Published in final edited form as:

Med Sci Sports Exerc. 2008 May ; 40(5): 806–807. doi:10.1249/MSS.0b013e3181684d03.

Curing the cure: utilizing exercise to limit cardiotoxicity

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Recently, considerable attention has focused on the efficacy of exercise training in treating diseases in which exercise intolerance has been traditionally observed. It has been speculated that further stress induced by exercise could be potentially detrimental, exacerbating the condition beyond the normal scope of the disease alone. The article by Hydock et al (4) provides further perspective into this area of study by examining the role of exercise in the treatment of cancer, a disease in which the most prevalent and unfavorable side effect of treatment may be overwhelming fatigue (5). The main result of their study is exercise training prior to treatment with DOX attenuates DOX-induced cardiac dysfunction by maintaining fractional shortening, developed pressure, and cardiac contractility. Maintenance of cardiac function was associated with prevention of increased β -myosin heavy chain (MHC) expression, a mechanism that has been implicated in the cardiac dysfunction resulting from DOX-induced cardiotoxicity and other cardiovascular disease (2,8). While this study is a unique addition to our current understanding of the role of exercise in diseases with severe contraindications to exercise, it also raises several vital and currently unresolved issues regarding exercise and its potential benefits.

One of these issues is the design of the exercise training protocol. Patients undergoing chemotherapy or diagnosed with other cardiovascular disease such as heart failure experience severe fatigue or display severe exercise intolerance. Consequently, the intensity and duration of exercise they are able to tolerate or successfully accomplish is likely to be severely limited. The treadmill training regimen used by Hydock et al (4) is considered to be of higher intensity and frequency in rat models and raises concern in regards to the clinical implications of their findings, as does the timing of their protocol (i.e. how many patients will have trained intensely 12 weeks before starting chemotherapy?). While their findings are not diminished by these realizations, several questions are raised in regards to how best to utilize exercise as a viable tool in the treatment of cancer or other disease in which cardiac function may be severely impaired. To their credit, previous work from this group has investigated the utility of low intensity exercise training during DOX treatment and saw maintenance of cardiac function in an isolated perfused heart preparation, however, β -MHC expression was not increased in the DOX group and exercise did not alter the MHC profile of any of the animals (1). The differences in exercise intensity and timing of the treatment (during DOX treatment as opposed to before) illustrate the importance of the experimental design in the interpretation and clinical applicability of studies of this nature..

Another interesting question raised by the Hydock study is the significance of changes in MHC expression on cardiac function in disease. It is generally accepted that a greater percentage of α -MHC protein expression is associated with a healthier myocardium and several studies have illustrated decrements in power output and systolic function in isolated cardiac myocyte and whole heart preparations over-expressing the β -MHC isoform, respectively (3,6,7,9). However, many of these studies have been in rats which express the α -MHC isoform predominantly- a sharp contrast to humans which express the β -MHC isoform almost

exclusively (8). While it has been shown that humans express the α -MHC isoform, its content is thought to compose a small percentage of the total ($\approx 10\%$), thus, shifts in MHC isoform expression in human disease occur to a lesser degree. A recent study demonstrated that although MHC isoform composition does affect sarcomere length dependent power output in cardiac myocytes, these differences were not observed when the changes in β -MHC isoform content were small (≈ 90 -100%) (7), indicating that shifts in MHC isoform expression observed in human disease may not occur to an extent large enough to impact cardiac function.

In conclusion, the authors are to be congratulated on a thorough and interesting study. The study by Hydock et al (4) illustrates how little is known about the appropriate intensity, frequency, duration, and timing of exercise that should be used for patients in these scenarios and underscores the importance of furthering our understanding of how commonly used molecular markers of disease impact cardiac dysfunction in humans.

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