Impaired Myofilament Function After Myocardial Infarction

While myocardial infarction (MI) is the major cause of heart failure, there are conflicting data over the roles of abnormal calcium handling and myofilament function. The acute injury leads to the activation of neurohormones and cytokines, subsequent myocardial remodelling, further decline in heart function, and finally overt heart failure. Depressed myocyte contractility in the remodelled myocardium can largely be explained by Ca$^{2+}$ handling abnormalities. Abnormalities in myofilament function are less well understood. A seminal study in pigs demonstrated that impaired pump function three weeks after MI can also be attributed to decreased maximal isometric tension in skinned cardiomyocytes in areas remote from the ischemic border zone. Somewhat paradoxically, the impairment occurred in the context of increased Ca$^{2+}$ sensitivity of the myofilaments. The authors attributed the increased Ca$^{2+}$ sensitivity following MI to reduced protein kinase A-mediated troponin I (TnI) phosphorylation. Increased myofilament Ca$^{2+}$ sensitivity has also been reported for end-stage human heart failure, apparently largely because of a reduction of TnI phosphorylation.

Benefit of Exercise Training Post MI

One of the most effective and least expensive therapies for cardiovascular disease is exercise. Clinical studies generally show a benefit of exercise training and a reduction of cardiac mortality after MI by 26%. The question remains of how soon to start exercising, especially after a large MI. In several clinical and animal studies, there were detrimental consequences when exercise began immediately after an MI.

In the current issue of Circulation Research, de Waard et al. present remarkable data addressing the question of exercise training early post MI. After a large MI, mice were subjected to 8 weeks of “voluntary” exercise training. Exercise had no detrimental effects on mortality and minimal effects on myocardial hypertrophy and left ventricular remodelling. Furthermore, there was a clear benefit in pump function and general exercise capacity. On the cellular level, exercise improved cell shortening and lowered elevated end-diastolic Ca$^{2+}$, whereas Ca$^{2+}$ transient amplitudes and Ca$^{2+}$ handling proteins (SERCA2a, phospholamban, Na$^{+}$/Ca$^{2+}$ exchanger) were relatively unaffected. Moreover, exercise normalized the depressed maximum developed force and also normalized the increased myofilament Ca$^{2+}$ sensitivity of the post-MI myocardium. The authors conclude that improved contractility with early exercise training following MI is because of improved myofilament function rather than the restoration of depressed Ca$^{2+}$ transients. The reduction in myofilament Ca$^{2+}$ sensitivity is presumably caused by improved β-adrenergic signaling.

Voluntary Exercise Is Better

Unlike most humans, mice like to run, and will do so endlessly when given the opportunity. Mice run more than 4 miles a day without needing any encouragement (see Figure 1A in their article). The authors take full advantage of this trait to assess the effect of early voluntary exercise after MI. The study design is amazingly simple: present 1 group of mice with a running wheel, and return 8 weeks later to see the results. Why is the voluntary aspect of exercise important? Because thus far, animal studies that have examined the question of early exercise after MI used forced, standardized exercise protocols (swimming or treadmill). These exercise studies considerably stress the animals which could offset the beneficial effects of exercise and may explain the adverse outcomes of earlier studies. Figure 1A provides another clue to why early exercise was better tolerated in the current study: During the first week after coronary ligation, recovering mice slowly titrated up their daily running activity, reaching distances similar to their sham-operated counterparts only later during the study.

Exercise Decreases Myofilament Ca$^{2+}$ Sensitivity

The comprehensive experimental data in the present article debunk the previously held notion that exercise sensitizes myofilaments to the effects of Ca$^{2+}$. The investigators were able to construct full pCa-force relationships in isometrically contracting myocytes. This technique is experimentally challenging. Previous studies have relied on simultaneous measurements of fractional shortening and Ca$^{2+}$ fluorescence in unloaded myocytes to estimate myofilament Ca$^{2+}$ sensitivity. Although experimentally a much simpler approach, there are a number of problems with this method. One is that maximal developed tension cannot be assessed in unloaded myocytes. As a result, any changes in developed tension are ignored when estimating apparent Ca$^{2+}$ sensitivity. A second problem...
is that basal sarcomere length is much shorter in unloaded myocytes (1.8 versus 2.2 micrometers), and more importantly, cannot be controlled. Thus, even slight changes in basal sarcomere length will confound the result. This technical problem is illustrated by comparing Figures 4 and 7 of the article: Figure 4 clearly demonstrates that exercise increased maximum developed force (panel C) and decreased myofilament sensitivity (panel D). Contrast this with data from unloaded myocytes (Figure 7), which establish that exercise increased fractional shortening (panel A) despite unchanged Ca²⁺ transients (panel B). Observations similar to those illustrated in Figure 7 have prompted other investigators to (wrongly) conclude that exercise increases myofilament Ca²⁺ sensitivity.⁹ Thus, the data presented here⁸ powerfully reveal why it is problematic to make inferences on myofilament function solely on the basis of unloaded shortening and Ca²⁺ measurements.

**Exercise Benefits Beyond Improved Myofilament Function?**

The de Waard et al study⁸ establishes that exercise is beneficial for myofilament function. But does it really make a difference? The lack of change in mortality in the MI group would suggest otherwise. This piece of data deserves further consideration.

The most common cause of mortality after MI is sudden cardiac death (SCD) because of arrhythmic events. About 60% of acute MI mortality is attributed to ventricular tachycardia or fibrillation, accounting for more than 250 000 deaths annually in the United States alone.¹⁰ The link between ischemia and arrhythmia has been known since the 1840s.¹¹ Arrhythmias remain the major cause of mortality even long after the MI event, as evidenced by the increasing use of highly effective (but expensive) implantable cardioverter-defibrillators.¹² In humans, exercise not only significantly decreases cardiac mortality, but also improves markers of electrical instability that are good predictors of malignant ventricular arrhythmias and SCD.¹³

So why don’t we see an effect on mortality in the de Waard et al study? The reason probably lies in the experimental model: Although mice clearly develop ventricular tachyarrhythmias,¹⁴,¹⁵ they simply do not die from them as easily as humans or other big mammals do.¹⁶ The survival plot in Figure 1C illustrates this point: After the high mortality rate during the first few days after coronary ligation, the line remains completely flat. No further deaths are observed. In contrast, a similar study in dogs reported that 21% of the animals in the sedentary group died between the sixth and tenth week following ischemia,¹⁷ and in this regard people are more like dogs than mice. It would have been helpful to record the incidence of ventricular arrhythmias during the 8-week observation period even in the present mouse study. Unfortunately, these data are not available, and may be quite difficult to get. Short of repeating the study, what can be deduced from the presented effects of exercise on Ca²⁺ cycling and myofilament function with respect to arrhythmogenesis?

First, MI significantly increases diastolic intracellular Ca²⁺, especially at fast heart rates. Exercise reversed this effect and lowered end-diastolic Ca²⁺ significantly. This has at least 2 important implications:¹⁸ Increased diastolic Ca²⁺ is a known independent trigger of delayed afterdepolarizations and triggered arrhythmia;¹⁹ and² more long-term, increased end-diastolic Ca²⁺ will induce ventricular remodelling by activating regulatory proteins such as calcineurin and calmodulin-dependent protein kinase-II (CaMKII). Upregulation of CaMKII in turn has been shown to be arrhythmogenic even after normalization of basal Ca²⁺. Together with the normalization of β-adrenergic responsiveness after exercise, these results suggest that exercise may reduce the incidence of ventricular arrhythmia post MI, as has been demonstrated convincingly in a dog study.¹⁷

The second key finding is the increase in myofilament Ca²⁺ sensitivity after MI and its reduction with exercise. The effect of increased Ca²⁺ sensitivity on arrhythmogenesis is not known. However, mutations in sarcomeric proteins that increase myofilament Ca²⁺ sensitivity cause familial hypertrophic cardiomyopathy, a disease characterized by high rates of ventricular arrhythmias in humans and animal models.¹⁴ Although speculative at this point, the data by de Waard et al⁸ nevertheless raise interesting questions regarding the role of altered myofilament Ca²⁺ sensitivity in the context of post-MI contractility and arrhythmogenesis.

In summary, the study by de Waard et al is a remarkable piece of work, which, as any good study, answers 1 and raises 5 new questions. The answers will have to wait until the authors present us with data from a similar study in pigs or dogs, ideally from a strain that has an inherent urge to exercise. Meanwhile, the odds are low that patients will start exercising voluntarily.

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**Disclosures**

None.

**References**


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