40% of that population. This raises a serious question about proceeding to transplantation in the first year of the disease, as four centers have advised on the basis of their perception that DCM had such a poor prognosis. In this published cohort, some recovered as late as six years after onset; would 40% of the transplanted children have recovered with normal contractility had they not been transplanted?

Although the title of their study asserts that transplantation for DCM will provide “improved outcomes,” that can only apply to the first few years after cardiac transplantation, which lasts on average 10 to 13 years. In contrast, 40% of all patients with DCM recovered systolic function without transplantation and were still normal eight years later. The difference between transplants and complete recovery does not take into account the morbidity of rejections and anti-immune treatments for the transplanted patients. If 40% of the transplanted children would have recovered, the overall outcome would certainly not be improved.

Finally, the reliability of separating myocarditis from idiopathic DCM is raised by their finding of no differences between the two groups for either “heart death” or for recovery of function. This important finding throws doubt on the criteria used to diagnose myocarditis.

In sum, this important study by Tsirka et al. (1) provided several important advances in our knowledge, even though the title made promises that were unwarranted.

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REFERENCE


REPLY

We appreciate Dr. Guntheroth’s remarks regarding our retrospective observational study (1) on pediatric dilated cardiomyopathy (DCM). His concerns appropriately point out the limitation of all observational studies—that one can never tell what would have happened to the treated group (in this case those who were transplanted) had they not undergone treatment because there is no valid comparison group. However, 75% of the patients transplanted in our study were on persistent inotropic support (UNOS status 1) at the time of transplant and had failed attempts to complete recovery does not take into account the morbidity of rejections and anti-immune treatments for the transplanted patients. If 40% of the transplanted children would have recovered, the overall outcome would certainly not be improved.

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Cell Transplantation and Fibrin Matrix

The recent study by Christman et al. (1) reports the results of an experimental study that evaluated a “novel approach to heart repair that uses an injectable biopolymer scaffold to deliver cells directly into the infarct wall.” The researchers “hypothesized that the injection of cells in a solution that becomes a semi-rigid scaffold
upon injection would increase cell transplant retention and survival within the infarct, compared with the standard injection technique.”

The investigators failed to acknowledge that this theory was presented by our group at the American Heart Association meetings in 2001 and the American College of Cardiology meetings in 2002 and 2003. Neither do they reference our published works (both experimental and clinical) evaluating the role of fibrin matrices as a scaffold for cell transplantation and as an angiogenic agent. Using transmission electron microscopy, we discovered that fibrin platform directs the morphofunctional process of capillary formation and accelerates neovascularization in ischemic myocardium in addition to enhancing the viability of transplanted endothelial cells (2,3).

We documented improvement in left ventricular ejection fraction, myocardial blood, and capillary density.

We avoided the possibility of higher graft rejection from using an inbred strain and allograft transplantation, the limitation the investigators mention, by employing autologous endothelial cells and autologous fibrinogen for fibrin sealant preparation. Endothelial cells (ECs) were cultivated from endothelium of the jugular veins of the same sheep (3). One week before EC transplantation, lial cells (ECs) were cultivated from endothelium of the jugular and autologous fibrinogen for fibrin sealant preparation. Endothelial inbred strain and allograft transplantation, the limitation the investigators mention, by employing autologous endothelial cells and autologous fibrinogen for fibrin sealant preparation. Endothelial cells (ECs) were cultivated from endothelium of the jugular veins of the same sheep (3). One week before EC transplantation, whole blood from each animal was collected, and a standard cryoprecipitate technique was used to prepare autologous fibrinogen from sheep plasma. Cultured in a two-dimensional fibrin matrix, ECs quickly formed a cobblestone monolayer that had a density 2- to 2.5-fold higher than in controls cultivated on a single-plane tissue culture surface (4). We also found that, cultured in a three-dimensional fibrin matrix, ECs formed true capillaries, while other vascular cells trapped in this matrix underwent apoptosis.

In our next investigation, we found that a fibrin-based sealant becomes vascularized when placed between two ischemic tissues and that aprotinin, added to fibrinogen, considerably increased the process of neovascularization (5). Fibrin-based sealant proved capable of delivering plasma proteins necessary to perform the functions of an extracelular matrix, anchoring ECs to the vessel wall (6).

Finally, we demonstrated that fibrin-based sealant accelerates angiogenesis in patients with peripheral artery disease (7).

We thank Christian et al. (1) for their interesting contribution on this subject and applaud the renewed interest in this worthy line of inquiry. With further preclinical and clinical investigation of the safety and efficacy of this technique, we believe that fibrin matrix as a scaffold for cell therapy, and the angiogenic potential of fibrin compositions, show promise for the treatment of heart disease.

REFERENCES


REPLY

Our report (1) is the first study to demonstrate the beneficial effects of intramyocardial injection of a biopolymer alone in inducing angiogenesis and reducing infarct expansion. Furthermore, we have demonstrated that compositions of fibrin glue injected into ischemic myocardium prevent the negative remodeling associated with a myocardial infarction (MI) (2). These dramatic results were shown both for fibrin glue alone, and in material compositions of fibrin glue combined with transplanted, healthy myoblasts. Additionally, our report demonstrated that a fibrin glue scaffold increased the survival of contractile-type muscle cells, more specifically myoblasts, transplanted into myocardial tissue.

One hypothesis we tested was that an acellular intramyocardial injection of a biopolymer alone could prevent infarct expansion and prevent the continued worsening in left ventricular (LV) function following an MI. Dr. Chekanov and colleagues provide corroborative data regarding the utility of biopolymers. However, the emphasis of the experiments cited by Chekanov and colleagues had different objectives. In their earlier citations (3), Chekanov et al. used an autologous biologic glue containing fibrinogen epidurally to enhance the healing process of cardiomyoplasty. The autologous biologic glue was used “as an interlayer between the stimulated latissimus dorsi muscle and the myocardium to improve adhesion formation and cardiomyoplasty results.”

Another hypothesis we tested was that fibrin glue matrix, in combination with myoblasts, enhances LV function. This test was specifically designed around use of a contractile type of cells. Accordingly, our work demonstrates an advancement by showing pronounced beneficial effects of fibrin glue-assisted myoblast transplantation into ischemic myocardium. Chekanov et al. (4) did report results of an experimental protocol to observe the effects of transplanting endothelial cells (ECs) in a fibrin matrix into ischemic myocardium. However, the experimental design was principally based upon a hypothesis of neovascularization and consisted of the following three groups: 1) ECs and fibrin matrix, 2) saline with denatured cells, and 3) a control group. The investigators did not include a fibrin matrix group alone or healthy ECs alone. Therefore, they did not test whether a biopolymer alone injected intramyocardially could produce angiogenesis or prevent the negative remodeling associated with an MI.

Additionally, without observing the effects of a healthy EC group without fibrin glue, the researchers could not determine the