Commentary

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The cardiac force-frequency relationship and frequency-dependent acceleration of relaxation are impaired in lipopolysaccharide-treated rats: is the phospholamban-SERCA axis a therapeutic target?

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Abstract

Sepsis-induced myocardial dysfunction has traditionally been thought of as principally affecting systolic heart function. One of the primary reasons for this concept is that systolic dysfunction is relatively easy to conceptualize, visualize, and measure. With the advent of preload-independent measurements for diastolic function, both measurement and conceptual difficulties are being resolved, and a new realm of evidence is beginning to emerge regarding the aberrations that are found during cardiac relaxation in sepsis. A recent article in *Critical Care* brings this issue into sharper focus.

In the previous issue of Critical Care, Joulin and colleagues [1] describe an animal model of lipopolysaccharide (LPS)-induced impaired myocardial systolic and diastolic function. Diastole is composed of two physiological phenomena: myocardial stiffness, which is energy independent, and active relaxation, which is an ATP-requiring process [2]. Current echocardiographic techniques can help distinguish which of the two is the predominant pathway, although these techniques may not always be practical in critically ill patients [3]. In some patients with sepsis, a reversible component to impaired ventricular relaxation has been demonstrated [4], which would imply that the energy-requiring component of diastolic function is more perturbed in certain patients. One might wonder why this is an important distinction to make, but considering that increased mortality in sepsis may be correlated with increasing fluid administration [5], it would seem that being able to distinguish between isolated systolic, diastolic, or combined dysfunction may prove to be life saving. In addition, therapeutic measures might reasonably be aimed at active relaxation.

Isolated and reversible left ventricular diastolic dysfunction was recently demonstrated in septic patients [4]. This was achieved by serial transesophageal echocardiographic measurement of standard indices of systolic function, as well as analyzing diastolic mitral inflow and annular tissue Doppler patterns, the current standard in echocardiographic grading of diastolic function [4]. This study highlighted the fact that we should be cognizant that not all patients suffering from sepsis and shock should be treated uniformly, and that choices of intravenous resuscitation and vasopressor therapies need careful consideration. The study further elucidated the reversible nature of the impaired ventricular relaxation in humans, suggesting that a metabolic or molecular process may be responsible.

Considerable work has been done on defining the molecular biology of diastole. An attractive mechanism currently thought to play a major role is that of calcium flux. Systole is initiated by rapid elevation of myocyte intracellular calcium, both through influx (through L-type calcium channels) and calcium-mediated calcium release from the sarcoplasmic reticulum (through the ryanodine receptor) [6]. Calcium itself then initiates conformational changes in the contractile apparatus that mediates contraction. Re-uptake of calcium into the sarcoplasmic reticulum by sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) allows for

LPS: lipopolysaccharide; SERCA: sarcoplasmic reticulum Ca^{2+}-ATPase.

cardiac relaxation. The ability of SERCA to pump calcium back into the sarcoplasmic reticulum is governed by phospholamban, a sarcoplasmic reticulum membrane-bound modulatory protein [7]. The rapidity at which calcium is returned to the sarcoplasmic reticulum is directly related to the rapidity of cardiac relaxation. In the unphosphorylated state, phospholamban inhibits calcium uptake by SERCA, and subsequently slows diastole. Signaling by protein kinase leads to phosphorylation of phospholamban, which, in turn, diminishes its inhibitory activity on SERCA, promoting cardiac relaxation. In a knockout mouse model lacking phospholamban, SERCA activity is uninhibited, and diastolic dysfunction with aging is not seen [8]. While other pathways, such as sodium-calcium exchange, are important in myocardial calcium trafficking, those are currently beyond the scope of this comment, and will not be described.

Joulin and colleagues, in their experiments, were able to demonstrate a SERCA-dependent aberration in diastolic cardiomyocyte behavior. In particular, in their experiments, they were able to demonstrate a SERCA-dependent aberration in diastolic cardiomyocyte behavior. The force-frequency relationship (that is, heart-rate-dependent increase in cardiomyocyte shortening) and frequency-dependent acceleration of relaxation are physiological phenomena that ensure maintenance of cardiac output with the decreased ejection and filling times that are consequences of higher heart rates. The group hypothesized that LPS would disrupt this delicate balance by exerting an effect on the molecular workings within the cardiomyocyte – principally through the inhibition of the phosphorylation of phospholamban. By utilizing echocardiographic measurements of diastole, and through western blot analyses, they were able to demonstrate a correlation between LPS-induced myocardial relaxation dysfunction (frequency-dependent acceleration of relaxation depression) and SERCA function.

It is important to note that this work was done in a murine model of LPS infusion, a model with potentially important differences from septic patients being treated in the intensive care unit [9]. It is well known that the mediators of the sepsis syndrome are numerous. Anesthetic agents were used to regulate heart rates, and real-time alterations in physiological functioning may have been missed. The group studied only the sarcoplasmic reticulum when calcium trafficking is also linked to mitochondrial function and integrity, nitric oxide production, the beta-adrenergic response, and potential protective effects on the myocardium during prolonged sepsis [10].

Would specific targeting of intracellular calcium, or SERCA-related protein kinase and phosphatase result in better hemodynamics in septic shock? There is already a body of evidence to suggest that calcium-sensitizing agents, such as levosimendan, may improve hemodynamics in sepsis. In two animal models, left ventricular relaxation was improved after treatment with levosimendan in contrast to inotropes, such as milrinone or dobutamine [11,12], and in a clinical trial, levosimendan proved useful in improving global hemodynamic measurements [13]. The study by Joulin and colleagues is certainly thought provoking, and will hopefully lead us closer to developing better strategies for dealing with sepsis-induced myocardial dysfunction – both its systolic and diastolic components.

Competing interests

The authors declare that they have no competing interests.

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