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Potential for Conflict Between Cardiac and Skeletal Needs

Steven D. Colan, MD

The importance of cardiomyopathy to the clinical course of the dystrophinopathies varies according to the nature of the dystrophin defect. In Becker muscular dystrophy (BMD), cardiac involvement is often the most important determinant of clinical status and long-term outcome. For the Duchenne muscular dystrophy (DMD) patient, cardiac manifestations are often masked by inactivity and respiratory muscle compromise. However, the increasing use of ventilatory assist devices has allowed cardiac failure to emerge as a more prevalent feature of the disease. Furthermore, a wide range of therapeutic interventions to improve skeletal muscle strength are being explored, some of which may not have equivalent benefit for cardiac muscle. The article by Jeffries et al is therefore timely, reporting the potential cardiac benefits of early treatment of patients with DMD and BMD with afterload-reducing therapy. These authors present a retrospective review of the outcome of their patients with DMD or BMD who were managed according to a clinical treatment protocol that included initiation of ACE inhibitor (ACEI) therapy at the time of first recognition of ventricular dysfunction. β-Blocker (BB) therapy was added for patients who had no evidence of improvement in their ventricular function after 3 months. There are at least 3 important findings in their reported experience. First, there were no significant adverse clinical effects attributable to medical therapy. Although these agents have a remarkable safety profile overall, neuromuscular diseases in general are notorious for unanticipated pharmacological responses, and this result is therefore reassuring. Second, over the average follow-up duration of 3.3 years, there was a significant improvement in ventricular function (ejection fraction) and evidence of improved ventricular geometry (reduced sphericity). Third, the authors report an association between cardiac involvement and specific exon deletion, which is perhaps the least expected of these 3 results.

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Despite the clear improvement in ventricular function documented in this study, it is fair to inquire whether afterload reduction therapy has the potential to fundamentally alter the course of the cardiomyopathy in DMD or BMD. The underlying pathology in the dystrophinopathies is progressive cell destruction with apparently normal contractility of the surviving myocytes, at least before the onset of congestive heart failure. Cell loss and secondary reduction in myocardial mass lead to a rise in wall stress, with the typical adverse consequences of afterload excess, which include reduced systolic function, ventricular dilatation and sphericalization, and increased myocardial oxygen consumption. The potential to interrupt this positive feedback loop is one of the more impressive benefits of afterload reduction therapy and can fully explain the improvement in systolic function, reduction in ventricular volume, and normalization of left ventricular shape observed by Jeffries et al. Given the nature of the underlying disorder, the primary predicted short-term benefit of afterload reduction therapy is to make it easier for the surviving cardiocytes to do their job, as was seen in this study. The question remains, however, whether this therapy alters the cardiomyopathy or merely masks the manifestations of a relentlessly progressive process. There is precedent for this question. The ventricular mechanics in anthracycline cardiomyopathy are quite similar to what is found in the dystrophinopathies, with reduced cell mass leading to sustained excess afterload. We were disappointed to find that administration of an ACEI in patients with ventricular dysfunction secondary to anthracycline therapy resulted in transient improvement but no long-term impact on the trajectory of deterioration. Is there any reason to anticipate a greater benefit in DMD and BMD?

The mdx mouse, a naturally occurring animal model of the dystrophin defect, has a high susceptibility to contraction-induced skeletal muscle injury. Interestingly, this is observed primarily during eccentric contractions, that is, contraction that occurs during muscle lengthening. This mode of contraction is common in skeletal muscles but not in cardiac muscle. Evidence that cardiac muscle in the mdx mouse has increased susceptibility to contraction-induced injury derives from the observation that cardiac dysfunction, which is otherwise subclinical, can be induced in the mdx mouse by prolonged exercise or by administration of β-adrenergic agents. Dys- trophin, in conjunction with the dystrophin glycoprotein complex, is believed to play a structural role in force transmission by providing a mechanical link between the intracellular cytoskeleton and the extracellular matrix. The pathogenesis of the muscle dysfunction in the dystrophinopathies is thought to include progressive cell death secondary to a mechanically induced increase in sarcosomall permeability due to membrane injury or to stretch-induced increase of traffic across ion channels. Similar to the mdx mouse, predisposition to exercise-induced cardiac damage is noted in
acute myocarditis, a disorder associated with loss of sarcolemmal integrity due to cleavage of dystrophin by enteroviral protease 2A. Observations such as these have led to the conclusion that in both skeletal and cardiac muscle, abnormal or deficient dystrophin predisposes to contraction-induced cell disruption and loss, and furthermore, the magnitude of force generation is an important determinant of cellular damage.

It is therefore reasonable to speculate that attenuation of the mechanical forces on the sarcolemma by means of pharmacological afterload reduction would reduce the rate of cell loss. The article by Jefferies et al does not permit any conclusions in this regard, but a recent study by Duboc et al provides some support to this hypothesis. These authors reported the results of a placebo-controlled trial of the ACEI perindopril in DMD patients older than 9.5 years who had normal ventricular function at the time of study entry. After 3 years of randomized therapy, all patients were changed to treatment with open-label drug. No difference in outcome was seen at the completion of the first 3 years, but after 2 years of open-label drug, the group of patients who had initially received placebo experienced a higher incidence of moderate to severe ventricular dysfunction. This observation supports the hypothesis that afterload reduction therapy during the initial time period led to better preservation of the myocardium, because therapy in the second phase was the same in both groups.

The ultimate cure for DMD and BMD depends on the ability to introduce a functional dystrophin gene into myocytes, and the recent phase I study of plasmid-based gene transfer is a promising step in that direction. Nonetheless, it is unpredictable when such therapies will be available. In the mean time, interventions that protect muscle mass could improve the length and quality of life for these patients. However, therapeutic strategies that target skeletal muscle may well be at odds with the best interests of cardiac muscle. The 2 stressors that have been used to elicit clinically apparent cardiomyopathy in the mdx mouse model are exercise and infusion of β-adrenergic agents. It is therefore possible that the markedly reduced exercise capacity of the DMD phenotype serves to limit cardiac injury. This relationship has been suggested to explain the severe cardiomyopathy of the BMD phenotype, in which the less severe skeletal muscle compromise permits exposure of heart to the stress of exercise. If this hypothesis is correct, then pharmacological therapies that selectively improve skeletal muscle function, such as pharmacological stimulation or disinhibition of regenerative satellite cells with insulin-like growth factor I or myostatin inhibitors, may increase the rate of cardiac muscle deterioration. Similarly, oral administration of the β-adrenergic agent albuterol to DMD and BMD patients has been reported to improve skeletal muscle function, but based on the experience in the mdx mouse, it would be predicted to exacerbate cardiac damage. In general, it cannot be assumed that interventions that improve skeletal muscle function will have a similarly beneficial effect on cardiac muscle.

Perhaps the most intriguing finding in the report by Jefferies et al is the relationship between the exon-specific location of the deletion and the risk of cardiomyopathy. It is somewhat surprising that DMD patients, in whom dystrophin is usually absent from the sarcolemma, should manifest such genotype-phenotype correlations. Deletions in specific locations previously have been noted to predispose to cardiomyopathy in DMD. In some patients with DMD, expression of dystrophin fragments may be important. For example, expression and localization at the cell membrane of dystrophin lacking the C-terminus and the β-dystroglycan binding domain have been described in DMD patients. There are other observations that support the concept that the loss of dystrophin per se is not sufficient to explain the differences in severity of muscular dystrophy. For example, there is marked disparity in pathology between species and muscle types in the dystrophinopathies. Differences in the severity of muscle dysfunction between heart and skeletal muscle are of particular interest. Point mutations in the dystrophin gene have been described in X-linked dilated cardiomyopathy, despite the absence of skeletal muscle involvement, which suggests that the function of dystrophin is not the same in the 2 locations. Observed differences in the pattern of cellular location between cardiac and skeletal muscle lend support to this hypothesis. Overall, these observations argue strongly in favor of the importance of epigenetic factors in disease severity and progression. They also provide further evidence of the potential for dissociation between cardiac and skeletal response to therapeutic strategies.

References


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