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Coagulation, fibrinolysis, and cell activation in patients and in shed mediastinal blood during coronary artery bypass grafting with a new heparin-coated surface

To the Editor:

Johnell and colleagues¹ recently reported the improved biocompatibility of a new heparin-coated surface. They also presented results after modifications of the anticoagulation protocol. They concluded that a low dose of systemic heparin might not be sufficient to maintain the antithrombotic activity and that a high dose resulted in increased blood activation.

The design of the study merits discussion; otherwise, the conclusion might be misunderstood. In particular, the reduction of anticoagulation, even combined with a thromboresistant extracorporeal circuit, might appear detrimental for patients undergoing cardiopulmonary bypass (CPB). The basis for a safe low anticoagulation protocol in combination with heparin-coated CPB circuits was described by Aldea and associates² in 1998. It includes many parameters derived from the scientific literature from the 1990s, such as controlled suction with cell-saving devices allowing washing before retransfusion, limitation of air-blood contact with closed circuits, specifically adapted anticoagulation through precise heparin and protamine titration, low prime volume facilitated by retrograde autologous prime, and normothermia. This tailored approach of CPB, adopted by our own center, has been found clinically beneficial³ and is therefore justified for routine surgical practice. One of the most important parameters omitted by the authors in the management of a low heparinized CPB is the retransfusion of highly activated blood into the circulation because cardiomyotomy suction has been used. The contact of blood with air or with the surgical field through the tissue pathway is followed by activation of inflammation and hemostasis disturbances, despite the use of a significant amount of fluid heparin, which appears to be an unperfected anticoagulant

for CPB although it is universally used. When a cell-saving device is used instead of cardiomyotomy suction, all the different markers of blood activation are excluded and not retransfused into the circulation. With this approach, it has been proved that circulating F_{1+2} levels do not correlate with activated clotting time (the lowest activated clotting time does not imply the highest F_{1+2}) and that a low anticoagulation protocol is safe for the patient.² Therefore some of the results presented by Johnell and colleagues¹ need to be taken with caution.

On the other hand, the study of Johnell and colleagues¹ provides important data about the detrimental effects of heparin, which could justify a low anticoagulation protocol. Evidence of proinflammatory and procoagulant effects of high-dose heparin was found, as in previous reports. The reduction of heparin dose during CPB with heparin-coated circuits reduces leukocyte adhesion on artificial surfaces⁴ and better preserves antithrombin III levels.⁵ In addition, low anticoagulation requires a low dose of protamine for titration and reduces the amount of heparin-protamine complexes known to activate the classic pathway of complement cascade.

The biocompatibility of new equipment must be assessed, particularly with respect to thromboresistance. Johnell and colleagues¹ successfully demonstrated the reduction of contact activation. However, it is fundamental that the experimental design respect some principles that have been previously elucidated when they are expected to be of major importance in the outcome. This is particularly true if CPB is managed with low anticoagulation.

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Myogenesis after myocardial stem cell transplantation

To the Editor:

I read the article of Chedrawy and colleagues,¹ "Incorporation and Integration of Implanted Myogenic and Stem Cells Into Native Myocardial Fibers: Anatomic Basis for Functional Improvements," in the Journal with great interest. Chedrawy and colleagues¹ described regenerated isogenic myofibrils injected into nonischemic normal myocardium. By 4 to 6 weeks, fully differentiated myocytes could be seen to interconnect among native cardiomyocytes. The authors attributed this desirable incorporation to cell-cell electromechanical junction. However, in a clinical setting with scar tissue and akinetic ventricular wall, the microenvironment is not conducive to electromechanical activity to induce a desirable environment to trigger phenotypic changes for transplanted cells. Is it possible that cytokines, such as transforming growth factor β or insulin growth factor, generated because of the presence of macrophage and monocytes, play a role in the genesis of proliferation and transformation of new myofibrils?

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cells into native myocardial fibers: anatomic basis for functional improvements. *J Thorac Cardiovasc Surg.* 2002;124:584-90.

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Reply to the Editor:

Dr Taheri made an important point in his comment, which we probably should have discussed in our article. However, first I, on behalf of my coauthors, wish to clarify that we did not inject "isogenic myofibril grafts," which would represent a differentiated anatomic unit of a muscle tissue. Instead, we transplanted either skeletal myoblasts, which are immature progenitor cells, or marrow stromal cells, which contain a pluripotent cell population. Such immature cells are able to migrate and self-assemble with preexisting supracellular structure, as we reported.

The hypothesis we postulated to explain the mechanism of this phenomenon should indeed predict that those donor cells, if implanted as an isolated island within a scar tissue, would lack the microenvironment to allow them to integrate into the preexisting native myocardial syncytium. We and others have pointed out that how such cells surrounded by scar contribute to the myocardial function, as has been reported experimentally and in some early clinical trials, remains unclear at present.¹ It is of some interest to recall how the strategy of implanting cells into scar started. In our studies in the early 1990s,^{2,3} which were the first attempts to use cell therapy for myocardial regeneration, we lacked the tools for cell labeling and thus created a homogeneous scar induced by cryoinjury. By implanting myoblasts within such a scar, we were able to show that the new myofibers surrounded by the scar tissue originated from our donor cells. Because turning noncontractile scar tissue into potentially contractile muscle tissue is an intuitively appealing idea, many investigators in the subsequent studies, both experimental and clinical, have continued to use the model of implanting cells within the scar tissue, even though there has been no convincing evidence that these isolated muscle fibers can actually contribute to the synchronized contractile function of the myocardium.

In studying the pathophysiologic roles of marrow stromal cells, it has been shown that tissue injuries, such as myocardial in-

farcion, can send a signal to recruit marrow stromal cells from the bone marrow, which traffic through the bloodstream to target the infarcted segment of the myocardium. There they undergo milieu-dependent differentiation, expressing a number of phenotypes.⁴ We have suggested that some of these cells that reached the peri-infarct zone became endothelial and vascular smooth muscle cells to participate in vasculogenesis and enhance collateral circulation. Some cells, which reached the scar tissue through patent collateral vessels, may express a myofibroblastic phenotype and participate in scar maturation to reduce scar expansion and rupture. The marrow cells in the peri-infarct zone that are in contact with viable and contracting host myofibers may differentiate into cardiomyocytes and integrate into the existing myofibers as we reported¹, and this may play a role in modulating the postinfarct remodeling process of the ventricle. Yet other mechanisms are possible. The neocardiomyocytes, which have received phenotypic signals from native cardiomyocytes at the peri-infarct zone, may then migrate toward the myocardial scar to reduce infarct size. Various transforming growth factors and cytokines coming from the surrounding cells and extracellular matrix may also play important roles, as suggested by Dr Taheri. Clearly, much needs to be learned, and from such understanding better clinical strategies to use cell therapy for myocardial injury may yet evolve in the future.

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Asymptomatic mitral valve incompetence: Is there evidence for surgery?

To the Editor:

The article by David and colleagues¹ in the May 2003 issue of the Journal, "Late Outcomes of Mitral Valve Repair for Floppy Valves: Implications for Asymptomatic Patients," stirs important unanswered questions and concerns. The conclusion that patients with asymptomatic mitral valve incompetence are candidates for surgery might be extrapolative yet beneficial—if it had stemmed from a different study design. In statistical terms, significance for operating was clearly established; however, this was more rhetorical than useful in clinical practice. The following issues were not mentioned in the discussion or among the discussants.

First, asymptomatic simply means no symptoms. Mitral valve surgery is feasible, but its benefits to the individual patient cannot be observed here because of the confounding variables in the methodology and results. To the reader, the concept of cause and effect is paramount to executing successful cardiovascular epidemiology. Whereas the scientific sequence of cause and effect is clear, the application of such a valid concept in this article leans to the reverse order. In other words, because surgery in patients without symptoms had a low morbidity and mortality (cause), it is recommended to operate for asymptomatic mitral incompetence (effect). Lowering the threshold to operate must stem from convincing data, and even if statistically significant the clinical indication is neither relative nor absolute. The patient's physiologic status must be the underlying cause for an operation, and the outcome of the operation (effect) must treat that cause. In this article despite the effect being feasible, the cause is far from a true clinical indication. The practicing surgeon can be confused with the paradigm of cause and effect that appears to argue that the mortality is higher among patients with symptoms. Drawing feasibility from such a statistic may introduce a new "fuzzy logic" dimension that has no order and no cause followed by effect features.² This logic results from many decision-making and problem-solving tasks that are too complex to be understood quantitatively; however, people succeed by using knowledge that is imprecise rather than precise.