EDITORIAL COMMENT

Did They Lower Stress in the Trial?

Or Was It Just Wasted Energy?*

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In this issue of the *Journal*, Duboc et al. (1) report the results of a multicenter clinical trial of perindopril, an angiotensin-converting enzyme (ACE) inhibitor, for the prevention of left ventricular dysfunction in young patients with Duchenne muscular dystrophy. The investigators showed positive benefit from this treatment after five years, with fewer patients in the treatment group exhibiting left ventricular dysfunction (ejection fraction <45%). At first glance this trial might not seem so important or the result particularly surprising, but it should be of real interest to pediatric cardiologists for two reasons. First, as one of an increasing number of clinical trials being performed in children, it illustrates many of the difficulties encountered in this population and the need for patience and perseverance on the part of investigators. Second, it adds another small piece to the puzzle regarding the role of cytoskeletal proteins in heart failure.

Until recently, few clinical trials had been performed in children with heart disease (2). In fact, before the year 2000 only about 20 randomized, controlled trials had been published in pediatric cardiovascular medicine (3). The last few years have seen clinical trials being performed in children in increasing numbers because of: 1) individual investigator initiative, as in this case; 2) programs sponsored by the National Institutes of Health (4); and 3) incentives provided to industry by the Food and Drug Administration Modernization Act and, subsequently, the Best Pharmaceuticals for Children Act (5). Although progress is being made thanks to these important initiatives, still most drugs used in children have not been tested adequately to understand the appropriate dose, the efficacy, and the safety.

This perindopril trial highlights some of the problems being faced by pediatric investigators. The 80 subjects screened for this trial represent 10 major hospitals in France caring for children with muscle disease. Of these, 57 subjects met entry criteria for the trial. Compared to most cardiovascular trials in adults, these are very small numbers,

barely enough to provide adequate statistical power. Fortunately for our species, but unfortunately for investigators, cardiovascular disease is rare in children. Networks such as the French Working Group of Heart Involvement in Myopathies, which carried out this trial, are indispensable for conducting clinical trials in children. No single center, or even small group of centers, has enough patients with these rare diseases to perform meaningful trials.

In addition to small numbers of patients, the time course needed to achieve clinically meaningful end points is often long. No difference in ventricular function was evident between treatment and placebo groups after the initial three-year, blinded, randomized Phase 1. Only after an additional two years of open-label treatment in Phase 2 was a difference detected. Even after five years, the only end point realized was a surrogate, ventricular function. An additional year of observation has shown a non-significant trend toward reduced mortality in the treatment group. One hopes the investigators will continue to persevere in following these patients in anticipation of demonstrating a mortality benefit. Even more importantly, it is essential that funding agencies understand the cost and the time needed to perform meaningful trials in children and build this into their evaluation of clinical research proposals.

The story of dystrophin and other cytoskeletal and extracellular matrix proteins in heart failure is an interesting, and somewhat unexpected, one (6). This molecular chain appears to connect the contractile apparatus within the myocyte with the extracellular structure of the muscle for force transduction across the sarcolemma. Components of the chain stabilize the sarcolemma during contraction and force transmission. Absence or certain mutations of components of the chain (dystrophin in Duchenne muscular dystrophy) appear to increase the likelihood of rupture of the sarcolemma during contraction, with cell death and fibrous replacement. The clinical correlates of this are the skeletal muscle atrophy and weakness that develop during childhood in Duchenne patients and the cardiomyopathy that appears usually in the second decade. In an experimental model of dystrophin deficiency, the extent of sarcolemmal damage was directly related to the mechanical stress placed on the muscle (7). Hence the hypothesis that led to this clinical trial of perindopril: reduction of left ventricular afterload (wall stress) should decrease the rate and extent of damage to the myocardium produced by contractions in the absence of dystrophin. The data presented by Duboc et al. (1) support this hypothesis. Their Figure 1 shows clear divergence in left ventricular function between the group treated for five years and that treated for two years with an ACE inhibitor. However, both groups exhibit significant reductions in function, suggesting that this treatment only reduces the rate of progression and does not completely prevent deterioration. The authors suggest beginning all children with Duchenne muscular dystrophy on ACE inhibitor therapy as early as nine years (the youngest

patients in their study population). The apparent cumulative benefit derived from this therapy, as illustrated in Figure 1 of their report, raises the question of whether therapy should be started even earlier. If further follow-up demonstrates reduced mortality in the treatment group, consideration should be given to starting treatment at diagnosis.

Many questions regarding the role of dystrophin in cardiomyopathy remain. For example, why does skeletal muscle myopathy precede the onset of cardiomyopathy in Duchenne patients when skeletal muscles are used sporadically while cardiac muscle works continuously? A major mechanism for development of cardiomyopathy in enteroviral myocarditis appears to be cleavage of dystrophin by a protease produced by the virus (8). Why is this acute cleavage of dystrophin associated with rapid onset and progression of cardiomyopathy while chronic absence of functional dystrophin in Duchenne muscular dystrophy is associated with onset of ventricular dysfunction only after a decade or more? Disruption of the dystrophin complex is seen in end-stage heart failure (9). Unloading the myocardium with use of a ventricular assist device leads both to regeneration of the dystrophin complex and, in some cases, to improvement in ventricular function and symptoms of heart failure (10). Is the dystrophin abnormality seen in end-stage heart failure the chicken or the egg? Is this really part of the pathophysiology or an epiphenomenon?

Alternatively, another pathway unrelated to dystrophin may be active here. Uncoupling proteins (UCPs) are mitochondrial proton transporters that lower the electrochemical gradient favoring formation of adenosine triphosphate. Uncoupling protein-2 appears to be up-regulated in chronic heart failure models (11), resulting in impaired myocardial energy efficiency. Chronic ischemic heart failure models have shown reduced creatine phosphate levels (12) despite disproportionately high oxygen consumption (13), and this can be reversed by ACE inhibitors (14). Studies in a rat model of chronic aortic regurgitation have shown that perindopril reduces expression of uncoupling protein-2, maintains normal levels of creatine phosphate, and prevents cardiac remodeling (15). Perhaps the prevention, or at least slowing of progression, of left ventricular dysfunction in this trial is more related to prevention of energy wasting than to prevention of mechanical disruption of myocytes.

Answers to questions such as these are likely to enhance our understanding of the cellular mechanics of heart failure. The skeletal and cardiac myopathies associated with abnormalities of the dystrophin complex, seen mostly in children, provide models in which answers to these and other questions are likely to be found. But these answers will be found only with patience and by study groups with access to sufficient patients.

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