Reply to the Editor:

We were pleased to read a comment written by Pichel and her colleagues regarding our article previously published in the *Journal*.¹ They presented well about the etiology, diagnosis, and prognosis of constrictive pericarditis (CP) from somewhat different perspectives.

From etiologic and prognostic points of view, patients with idiopathic and tuberculous CP were included in our study. We also saw increasing cases of postoperative CP. We excluded patients with significant valvular and coronary artery diseases and other serious comorbidities, however, to obviate problems arising from the confounding effects of other diseases on mortality and to evaluate the pure prognosis of patients with isolated CP after pericardiectomy. It was reported that idiopathic CP had the best prognosis, followed by post-surgical and postradiation CP.² The mortality after pericardiectomy in patients with postradiotherapy CP is reportedly high, but none of our patients had this etiology. We should note, however, that the prognosis of CP that develops after cardiac surgery and chest irradiation could be largely influenced by underlying diseases, such as ischemic or valvular heart disease and malignancy.

When it comes to the diagnosis of CP, the role of other cardiac imaging modalities, such as magnetic resonance imaging and computed tomography, has been extended. A transient CP that can be reversed by medical management can be identified by the use of magnetic resonance imaging assessing a late gadolinium enhancement, suggestive of pericardial inflammation.³ These modalities may help to identify and treat patients with CP at an earlier stage. Despite the increasing usefulness of cardiac imaging in this clinical field, Doppler echocardiography still has a pivotal role. Echocardiography is easily accessible clinically and provides us with quantified

hemodynamic information of patients, such as an exaggerated ventricular interdependence. Our study demonstrated that preoperative Doppler echocardiographic evaluation may be valuable not only for diagnosing CP but also for predicting prognosis after pericardiectomy. We acknowledge that the Doppler echocardiographic findings of our study must be validated in a large population with various etiologies. Furthermore, as described in our analysis of study limitations, our results may be mainly applicable to patients with CP caused by idiopathic and tuberculous pericarditis and should not be extrapolated to patients with CP of other etiologies, such as postirradiation, postsurgical, and collagen vascular disease. The cutoff value of E velocity determined for predicting prognosis after pericardiectomy in this study cannot be applied to patients with significant mitral valvular disease and patients who have prosthetic mitral valves.

Further development of imaging technology and studies investigating prognosis will, it is to be hoped, result in fine stratifications, early detection, and early treatment of CP, leading to a better prognosis for the affected patients.

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**SOMETHING TO CONSIDER:
PORCINE INTESTINAL
SUBMUCOSA AS A BIOLOGIC
SCAFFOLD, NOT A SIMPLE
PATCH**

To the Editor:

We read with interest the somewhat disappointing results presented in the recent article by Zaidi and colleagues¹ regarding the histology and timing of failure after valve repair with autologous pericardium or extracellular matrix (ECM; CorMatrix Cardiovascular, Inc, Roswell, Ga). In particular, the histology presented by Zaidi and colleagues¹ demonstrating inflammatory cell infiltration of the ECM bioscaffold is in contrast to our own experience with the histology of aortic valve failures after ECM reconstruction. We have had 2 failed repairs after ECM aortic valve repair, necessitating reoperation at 158 days in a 21-year-old woman and at 338 days in a 5-year-old boy. In both cases, a nearly total valve replacement was performed because of extensive leaflet disease, necessitating reconstruction with an ECM cylinder valve. Failures occurred, in part for technical reasons, at inadequately supported neocommissural attachments to the aorta, resulting in insufficiency.

Leaflets at reoperation were pliable without calcification but were slightly thicker than normal valve cusps. Representative histologic specimens are shown in Figure 1 for failure at 158 days (Figure 1, A, C, and E) and from failure at 339 days (Figure 1, B, D, and F). In addition to hematoxylin and eosin staining (Figure 1, A and B), analysis with pentachrome staining (Figure 1, C and D) was performed to localize and identify proteoglycans, elastin, and collagen. The localization of leaflet constituents was not

completely normal, but all three typical constituents could be seen to be present.² Specific F4/80 antibody staining for macrophages (Figure 1, E and F) showed limited macrophage infiltration at 6 months (Figure 1, E), with none present in the later specimen (Figure 1, F). There was no evidence for microcalcification, nor could we clearly identify any remaining ECM with its more open and layered appearance; however, we

acknowledge that the ECM would be indistinguishable from collagen with our staining methods.

Two prominent cellular components of cardiac valves are the valve endothelial cells and valve interstitial cells.^{2,3} The valve endothelial cells can act as progenitor cells along the surface of the leaflets and are in continuity with the endocardium.² The valve interstitial cells reside in subendothelial locations, are derived

from valve endothelial cells through epithelial to mesenchymal transition, and are responsible for synthesizing and assembling the ECM of each layer.³ With this in mind, we always attempt to suture the ECM to normal tissues (normal endothelium), which may provide more robust endothelialization and thus promote organized bioscaffold replacement. We have therefore been aggressive in our resection of pathologic tissue before ECM

FIGURE 1. Representative histologic images for failed valve repair with extracellular matrix. A, C, and E, Specimens from failure at 158 days. B, D, and F, Specimens from failure at 339 days. A and B, Staining with hematoxylin and eosin. C and D, Pentachrome staining to localize and identify proteoglycans (blue), elastin (black), and collagen (yellow). The localization of leaflet constituents is not completely normal, but all three typical constituents are present. E and F, Specific staining for macrophages (F4/80 antibody staining), showing limited macrophage infiltration at 6 months (E), with none present in the later specimen (F). There was no evidence of microcalcification. No signs of remaining extracellular matrix were detected; however, the extracellular matrix would be indistinguishable from collagen by this staining.

reconstruction. In our particular cases, little normal tissue was available to perform leaflet repair because of the numbers of procedures previously performed. Likewise, Zaidi and colleagues¹ reported the majority of failures in patients with multiple previous procedures. Could the inflammatory infiltration of the ECM be a result of adjacent damaged tissues, or perhaps a response to a proinflammatory state (ie, concomitant left ventricular assist device)? In contrast to all other patch materials, an ECM bioscaffold is intended to be replaced by the body over time. The local and systemic milieu in which the bioscaffold is implanted could thus be more important than simply its use for repairing one heart structure or another.

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Reply to the Editor:

We thank McConnell and Hibino for their interest in our article and for contributing more information about the behavior of CorMatrix used for valve repair in congenital heart defects.

Similar to our experience, neither of the cases shows histologic evidence

of remodeling to any structure resembling native valve tissue. The hematoxylin and eosin histologic staining from the case of reoperation at 158 days (Figure 1, A, in the letter of McConnell and Hibino) shows residual CorMatrix surrounded by a mild chronic inflammatory response composed of predominantly macrophages, a compact fibrin or proteinaceous layer, and thin pannus overgrowth. The compact surface fibrin and pannus is the likely anatomic explanation for the slightly thicker than normal valve cusps. The hematoxylin and eosin histologic staining from the case of reoperation at 339 days (Figure 1, B, in the letter of McConnell and Hibino) shows only unmodified CorMatrix with few or no cells and surrounded by loosely organized fibrin. McConnell and Hibino have expressed some ambiguity regarding the nature of the tissue (residual CorMatrix extracellular matrix vs tissue remodeled to collagen); however, the tissue does not contain any viable cells (as a remodeled tissue would) and does have the histologic appearance of CorMatrix that we have observed after only a few weeks in situ (before it could possibly have been remodeled to native collagen). The appearance is also in keeping with our clinical and experimental experience of the histology of unimplanted CorMatrix. These figures reinforce the fact that CorMatrix in the distal leaflet remains intact, with minimal infiltration by host cells, as long as 1 year after implantation.

As we and others have noted, inflammatory cells predominantly enter the prosthetic leaflet from its basal end, which is in contact with native tissue. Because McConnell and Hibino have described the implantation of an extracellular matrix cylinder valve after nearly total removal of diseased native valve tissue rather than surgical valvuloplasty, we would not expect to see the same degree of inflammation in the part of the leaflets shown in the figures as a result of the fact that these may have

been quite distant from native tissue. In fact, most of the inflammation that we observed was centered in the native tissue adjacent to the CorMatrix, with extension as a wave into the CorMatrix over various distances. In the time since our article was accepted, we have seen 4 additional cases in our clinical and consultation practices with similar histologic findings at the material-tissue interface. It would be interesting to see histologic sections from the surgical anastomosis between the native tissue and the CorMatrix in the cases described by McConnell and Hibino, because this may show inflammation that is more characteristic of our experience. Specifically, McConnell and Hibino have described the valve failures at the neocommissural attachments to the aorta and at least partially attributed the failures to technical reasons; it is also possible that inflammation at these attachment sites may have led to weakening of the tissues in these areas and contributed to the failures.

Although there is increasing evidence for the importance of endothelial-to-mesenchymal transformation for maintaining the interstitial cell population in native valves, it is unclear whether this transformation occurs in prosthetic leaflets. The neoendothelialization or pannus formation that we described, and which is shown in Figure 1, A, of the letter of McConnell and Hibino, seems more consistent with encasement of foreign material such as one sees in pannus overgrowth onto the cusps of a stented surgical bioprosthetic valve than with remodeling toward a functional leaflet.

We did not observe any significant inflammatory response after the use of autologous pericardium in our patients, strongly suggesting that the inflammation was related more to the presence of CorMatrix than to damaged native tissue, which would be present in both cases. Although we did not investigate this specifically, none of our patients seemed more predisposed toward an inflammatory state than any other patient