Commentary: Building evidence to support empiric observations—Molecular cross talk, or simply crossed wires?

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Central Message

Although impressive clinical results have been reported with pulmonary artery banding in children with cardiomyopathy, supporting mechanisms at a cellular and molecular level remain elusive.

See Article page 2416.

Surgeons are reductionists; we know what works for patients, often on the basis of personal experience. We can sometimes suggest a plausible mechanism, citing basic mechanisms at work. Surgeons are also sceptics; we value clarity and simplicity and are quick to note when the "science" fails to demonstrate mechanisms supporting observations made in the clinical domain. There is a lot to be sceptical about, because so many procedures lack an evidence base or a defined mechanism of action.

So it is when Yerebakan and colleagues[1] in this issue of the *Journal* present a series of animal experiments that seek to demonstrate cellular and molecular mechanisms underlying the apparent beneficial effects of pulmonary artery banding in children with cardiomyopathy. The Giessen group and an international collaborative[2] have reported benefits of this approach in clinical practice, and there is a registered clinical trial[3] underway. Septal repositioning and initiation of a regenerative response are proposed as mechanisms, drawing on experience suggested by similar approaches in L-transposition,[4,5] albeit a very different clinical presentation.

Important experimental design and methodologic issues need to be considered. First, the mortality from both initial and sham banding was substantial, and medical therapy was not used on either group. Second, the criterion standard assessment of ventricular performance with conductance catheters largely failed to demonstrate a difference between treatment and control groups, which is surprising considering the gross morphologic changes. Finally, analysis of ventricular muscle was limited to simple histologic examination, without comprehensive analysis of cell type, proportion of *c-kit*-positive cells, angiogenic milieu, measures of apoptosis, or gene expression data that might support the regenerative hypothesis.

In a drug-toxicity model of ventricular failure, damage is caused primarily by oxidative stress,[6] and this may not adequately mimic the pathogenesis of dilated cardiomyopathy, where disruption of the dystrophin-associated complex is a more prominent feature.[7]

Nevertheless, there were improvements in left ventricular size and ejection fraction in the treatment group, and it is suggested that in this way the model recapitulates the therapeutic effect of central pulmonary artery banding in cardiomyopathy. It is an important step toward better understanding a phenomenon that may be useful in preventing or delaying the need for mechanical support and transplantation in children. Should molecular evidence be forthcoming in future studies, it will be broadly relevant to management of corrected transposition and perhaps even in the achievement of "growth" in hypoplastic ventricles.

For now, the big picture remains fuzzy. The reductionists amongst us still seek an understanding of the basic mechanisms. and the sceptics will prevail until molecular data support the intimation that there is regeneration and improved "cross talk" between ventricles. Could we simply be observing the superimposition of restrictive physiology on the pathology of dilated cardiomyopathy?

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