Diagnostic Usefulness of Histological Examination of the Left Ventricular "Core" Excised to Insert a Left Ventricular Assist Device in Patients With Severe Heart Failure

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The left ventricular assist device (LVAD) has proven to be beneficial for patients with severe heart failure poorly responsive to anti heart failure medicine. To examine both grossly and histologically the portion of left ventricular (LV) free wall excised ("the left ventricular core") to insert a LVAD in 337 patients with severe heart failure from a variety of causes. We collected together all photographs of LV "cores" and the histologic sections prepared from them and reexamined both. Despite the fact that these LV cores usually weighed >100 times the quantity of myocardium available to examine compared with that available by biotome inserted via a transvenous catheter, the number in which histologic study allowed an unequivocal diagnosis was limited. Examination of the clinical records usually was required to establish the definitive diagnosis. Although the presence of a scarred myocardial wall usually suggested ischemic cardiomyopathy (IC), the scarring may not have involved the LV apex resulting in a nonscarred portion of myocardium simulating idiopathic dilated cardiomyopathy (IDC). Moreover, about 10% of the patients with IDC have myocardial scars thus simulating IC. Involvement of the LV core by amyloid, sarcoid, myocarditis, and acute infarction, of course, allowed a specific anatomic diagnosis. Despite the presence of ample tissue to secure a definitive diagnosis, the combination of clinical input and morphologic assessment was required to arrive at a definite diagnosis in most patients. **(Am J Cardiol 2020;137:71−76)**

Percutaneous transvenous endomyocardial biopsy via the bioptome of the ventricular septum has been performed since 1962.[1] Usually, multiple minute fragments of myocardium are obtained by this procedure and altogether the fragments weight <0.1 g.[2] The introduction of the left ventricular assist device (LVAD) in 1971 required the removal of a much larger portion of myocardium to insert the LVAD than available simply by percutaneous biopsy, >100 times larger. The present report describes the diagnostic utility of histologic examination of the "left ventricular core" excised in 337 patients receiving a LVAD.

Methods

From March 1998 through December 2017 (a period of nearly 20 years), a total of 337 patients had a portion of their LV free wall excised to insert a LVAD at Baylor University Medical Center (BUMC) at Dallas. Nine different surgeons performed these operations. All the "left ventricular cores" were submitted to the surgical pathology division of the BUMC Department of Pathology. All 337 were described and weighed by one of us (WCR) and they were photographed (mainly by Saba Ilyas). After photography, the "cores" were sectioned, processed in alcohol, and xylene and 6-micron thick sections were prepared: One section was stained by hematoxylin/eosin and another by trichrome. All sections were examined and the official report was submitted by one of us (WCR). For the present study, the histologic sections were re-examined by one of us (WCR) in 266 of the 337 cases; in the remaining 72, the findings were those described in the initial report prepared by WCR. The clinical records were examined in all 337 patients.

Patient demographics and clinical characteristics were presented as proportions for categorical variables and means/medians for continuous variables. Comparisons were done using Chi-square/Fisher exact tests for proportions and Wilcoxon rank-sum/Student *t* tests for continuous variables, as appropriate. Analyses were done using STATA 14.1.

Results

Certain clinical and morphologic features in the 337 patients, divided by gender, are summarized in Table 1. The patients ranged in age from 17 to 81 years (mean 57); 269 (80%) were men and 68 (20%) were women. Percutaneous coronary intervention had been performed earlier in

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See page 76 for disclosure information.

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Table 1
Characteristics of patients having insertion of a left ventricular assist device at Baylor University Medical Center 1998-2017 and morphological findings in the operatively excised portion of the left ventricular free wall

Variable	All Patients (n = 338)	Men (n = 270)	Women (n = 68)
1.Age (years): range (mean)	17-81(57)	19-81(58)	17-77(53)
2. Coronary artery disease (angiogram)	194	165	29
a) Prior coronary artery bypass grafting	96	80	16
b) Prior percutaneous coronary intervention	112	92	20
3. Cause of heart failure			
a) Ischemic cardiomyopathy	164 (48.5%)	139 (51.7%)	25 (36.8%)
b) Idiopathic dilated cardiomyopathy	142 (42.0%)	108 (40.0%)	34 (50.0%)
c) Acute myocardial infarction	9 (2.6%)	5 (1.8%)	4 (5.9%)
d) Sarcoidosis	5 (1.5%)	4 (1.5%)	1 (1.5%)
e) Myocarditis	3 (.9%)	1 (.4%)	2 (2.9%)
f) Hypertrophic cardiomyopathy	4 (1.2%)	4 (1.5%)	0
g) Chemotherapy/radiation	4 (1.2%)	2 (.7%)	2 (2.9%)
h) Aortic Stenosis	2 (.6%)	2 (.7%)	0
i) Infective endocarditis with ring abscess	1 (.3%)	1 (.4%)	0
j) Congenital transposition	1 (.3%)	1 (.4%)	0
k) Subaortic stenosis	1 (.3%)	1 (.4%)	0
l) Amyloidosis	1 (.3%)	1 (.4%)	0
m) Unclear	1 (.3%)	1 (.4%)	0
4. Subsequent heart transplant (HT)	106	88	18
5. Interval (months) LVAD to HT: range(mean)	<1-63 (14)	<1-63 (13)	2-58 (19)
a) ≤2	7 (6.6%)	6 (6.8%)	1 (5.6%)
b) >2-12	54 (50.9%)	48 (54.6%)	6 (33.3%)
c) >12	45 (42.5%)	34 (38.6%)	11 (6.2%)
6. LVAD implanted between 1998 and 2011	87 (25.7%)	63 (23.3%)	24 (35.3%)
a) Alive	41 (47.1%)	31 (49.2%)	10 (41.7%)
b Dead	46 (52.9%)	32 (50.8%)	14 (58.3%)
7. LVAD implanted from 2012 to 2016	251 (74.3%)	207 (77.7%)	44 (64.7%)
a) Alive	167 (66.5%)	139 (67.1%)	28 (63.6%)
b) Dead	84 (33.5%)	68 (32.9%)	16 (36.4%)
8. Weight of LV core (grams): range(mean)	0.23-6.28(2.79)*	0.23-6.28(2.82)	0.38-5.7(2.71)
9. Floating LV cores			
a) Number of LV cores that floated	43/132 (32.6%)	33/110 (30%)	10/22 (45.5%)
b) Number of LV cores that did not float	89/132 (67.4%)	77/110 (70%)	12/22 (54.5%)
11. LVAD replaced with another LVAD	26 (7.7%)	24 (8.9%)	2 (2.9%)
12. Died	130 (38.5%)	100 (37.0%)	30 (44.1%)
a) ≤30 days after insertion of LVAD	22 (16.9%)	18 (18.0%)	4 (13.3%)
b) >30 days after insertion of LVAD	108 (83.1%)	82 (82.0%)	26 (86.7)
1) After HT	18 (16.7%)	14 (17.1%)	4 (15.4%)
2) Never received HT	90 (83.3%)	68 (82.1%)	22 (84.6%)

Abbreviations: HT = heart transplant; LV = left ventricular; LVAD = left ventricular assist device.

* 11 patients had LV cores weighing less than 1g. These cores might have been removed in multiple fragments with some of those fragments not being submitted to pathology. Nine different surgeons performed all of these LVAD implantations.

112 patients (33%) and coronary artery bypass grafting, in 96 patients (28%).

The cause of the severe heart failure was ischemic cardiomyopathy (IC) in 164 patients (48%), idiopathic dilated cardiomyopathy (IDC) in 142 (42%), and one of the 8 "other" conditions in 31 patients (10%) (Table 1). Diagnosis of either IC or IDC was based on the presence of coronary narrowing by angiography in the case of IC, and on the absence of coronary narrowing by angiography and the absence of any of the "other" 8 conditions (sarcoid, amyloid, etc.) in the case of IDC. Specifically, neither IC nor IDC was diagnosed histologically without knowledge of the angiographic status of the epicardial coronary arteries. Likewise, the histologic findings in hypertrophic cardiomyopathy, chemotherapy/irradiation, valvular heart disease, and congenital heart disease also were nonspecific and required review of the clinical records to learn of the presence of any of these 4 conditions (Figures 1−11).

The excised portion of the LV free wall ("apical core") ranged in weight from 0.34 to 6.28 g (mean 2.79 g; median 2.67 g). The apical core in 11 patients weighed less than 1 g. The quantity of subepicardial adipose tissue was so excessive in 43 of 132 patients where it was measured (33%) that the "LV cores" floated in the container of formaldehyde.

The number of histologic sections of LV core examined ranged from 1 to 4 (mean 2.1). Fibrous adhesions were present on the epicardial surface in 76 patients (28.6%), and fibrinous deposits were present on the epicardial surface in 5 patients (1.9%). (These patients previously had had a cardiac operation.) A focal increase in interstitial fibrous tissue was observed in 217 (82%) and focal

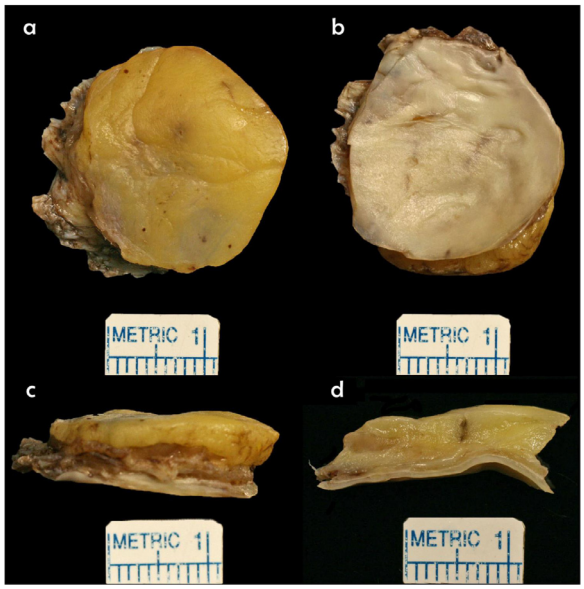

Figure 1. Left Ventricular apical "core" in a 68-year-old obese man with ischemic cardiomyopathy (healed myocardial infarct and dilated left ventricular cavity). The quantity of subepicardial adipose tissue is increased (a), the mural endocardium is fibrotic (b), the myocardium is focally scarred (c), and on cross-section the myocardial wall has been infiltrated by adipose tissue.

replacement fibrosis, in 125 (47%) specimens. Foci of necrosis (excluding foci of contraction-band necrosis adjacent to the borders of the specimens) were seen in the myocardial walls in 19 (7%) specimens, and foci of

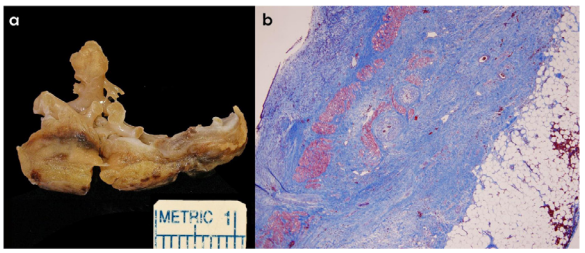

Figure 2. Left Ventricular apical "core" (a) and a histological section of its central portion (b) in a 54-year-old man with ischemic cardiomyopathy. The myocardial wall is extensively scarred (blue in the section) and a few islands of myocardium remain incorporated into the scar tissue (b). Trichrome stain (b) X 40.

inflammatory cells, usually mononuclear, in 22 (8.3%) of the "LV cores". Collections of adipose tissue cells were present in the myocardial walls in 144 specimens (54%). The myofibers appeared to be enlarged (as indicated by large nuclei) in 265 (99%) specimens. The intramural coronary arteries were normal in 99% of the specimens. The mural endocardium was focally or diffusely thickened by fibrous tissue in 225 specimens (84%) and mural thrombus was superimposed on the thickened endocardium in 4 patients (2%).

Discussion

The present report describes findings in 337 patients who had a portion of their LV free wall excised to insert a LVAD. The portion of LV free wall was examined both

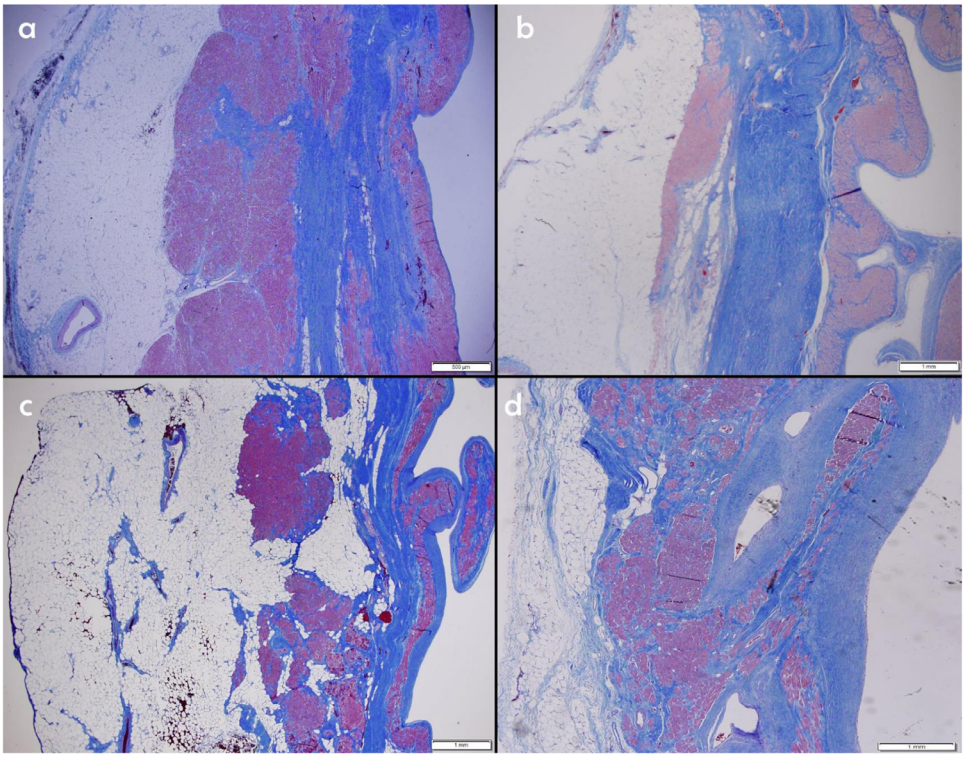

Figure 3. Photomicrographs of the midportion of the left ventricular apical "core" in 4 patients with ischemic cardiomyopathy and excessive subepicardial adipose tissue. Each is extensively scarred (blue) and the mural endocardium in b and d is thickened by dense fibrous tissue. a, 54-year-old man; b, 57-year-old man; c, 68-year-old man, and d, 74-year-old man. Trichrome stains, each X 20.

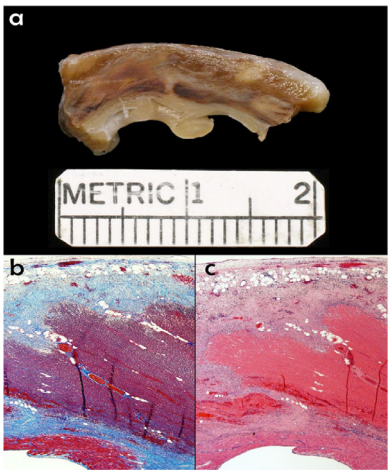

Figure 4. Left ventricular "core" (a) and histologic section (b and c) of the "core" in a 52-year-old diabetic man with acute myocardial infarction complicated by cardiogenic shock and severe heart failure unimproved by intra-aortic balloon pump and coronary bypass. The myocardium of the left ventricular "core" is mainly neurotic with inflammatory margins and early fibrosis. Trichrome stain (b) and hematoxylin /eosin stain (c); each X 40.

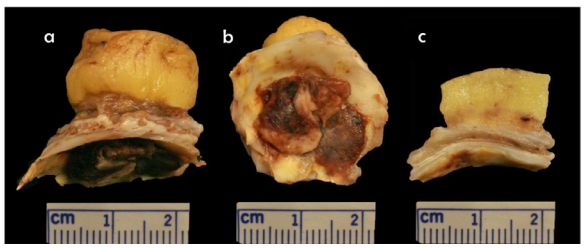

Figure 5. Left ventricular "core" in a 58-year-old man who had a coronary bypass at age 52, known diabetes mellitus, obstructive sleep apnea, and unrelenting heart failure. (a) View of the LV "core" laterally showing a huge quantity of subepicardial adipose tissue, and virtually totally scarred myocardial wall. (b) View of endocardial surface nearly covered by a thrombus. (c) Cross section cut showing the thick layer of epicardial fat and the underlying thin-scarred myocardial wall.

grossly and histologically to determine how useful its examination would be for a specific cardiac diagnosis. Of the 337 specimens, the cause of the severe heart failure – the reason for the insertion of the LVAD – was either IC or

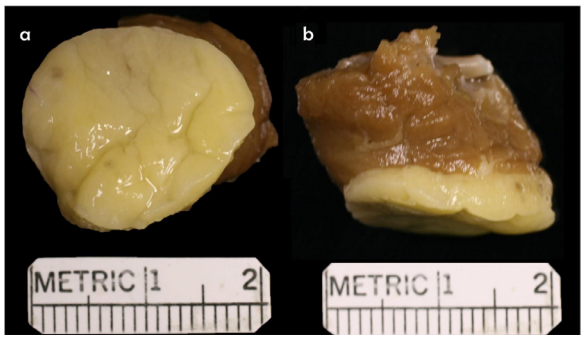

Figure 6. Left ventricular "core" in a 66-year-old woman with idiopathic dilated cardiomyopathy. (a) Epicardium completely covered by adipose tissue. (b) Lateral view showing the thickness of the layer of epicardial fat compared to that of the underlying myocardial which is free of grossly visible lesions.

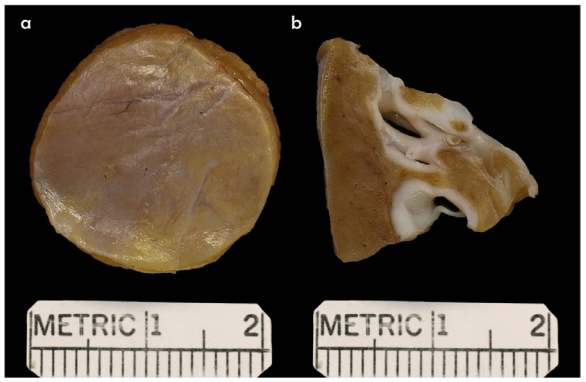

Figure 7. Left Ventricular "core" in a 66-year-old man with idiopathic dilated cardiomyopathy. It weighed 2.5g. (a) Epicardium almost devoid of adipose tissue; (b) cross-section showing marked fibrous thickening of the mural endocardium but no underlying myocardial scarring.

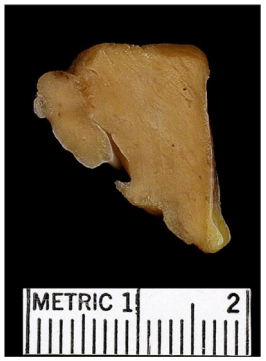

Figure 8. Transverse section of a left Ventricular "core" in a 39-year-old woman with idiopathic dilated cardiomyopathy. The myocardium is free of lesions, the epicardium is virtually devoid of adipose tissue, and the mural endocardium is not thickened by fibrous tissue.

IDC in 90% of the patients. Although several features of the "LV core" specimens strongly suggested that the proper diagnosis was IC or IDC there was overlap in the morphologic characteristics such that a separation of the 2 histologically was not conclusive. Proper morphologic diagnosis was specific in the specimens with cardiac amyloidosis, sarcoidosis, myocarditis, and acute myocardial infarction.

Certain findings provide strong clues to separate the patients with IC from those with IDC. The patients with IC usually had LV wall scarring but if the scarring did not

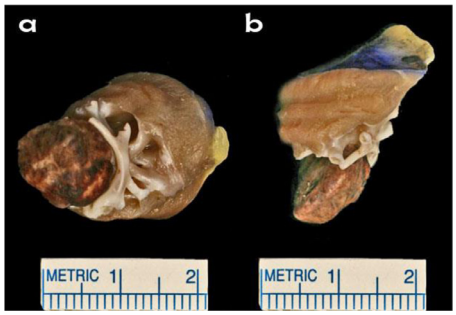

Figure 9. Left Ventricular "core" in a 20-year-old woman with idiopathic dilated cardiomyopathy. A thrombus is present on the endocardial surface which also is focally thickened by fibrous tissue. (a) Apical view; (b) Lateral view showing the protruding thrombus.

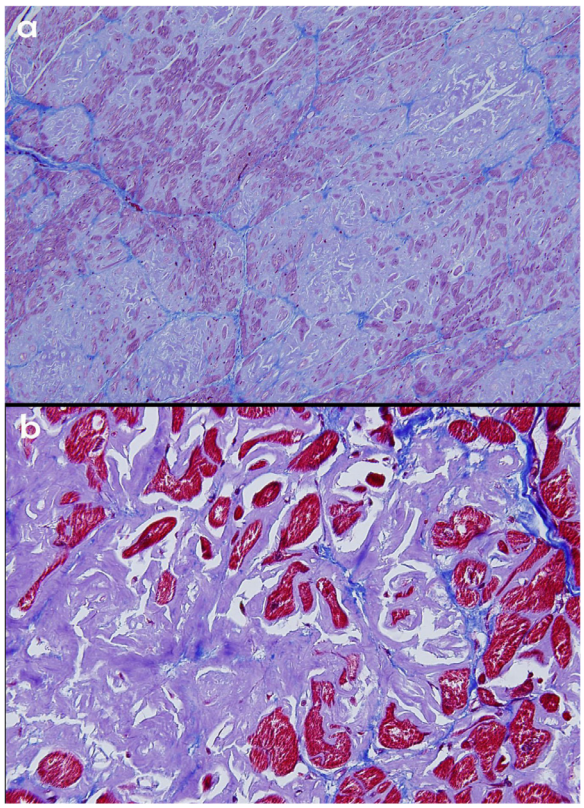

Figure 10. Amyloidosis in a 61-year-old man, Trichrome stains: X 100 (a) and X 400 (b).

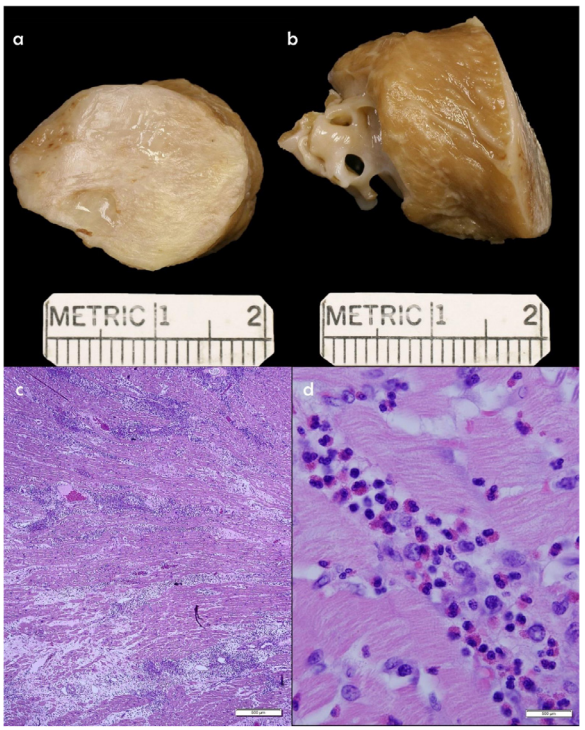

Figure 11. Left ventricular "core" in a 64-year-old woman with known idiopathic dilated cardiomyopathy who a month before the left ventricular assist device was scheduled developed severe unrelenting heart failure. Histologic study of the left ventricular "core" showed severe eosinophil myocarditis. (a) View of epicardium which is severely thickened by fibrous tissue. (b) Lateral view showing no grossly visible myocardial lesions. Histologic sections of eosinophilic myocarditis (Hematoxylin and eosin stain x 40 and 1000)

involve the LV apex, the site of excision of the portion of LV wall, the specimen more resembled the usual finding in patients with IDC. About 10% of patients with IDC had LV wall scars and, if the scarring involved the LV apical wall, the specimen would then be similar to most of the specimens in patients with IC.[3] Two additional features suggest IC: (1) the presence of epicardial adhesions usually suggests a previous cardiac operation, mainly coronary bypass, and (2) the presence of huge quantities of subepicardial adipose tissue, which usually indicates the presence of obesity, is something more frequent in patients with IC than in those with IDC. (These specimens usually floated in containers of formaldehyde because adipose tissue is lighter than myocardium.[4]) It is unusual to find epicardial adhesions in patients with IDC. The presence of increased quantities of interstitial fibrous tissue by histologic study was not helpful in distinguishing IC from IDC.

A specific cardiac diagnosis could usually be determined in the non-IC patients with an infiltrative condition: Cardiac amyloidosis, cardiac sarcoidosis, and myocarditis. Acute myocardial infarction was clear in 9 patents. Examination of the "LV core" in patients with hypertrophic cardiomyopathy, adriamycin toxicity, aortic stenosis, subaortic stenosis, and infective endocarditis, also was nonspecific, and the cause of the heart failure in these patients was obtained from the clinical records.

Although it is not the first to describe morphologic features of patients having the "LV core" excised to insert a LVAD, the present report describes these findings in by far the largest number of patients and in greatest detail. Milting and collagen[5] describing the collagen content (percent of 4-hydroxypardine) in the LV apical sample in 24 patients having a LVAD inserted. The point that mechanical unloading did not alter the total collagen of the supported failing heart. Rose and Park[6] described findings in "apical cores" in 21 necropsy patients in whom have a LVAD had been inserted. They found that inserting the LVAD "significantly reduced the amount of coagulative necrosis, myocytolysis and myocyte waviness in the left ventricle." Soderlund et al[7] studied apical cores in 29 sequential subjects and found "little prognostic utility in guiding patient management." Cazes et al[8] studied the LV cores in 60 patients having a LVAD inserted and found that the "pathological analysis provides definite diagnosis and contributes to determine the cases which the cardiac disease has a possibility to recover under (L)VAD."

Some positive features of the present study include the following: (1) a large number of "LV cores" were examined, namely 337; (2) all were examined, described and reported by the same person, namely WCR; (3) all specimens were weighed by the same individual, an item not reported previously; (4) all histologic sections were stained by both the trichrome method and by hematoxylin/eosin; (5) nearly all specimens were photographed, and (6) the clinical records were examined by one or more of the authors.

Limitations of the study include the following: (1) the "LV cores" were excised by 9 different surgeons, and (2)

there was considerable variation in the weights of the excised LV specimens. The specimens ranged in weight from 0.34 to 6.28 g, a 27 times difference between the smallest and largest specimens. Of the 337 patients, the LV cores in 11 (3%) weighed <1.0 g. Some specimens were excised in a single block; others, in several different fragments.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

1. Sakakbara S, Konna S. Endomyocardial biopsy. *Jpn Heart J* 1962; 3:537–543.
2. Ferrans VJ, Roberts WC. Myocardial biopsy: a useful diagnostic procedure or only a research tool? *Am J Cardiol* 1978;41:965–967.
3. Roberts WC, Siegal RJ, McManus BM. Idiopathic dilated cardiomyopathy: analysis of 152 necropsy patients. *Am J Cardiol* 1987;60:1340–1355.
4. Roberts WC, Roberts JD. The floating heart or the heart too fat to sink. Analysis of 55 necropsy patients. *Am J Cardiol* 1983;52:1286–1289.
5. Milting H, Jacob M, Kassner A, Heimann P, Mannherz HG, Becker G, Meyer HE, Bothing D, Arksoglu L, Morshuis M, Korfer R, El Banayosa A. The structural examination of myocardial samples from patients with end-stage heart failure supported by ventricular assist devices using electron microscopy and amino acid analysis reveals low degree of reverse remodeling. *J Heart Lung Transplant* 2004;23:396–404.
6. Rose AG, Park SJ. Pathology in patients with ventricular assist devices. A study of 21 autopsies, 24 ventricular apical core biopsies and 24 explanted hearts. *Cardiovas Pathol* 2005;14:19–23.
7. Soderlund KA, Chivukula RR, Russell SD, Conte JV, Mudd JO, Halushka MK. Prognostic value of left ventricular apical tissue removed for HeartMate II left ventricular assist device placement. *Cardiovas Pathol* 2009;18:217–222.
8. Cazes A, Duong J-P, Huyen V, Fornes P, Amrein C, Guillemain R, Grinda J-M, Bruneval P. Mechanical ventricular assistance in heart failure: pathology of the cardiac apex removed during device implantation. *Cardiovas Pathol* 2010;19:112–116.