Reply to Letter to the Editor

Nonlinear biphasic relationship between the time constant tau and load

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To the Editor,

I appreciate the excellent points raised by Leite-Moreira et al. regarding my manuscript examining the load sensitivity of left ventricular (LV) relaxation in heart failure [1], and welcome the opportunity to respond. As has been detailed by these authors and others previously, relaxation behavior is complex and can be influenced by multiple factors including the magnitude of load, the timing of load, and the manner in which the load is applied. This study examined the effect of load on LV relaxation in the intact state during transient reductions in preload while controlling such variables as heart rate and neurohumoral reflexes. These experimental conditions are quite different than those used by the authors in their previous studies describing a J-shaped tau-load relation [2,3], which examined the effect of single beat elevations in afterload on LV relaxation. Prior studies examining the influence of transient changes in preload on tau [4,5], including one recently published by the authors [5] have reported a direct linear relationship between load and tau. It is in this context that the finding of a biphasic relationship between tau and load during preload reduction is novel. As outlined in the paper, differences between my results and these prior studies may be secondary to differences in experimental design (e.g. heart rate and reflex effects) and the degree of load reduction achieved. Thus, I would view my study and those by Leite-Moreira, Gillebert, and coworkers [2,3] as describing complementary but not identical phenomena regarding the influence of load on LV relaxation.

I agree with Leite-Moreira et al. that transient caval occlusion alters both preload and afterload (an expected occurrence in the intact state when a series of beats is assessed following an isolated initial load change), and invokes the first phase of the myocardial stretch response. On the other hand, the effects of length-dependent activation on myocardial function manifest significantly later, occurring several minutes after the initial change in muscle length [6,7]. This is well beyond the time period examined in my study, in which transient caval occlusion was only performed for 10 seconds. Furthermore, an exaggerated biphasic response of tau to load was noted in heart failure, a pathophysiologic state characterized by attenuation of length-dependent activation [8,9]. Thus, it is unlikely that length-dependent activation significantly influenced the results reported.

In summary, studies examining the influence of load on left ventricular relaxation have utilized several types of interventions to alter load: long-term steady-state changes, short-term transient changes (as with caval occlusion in my study), and single beat changes (as performed by Leite-Moreira and coworkers). When considered together, these studies provide a complementary and comprehensive assessment of the complex influence of load on LV relaxation. Unlike steady-state changes, the time course of transient caval occlusion precludes a significant impact of length-dependent activation on myocardial function.

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