One potential reason for avoiding strategies that have mixed cardioplegia and systemic perfusion temperatures (cold for one with warm or tepid for the other) is the concern that the myocardial temperature in the mixed temperatures situation would likely result in highly variable and inconsistent myocardial temperatures.¹ It has been demonstrated that the delivery of cold cardioplegia results in decreased subepicardial and midwall ventricular perfusion. This datum, coupled with information that myocardial temperature is variable with cold cardioplegia, suggests that myocardial protection may be compromised by such a mixed temperature environment.²

However, others have shown no increase in the release of myocardial injury markers (troponin I and T) after normothermic systemic perfusion relative to hypothermic systemic perfusion when a regimen of cold cardioplegia with topical cooling was used for myocardial protection, and acceptable clinical results are possible.³ Furthermore, acceptable clinical results have been reported with the technique of cold cardioplegia with warm systemic perfusion.⁴ Thus considerable controversy continues to exist regarding whether cold cardioplegia with warm systemic perfusion is harmful; however, there are no studies demonstrating its superiority to the strategy of warm cardioplegia with tepid systemic perfusion.

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Nickel allergy to the percutaneous patent foramen ovale occluder and subsequent systemic nickel allergy

To the Editor:

We read with great interest the article "Systemic Allergic Reaction to the Percutaneous Patent Foramen Ovale Occluder" by Fukahara and colleagues.¹ In that article, Fukahara and colleagues¹ described the case of a 37-year-old patient who underwent patent foramen ovale closure with the Star device (Cardia Inc, Burnsville, Minn). In the following 2 months, the patient began demonstrating hypersensitivity to the device, confirmed by skin patch testing as an allergy to nitinol. Removal of the device ultimately led to this patient's recovery.

In October 2001, we treated an 11-year-old boy who had undergone transcatheter closure of a secundum type atrial septal defect with the HELEX Septal Occluder (W.L. Gore and Associates, Flagstaff, Ariz).² Similar to Fukahara and colleagues' patient, our patient had a similar reaction to the device; he ultimately had positive skin patch test results for nickel allergy. This patient underwent uneventful removal of the device as well but also required subsequent removal of the sternal wires, which had trace amounts of nickel. This patient was initially unavailable for follow-up at our institution. To our knowledge, however, he has had an otherwise uneventful recovery.

We thank Fukahara and colleagues¹ for their report on the subject. We encourage the cardiothoracic community at large to report such events to determine objectively the incidence of adverse outcomes that may be associated with these emerging technologies.

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Activated prothrombin complex concentrates and recombinant factor VIIa in the bleeding patient: Are they appropriate and safe?

To the Editor:

I read with great interest the article of Bui and colleagues,¹ "Fatal Thrombosis After Administration of Activated Prothrombin Complex Concentrates in a Patient Supported by Extracorporeal Membrane Oxygenation Who Had Received Activated Recombinant Factor VII," in the October 2002 Journal. Many issues related to the administration of activated prothrombin complex concentrates presented by this case were too simply discussed.

First, the patient had evidence of disseminated intravascular coagulation both before the cessation of heparin and after its discontinuation, with prolonged prothrombin time and partial thromboplastin time. No data are available regarding the patient's platelet count before or after surgical intervention. Both recombinant factor VIIa and factor VIII bypassing activity (FEIBA) were used off-label, about which the authors made little comment. Cardiac surgery with extracorporeal membrane oxygenation is known to activate clotting, and death might well have occurred even without either biologic agent. The cardiac death may not have been from thrombus, but of another origin; because no autopsy was performed, however, all this is pure speculation.

The authors stated with great conviction that thrombosis with recombinant factor VIIa is less common than with FEIBA. Continued hemorrhage itself is a cause of activation of coagulation. Agents known to aid in stopping hemorrhage in patients with coagulation defects have caused thrombotic episodes.

Almost all the life-threatening thrombotic events with FEIBA have occurred with doses exceeding those recommended.² Bui and colleagues¹ provided no data regarding the dose of FEIBA given. Thrombotic events, including myocardial

infarctions, have also been reported for recombinant factor VIIa.³ The relative risks of these two biologic agents are unknown; there are no prospective comparative data available to make such a determination. The cumulative clinical anecdotal data for recombinant factor VIIa are from a much briefer span than those for FEIBA.

Case reports can at times be important for recognition of new diseases and during postlicensing surveillance for adverse events. Recently, a report has demonstrated that the combination of recombinant factor VIIa and FEIBA may, if anything, be additive without increasing adverse responses.^{4,5}

I caution the authors that conclusions presented with inadequate data may well lead readers to incorrect interpretations of the events described.

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A few critical aspects—and Achilles heels—of tissue engineering approaches to restore injured myocardium

To the Editor:

We enjoyed reading Osawa and colleagues' article about histologic changes of

biomaterials used to repair ventricular heart defects in small animals¹ as published in this *Journal* and also have followed this group's work elsewhere.² Our own review on the current literature in this area has spawned many questions and suggestions for future study designs.

Most published studies do not present clinically applicable, reparative options. We believe that a critical analysis of these studies with respect to geometry, physiology, and inflammatory and immunologic responsiveness of myocardium will help identify flaws in current study designs and also help define standardized quality criteria to guide future attempts to manufacture implantable myocardium.

Few studies, for instance, have reliably and convincingly proved enhancement of cardiac function after induction of myocardial injury relative to control values. We frequently see distorting scaffolds "sitting" on the heart, or replacing previously beating muscle, and identify in most of the cases significant foreign-body reaction and reactive neovascularization³ interpreted as angiogenesis. Frequently the immunologic response to the implanted scaffold and the inoculated cells is neglected, even when species barriers are crossed. Furthermore, many study designs fail to adhere to well-described "hard problems" in the development of bioartificial myocardium:

1. With respect to cardiac geometry, the ventricular muscle constitutes a complex helical structure.⁴ Symmetric and isotropic matrices would promote scarring and aneurysm formation. The issues of asymmetry and anisotropy of the heart have never been addressed.
2. With respect to cardiac hemodynamics, the modified law of Laplace for the heart* defines circumferential wall stress values that would not be tolerated by most of the described matrices. Very likely these matrices would decompose, leading to severe hemorrhage, or would form aneurysms.
3. With respect to microscopic structure, we are unaware of approaches that involve both including nerves (conductive microstructures) and preformed chaotic and plastic microchannels simultaneously.
4. With respect to issues of storage, conservation, and scale, an infant or child with congenital defects will

*CWS = $Pb/h \times (1 - b^2/2a^2 - h/2b + h/8a^2)$, where: CWS is circumferential wall stress (in dyne/cm² × 10³), P is left ventricular pressure (in dyne/cm²), a and b are major and minor semiaxes, respectively (in cm) and h is left ventricular wall thickness (in cm).

Figure 1. Triple staining of carboxyfluorescein diacetate succinimidyl ester-labeled cells in 3-dimensional scaffold consisting of collagen type 1. Nuclei stain blue. Red "halo" marks myocytes (MF 20 stain). Here, cluster of cells aligns along fibers (longitudinal structures at left encompassing the cells) of collagen network.