Cardiac Regeneration in the Human Left Ventricle After CorMatrix Implantation

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CorMatrix is an organic extracellular matrix (ECM) derived from porcine small intestine submucosa and is used for pericardial closure and cardiac tissue repair. During explantation of a HeartMate II (Thoratec Corp, Pleasanton, CA) left ventricular assist device (LVAD) because of infection, CorMatrix was used to repair the left ventricular apex and aorta. Three months later, a HeartWare HVAD (HeartWare International, Inc, Framingham, MA) was implanted for recurrent heart failure. Excised apical CorMatrix samples showed cardiac tissue remodeling with viable cardiomyoblasts similar to native myocardium. Excised CorMatrix from the aorta showed organization of collagen and elastin similar to native aortic tissue.

(Ann Thorac Surg 2017;104:e239–41)

The decision about whether to close the pericardium after cardiac operations or to leave it open has been an area of dispute because of the lack of available meaningful clinical outcomes and evidence. For both reconstruction of myocardium and aorta, current materials used are polyester, polytetrafluoroethylene, and bovine/patient-derived pericardium. In particular, a number of studies in the past few years have documented the benefits of using CorMatrix to repair intracardiac structures such as the pericardium, tricuspid valve, aortic root, and ventricular tissue. In our case, cardiac remodeling occurred after the use of CorMatrix.

A 62-year-old white man with a history of hypertension, type II diabetes mellitus, atrial fibrillation with an automatic implantable cardioverter defibrillator, and New York Heart Association class IV congestive heart failure underwent implantation of a HeartMate II (Thoratec Corp, Pleasanton, CA) left ventricular assist device (LVAD) for ischemic cardiomyopathy in 2011. Because of a persistent ventricular assist device (VAD) pocket infection, his HeartMate II LVAD was explanted 3 years later. All foreign material was removed, and a single laminated layer of CorMatrix was used to reconstruct the old aortic graft anastomosis site and left ventricular apex defect. Three months after the explantation, the patient presented with worsening heart failure and underwent implantation of a HeartWare HVAD with excision of the apical and aortic CorMatrix patches.

Comment

CorMatrix is an acellular organic extracellular matrix (ECM) derived from porcine small intestine submucosa that when implanted provides an interim bioscaffold onto which a patient's cells will migrate, lay down collagen to replace foreign ECM with permanent tissue, and integrate to repair damaged tissues. CorMatrix has been used to repair cardiac structures such as pericardium, tricuspid valve, aortic root, and ventricular tissue [1–4]. ECM of various tissue types has structural and functional roles depending on their composition, but all ECM share these common factors: structural proteins, adhesion glycoproteins, glycosaminoglycans and proteoglycans, and matricellular proteins. As an acellular bioscaffold, CorMatrix does not activate the human complement cascade, thus avoiding acute rejection responses.

To date, CorMatrix has been implanted in more than 50,000 patients worldwide in a number of cardiac closure applications [1]. Our case provided the opportunity to examine the histopathologic fate of CorMatrix after just 3 months of in vivo implantation. CorMatrix samples were specifically taken from the aorta (where the previous Heartmate II outflow graft was reconstructed) and the left ventricular CorMatrix reconstruction (where the inflow cannula was previously removed) to be stained for cells and matrix structure (Fig 1).

Histologic examination revealed cardiac tissue growing on the endoluminal apical CorMatrix material, and cardiac striations were visualized that were similar to that of native cardiac tissue (Fig 2). H&E staining demonstrated mature cardiomyocytes within the same plane as the CorMatrix in a background of dense fibrotic stroma at a lower magnification (Fig 2A), which is likely secondary to resorption of CorMatrix after resolution of the initial inflammatory response after CorMatrix implantation [5]. These cardiomyocytes are also visualized in Figure 2B (black arrows) where over time, CorMatrix material was naturally incorporated into the heart. Biopsy specimens of the aorta CorMatrix show elastin and collagen growth patterns comparable to those found in normal aortic histologic patterns (Figs 2C, 2D). Histologic findings were reported and confirmed independently by the institutional pathology department.

To investigate cardiac regeneration and the potential growth of new cardiomyoblasts, we focused on the *HOP* gene involved in the developing heart [6]. CorMatrix

Accepted for publication March 20, 2017.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2017.03.044

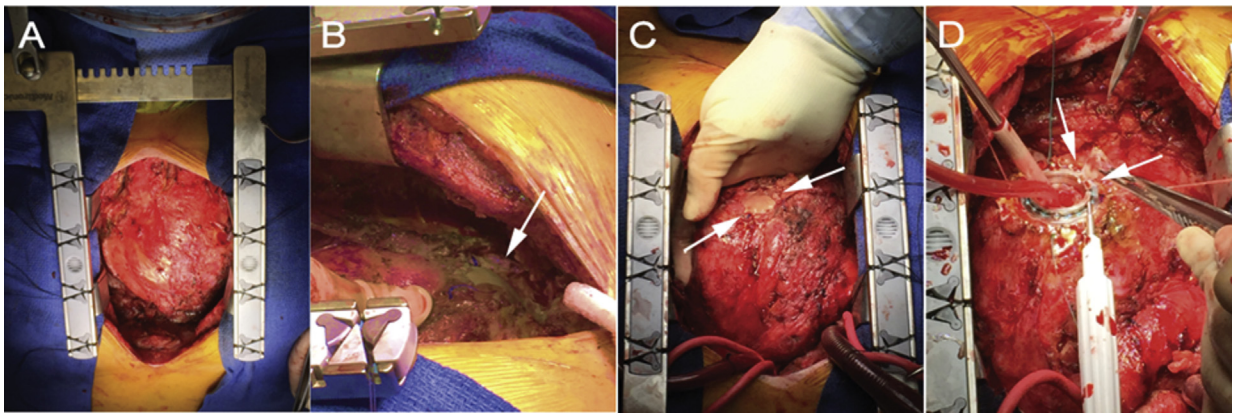

Fig 1. Intraoperative images showing position of left ventricular apical CorMatrix patch after explantation of HeartMate II. (A) Heart before removal of CorMatrix. After patient had HeartMate II left ventricular assist device (LVAD) explanted, CorMatrix was placed on heart for closure of defects in (B) the left ventricular apex and aorta. After 3 months, the patient required a HeartWare LVAD implant as destination therapy, and during this procedure CorMatrix biopsy specimens were taken for analysis. White arrows denote where the CorMatrix patch is visible. (C and D) CorMatrix biopsy samples were specifically taken from the aorta and the rim of the device.

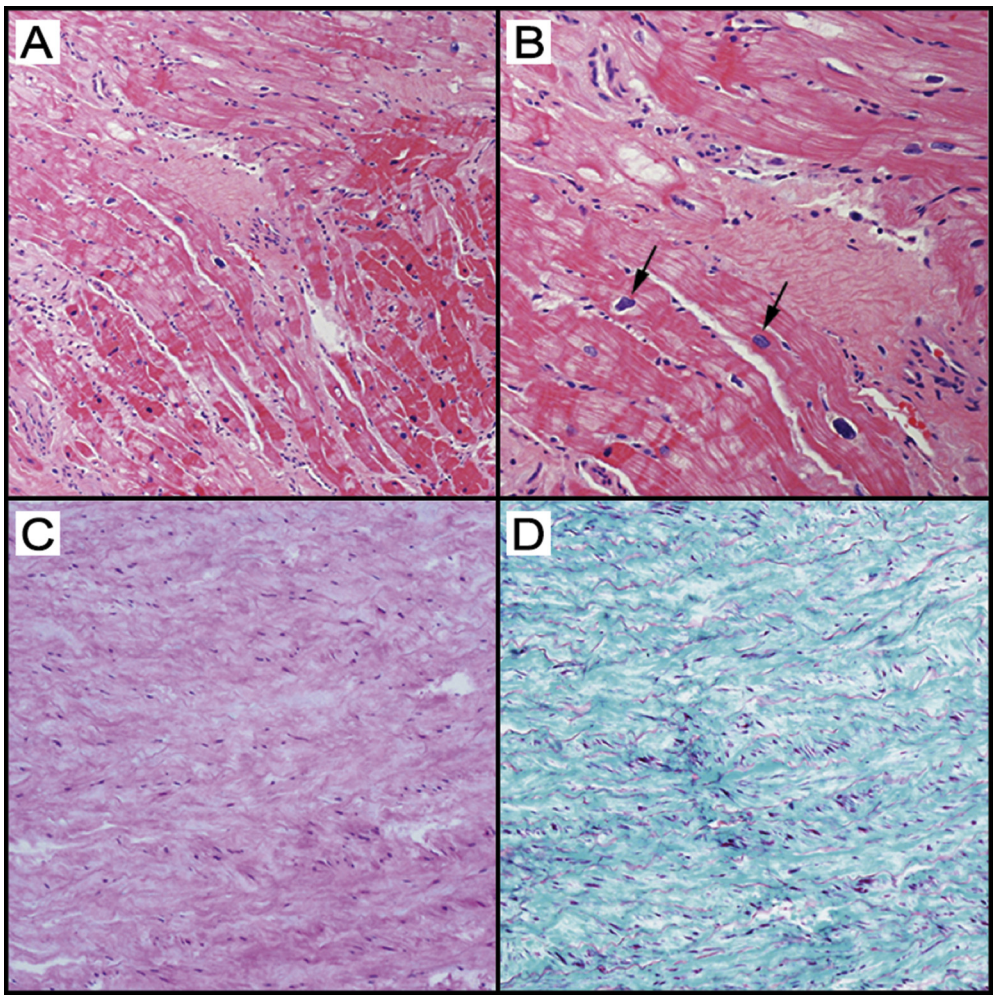

Fig 2. Excised 3-month-old CorMatrix from left ventricular apex. (A) H&E-stained sections show mature cardiac myocytes in a background of dense fibrotic stroma (×100). The myocytes have conspicuous cross-striations and frequent vacuolar cytoplasmic change. No coagulative necrosis or wavy fibers are seen; however, hypereosinophilic fibers are apparent on the right. Myocyte nuclei are readily apparent throughout, and size is normal to slightly enlarged. In area of hypereosinophilic change, myocyte nuclei are hyperchromatic. Blood vessels are regularly distributed within interstitium. (B) On higher power (×200), myocyte cross-striations are readily apparent, as is cytoplasmic vacuolization. Cardiomyocytes are present within dense fibrotic stroma, shown by black arrows. Blood vessels are regularly distributed and appear normal. Biopsy specimens of the aorta CorMatrix stained with hematoxylin and eosin (C) and trichrome (D) show elastin and collagen growth patterns comparable to those found in normal aortic histologic patterns.

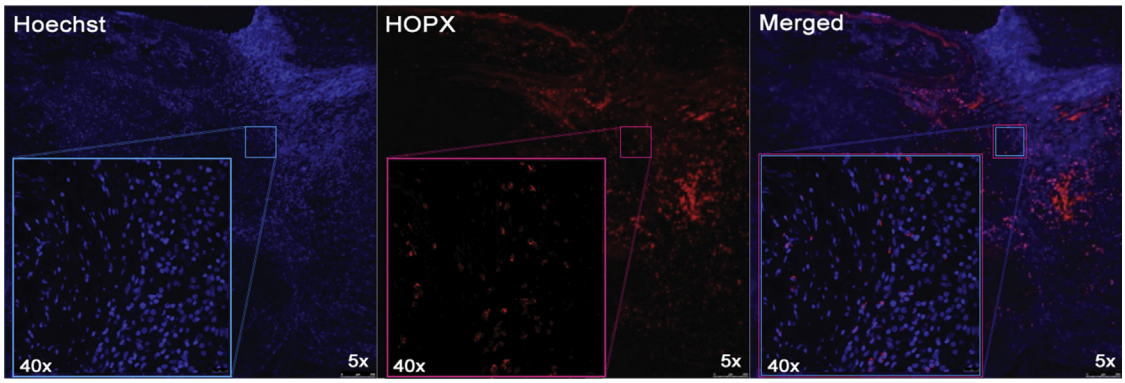

Fig 3. CorMatrix sections from the apex, but not from the aorta, stained positive for anti-HOPX antibodies, suggestive of cardiomyoblastic growth in regenerating cardiac tissue. Hoechst staining was used to stain for DNA of fixed cells (left panel), while anti-HOPX staining was used to identify which of those cells were new cardiomyoblasts (middle panel). Samples from the aorta were negative for anti-HOPX staining (data not shown). The right panel shows the overlay of both stains, which demonstrates in vivo cardiac tissue regeneration within the left ventricular apical CorMatrix patch.

sections from the apex, but not from the aorta, stained positive for anti-*HOPX* antibodies, suggestive of cardiomyoblastic growth in regenerating cardiac tissue (Fig 3). Because the aorta does not possess the regenerative capability of the heart, anti-*HOPX* staining served to identify new cardiomyoblast involvement at the cardiac apex, and staining of aorta CorMatrix also served as a negative control.

This case report describes explanted human evidence of left ventricular and aortic regeneration over a 3-month period after surgical reconstruction and repair of the left ventricular apex and aorta using CorMatrix ECM. These findings support our hypothesis that CorMatrix plays an essential role in neocardiac remodeling and growth. In another similar case report, CorMatrix was found to be involved in remodeling of cardiac tissue into neopericardium [2]. Therefore, placement of CorMatrix within its surrounding microenvironment likely determines the phenotypic and tensile properties of the regenerating tissue during repair.

The authors wish to thank the patient and family and the Division of Cardiothoracic Surgery, Department of Surgery, University of Arizona College of Medicine.

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