure were initially positive with improved patient functional capacity, long-term outcomes were less encouraging, and with better treatment now available, the surgery is not widely performed in the United States. Biventricular pacing for asynchronous heart failure reduces ventricular volume and...
improves performance. This form of therapy is targeted to select patients with heart failure and produces a small but significant improvement in ejection fraction and functional capacity.

There has been an explosion of information defining the biochemical, cellular, and ultrastructural components of the contractile process and how contraction and energy utilization affect oxygen consumption. Furthermore, systems biology approaches are currently evolving which utilize multiscale biophysical models of mitochondrial energetics that respond to inputs from the nucleus and mitochondrial genome, proteome, cytoplasm, and extracellular signals (1, 2). When integrated with cell, tissue, and organ studies, these models will soon enable predictions of ATP synthesis, O2 consumption, reactive oxygen species production, electron transport, and energetic and quantitative testing in experimental paradigms and human subjects (3).

A systems biology approach to cardiac function will provide an integrative and logical extension of the foundation laid by Sarnoff and Neely nearly one-half century ago. This brings cardiac research full circle, from the physiological observations made by Sarnoff and Neely, to a better understanding of the cellular and subcellular events modulating cardiac contraction, and then back to whole organism physiology to achieve an understand of the composite organism.

REFERENCES