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 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 extracelluar 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 Christman 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.

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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 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 fibrogen epidermically 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 cardio-myoplasty 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...
extent to which a fibrin matrix is beneficial in increasing cell transplantation and survival in the setting of myocardial injections. Still further, Chekanov and colleagues did not report any test protocols or observations regarding intramyocardial injections of fibrin glue in combination with contractile types of cells such as myoblasts.

The work done by Chekanov and colleagues is very interesting with respect to the objectives, experiences, observations, and results of their specific studies. Also, our work (1,2) does share some basic common features with the findings cited by Chekanov et al. However, the advances we made provide substantially new and different compositions of therapeutic materials, in vivo applications, and observations and results. Our work thus offers unique advancements and implications with respect to possible future applications to patient care. This is in particular the case with respect to demonstrating the benefits of injecting (a) acellular fibrin glue agents and (b) fibrin glue agents together with transplanted contractile-type cells (e.g., myoblasts) into ischemic myocardium.

Despite the distinct differences noted, we thank Dr. Chekanov and colleagues for sharing their experience with fibrin glue and to the advancement of the use of polymers as potential therapeutic agents.

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