

# The role of endomyocardial biopsy in the management of cardiovascular disease

## A Scientific Statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology

### *Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology*

Leslie T. Cooper, MD, FAHA, FACC; Kenneth L. Baughman, MD, FAHA, FACC; Arthur M. Feldman, MD, PhD, FAHA, FACC; Andrea Frustaci, MD; Mariell Jessup, MD, FAHA, FACC; Uwe Kuhl, MD; Glenn N. Levine, MD, FAHA, FACC; Jagat Narula, MD, PhD, FAHA; Randall C. Starling, MD, MPH; Jeffrey Towbin, MD, FAHA, FACC; and Renu Virmani, MD, FACC

Online publish-ahead-of-print 24 October 2007

#### KEYWORDS

Scientific statements; Biopsy; Transplantation; Heart failure; Cardiomyopathy; Myocarditis

The role of endomyocardial biopsy (EMB) in the diagnosis and treatment of adult and pediatric cardiovascular disease remains controversial, and the practice varies widely even among cardiovascular centers of excellence. A need for EMB exists because specific myocardial disorders that have unique prognoses and treatment are seldom

diagnosed by noninvasive testing.<sup>1</sup> Informed clinical decision making that weighs the risks of EMB against the incremental diagnostic, prognostic, and therapeutic value of the procedure is especially challenging for nonspecialists because the relevant published literature is usually cited according to specific cardiac diseases, which are only diagnosed after EMB. To define

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee on July 2, 2007; the American College of Cardiology Foundation Board of Trustees on May 21, 2007; and the European Society of Cardiology Committee for Practice Guidelines on April 3, 2007.

When this document is cited, the American Heart Association, the American College of Cardiology Foundation, and the European Society of Cardiology request that the following citation format be used: Cooper LT, Baughman K, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *Eur Heart J* 2007;28:3076–3093. doi:10.1093/eurheartj/ehm456.

This article has been copublished in the *Journal of the American College of Cardiology* and *Circulation*.

Copies: This document is available on the World Wide Web sites of the American Heart Association ([my.americanheart.org](http://my.americanheart.org)), the American College of Cardiology ([www.acc.org](http://www.acc.org)), and the European Society of Cardiology ([www.esccardio.org](http://www.esccardio.org)). Bulk reprints are available from Oxford University Press by contacting Special Sales ([special.sales@oxfordjournals.org](mailto:special.sales@oxfordjournals.org)), Journals Division, Oxford University Press, Great Clarendon Street, Oxford, OX2 6DP, UK. Phone +44 (0) 1865 353827, Fax +44 (0) 1865 353774, Work Mobile +44 07841322925. A single reprint is also available by calling 800-242-8721 (US only) or writing to the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0421. To purchase *Circulation* reprints, call 843-216-2533 or e-mail [kelle.ramsay@wolterskluwer.com](mailto:kelle.ramsay@wolterskluwer.com).

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the European Society of Cardiology or the American Heart Association. Please direct requests to [journals.permissions@oxfordjournals.org](mailto:journals.permissions@oxfordjournals.org) (Web site located at [http://www.oxfordjournals.org/access\\_purchase/rights\\_permissions.html](http://www.oxfordjournals.org/access_purchase/rights_permissions.html)) or visit the Web site located at <http://www.americanheart.org/presenter.jhtml?identifier=4431>.

The content of this scientific statement has been published for personal and educational use only. No commercial use is authorized. No part of this document may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the *European Heart Journal* and the party authorized to handle such permissions on behalf of the ESC.

Disclaimer. The scientific statement represents the views of the ESC, which were arrived at after careful consideration of the available evidence at the time they were written. Health professionals are encouraged to take them fully into account when exercising their clinical judgement. The document does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

© The European Society of Cardiology, the American Heart Association, Inc, and the American College of Cardiology Foundation 2007. All rights reserved. For Permissions, please e-mail: [journals.permissions@oxfordjournals.org](mailto:journals.permissions@oxfordjournals.org)

the current role of EMB in the management of cardiovascular disease, a multidisciplinary group of experts in cardiomyopathies and cardiovascular pathology was convened by the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC). The present Writing Group was charged with reviewing the published literature on the role of EMB in cardiovascular diseases, summarizing this information, and making useful recommendations for clinical practice with classifications of recommendations and levels of evidence.

The Writing Group identified 14 clinical scenarios in which the incremental diagnostic, prognostic, and therapeutic value of EMB could be estimated and compared with the procedural risks. The recommendations contained in the present joint Scientific Statement are derived from a comprehensive review of the published literature on specific cardiomyopathies, arrhythmias, and cardiac tumors and are categorized according to presenting clinical syndrome rather than pathologically confirmed disease. The ultimate intent of this document is to provide an understanding of the range of acceptable approaches for the use of EMB while recognizing that individual patient care decisions depend on factors not well reflected in the published literature, such as local availability of specialized facilities, cardiovascular pathology expertise, and operator experience. The use of EMB in the post-transplantation setting is beyond the scope of this document.

This Scientific Statement was approved for publication by the governing bodies of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology and has been officially endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology.

The classifications of recommendations used in this document are

- *Class I*: conditions for which there is evidence or there is general agreement that a given procedure is beneficial, useful, and effective;
- *Class II*: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
- *Class IIa*: conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy;
- *Class IIb*: conditions for which usefulness/efficacy is less well established by evidence/opinion; and
- *Class III*: conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

The levels of evidence are

- *Level A (highest)*: multiple randomized clinical trials;
- *Level B (intermediate)*: limited number of randomized trials, nonrandomized studies, and registries; and
- *Level C (lowest)*: primarily expert consensus.

## Technique and risks of EMB

The first nonsurgical techniques for heart biopsy were reported in 1958.<sup>2</sup> In the 1960s the safety of heart biopsy improved, with vascular access through the right external or internal jugular vein, sampling of the right interventricular septum, and designation of the heart borders by right

heart catheterization before biopsy.<sup>3</sup> Sakakibara and Konno<sup>4</sup> introduced the use of a flexible biptome with sharpened cusps that allowed EMB by a pinching as opposed to a cutting technique. Caves et al.<sup>5</sup> modified the Konno biopsy forceps (Stanford Caves-Shulz biptome) to allow percutaneous biopsies through the right internal jugular vein with only local anesthesia and rapid tissue removal. The reusable Stanford-Caves biptome and its subsequent modifications became the standard device for EMB for approximately 2 decades.<sup>6,7</sup> Single-use biptomes and sheaths allow access through the right and left jugular or subclavian veins, right and left femoral veins, and right and left femoral arteries and may be associated with lower risk of pyrogen reaction and transmission of infection than reusable biptomes.

The right internal jugular vein is the most common percutaneous access site for right ventricular EMB in the United States. In Germany and Italy, the femoral vein is commonly used for percutaneous access.<sup>8</sup> Sonographic techniques to identify the location, size, and respirophasic variation in size of the internal jugular vein decrease the duration of the procedure and complications.<sup>9,10</sup> Monitoring should include electrocardiographic rhythm, blood pressure, and pulse oximetry. The subclavian vein also may be used occasionally.

The femoral artery may be used as a percutaneous access site for left ventricular biopsy.<sup>11,12</sup> This approach requires insertion of a preformed sheath to maintain arterial patency. All arterial sheaths must be maintained under constant pressurized infusion to avoid embolic events. Aspirin or other antiplatelet agents may be used in addition to heparin during left heart biopsy procedures to decrease the risk of systemic embolization. No comparative studies exist on which to base a recommendation for left versus right ventricular biopsy; however, left ventricular biopsy has been used in case series to define cardiomyopathic processes limited to the left ventricle.<sup>13</sup>

EMB usually is performed safely under fluoroscopic guidance. Fluoroscopy is generally better than 2-dimensional echocardiography to guide EMB because it provides more information to the operator about the course of the biptome and site of biopsy.<sup>14,15</sup> The echocardiographic technique without fluoroscopy has been used primarily to biopsy intracardiac masses. Some operators use fluoroscopy and echocardiography in combination to enhance entry into the right ventricle and direction of the biptome. Noninvasive computed tomography (CT) or cardiac magnetic resonance (CMR) imaging may be of value in patients scheduled for EMB. CT scanning may be used to assess the angle of the intraventricular septum relative to the superior vena cava or inferior vena cava. Knowledge of this angle may lessen the risk of inadvertent biopsy of the right ventricular free wall during a fluoroscopically directed biopsy. In addition, CMR detection of a focal disease process may identify the area of the left or right ventricle that would be most likely to demonstrate the underlying pathological process.<sup>13,16</sup> Three-dimensional echocardiography may enhance visualization and reduce the reliance on radiographic imaging in the future.<sup>17</sup>

The risks of EMB may be divided into those that are acute and those that are delayed. Immediate risks of biopsy include perforation with pericardial tamponade, ventricular or supraventricular arrhythmias, heart block, pneumothorax, puncture of central arteries, pulmonary embolization, nerve paresis, venous hematoma, damage to the tricuspid valve, and creation of arterial venous fistula

within the heart. The risks of EMB likely vary with the experience of the operator, clinical status of the patient, presence or absence of left bundle-branch block, access site, and possibly biptome. The use of a long sheath that crosses the tricuspid valve may decrease the risk of biptome-induced tricuspid valve trauma. Delayed complications include access site bleeding, damage to the tricuspid valve, pericardial tamponade, and deep venous thrombosis. Most complications are known from case reports, and therefore the precise frequency of these events is not known.

The data on EMB risks are derived from several single-center experiences and registries that have been reported in the literature. Fowles and Mason<sup>18</sup> reported an overall complication rate of <1% in >4000 biopsies performed in transplantation and cardiomyopathy patients, including 4 with tamponade (0.14%), 3 pneumothorax, 3 atrial fibrillation, 1 ventricular arrhythmia, and 3 focal neurological complications.<sup>18</sup> Olsen, in an unpublished series referenced by Fowles and Mason,<sup>18</sup> reported an overall complication rate of 1.55% in 3097 cardiomyopathy patients biopsied in Europe. Sekiguchi and Take<sup>19</sup> reported a 1.17% complication rate in a worldwide questionnaire of 6739 patients, including perforation in 28 patients (0.42%) and death in 2 patients (0.03%). Deckers *et al.*<sup>20</sup> prospectively recorded complications from 546 consecutive right heart biopsy procedures in patients with new-onset unexplained cardiomyopathy. These are the most reliable data in the literature;<sup>20</sup> the complication rates of sheath insertion and biopsy procedure were reported as 2.7% and 3.3%, as noted in *Table 1*.

The death rate associated with EMB is a result of perforation with pericardial tamponade.<sup>20</sup> Patients with increased right ventricular systolic pressures, bleeding diathesis, recent receipt of heparin, or right ventricular enlargement seem to be at higher risk. Echocardiography is used to confirm myocardial perforation and should be done in any patient in whom the operator believes perforation may have occurred, even without cardiovascular collapse, before central venous access is removed or the patient leaves the catheterization laboratory. Immediate pericardiocentesis and the capability to surgically evacuate the pericardial space should be available at centers that perform EMB.

Careful attention to technique can minimize procedural risks. The risk of pneumothorax can be minimized by taking a relatively high internal jugular approach and avoiding the immediate supra-clavicular location. Patients with preexistent left bundle-branch block may develop complete

heart block when any catheter is placed into the right ventricle and presses against the intraventricular septum.<sup>20</sup> If this occurs, the biptome and/or sheath must be removed, and the patient may require temporary ventricular pacing. Rarely, the heart block may be permanent. Lidocaine in the jugular venous and carotid sheath may result in Horner syndrome, vocal paresis, and, infrequently, weakness of the diaphragm. These complications last only for the duration of the lidocaine effect, unless permanent damage has been done by trauma from the needle itself.

The risks of EMB depend on the clinical state of the patient, the experience of the operator, and the availability of expertise in cardiac pathology. If a patient with an indication for EMB presents at a medical center where expertise in EMB and cardiac pathology is unavailable, transfer of the patient to a medical center with such experience should be seriously considered. Additionally, patients with cardiogenic shock or unstable ventricular arrhythmias may require the care of specialists in medical and surgical management of heart failure, including ventricular assist device placement and potentially heart transplantation.

## Analysis of EMB tissue

### EMB processing

Samples should be obtained from >1 region of the right ventricular septum. The number of samples obtained should range from 5 to 10, depending on the studies to be performed, and each sample should be 1 to 2 mm<sup>3</sup> in size. The sample must be handled carefully to minimize artifacts and transferred from the biptome to fixative (10% neutral buffered formalin) by use of a sterile needle and not with forceps.<sup>21,22</sup> The fixative should be at room temperature to prevent contraction band artifacts.<sup>23</sup>

The clinical reason for the biopsy determines how many samples are removed and how they are fixed. In general, at least 4 to 5 samples are submitted for light microscopic examination, but more may be submitted for transmission electron microscopy if the clinical question is anthracycline cardiotoxicity.<sup>22,24,25</sup> Transmission electron microscopy may also be helpful for the assessment of suspected infiltrative disorders such as amyloidosis, glycogen storage diseases, lysosomal storage diseases, and occasionally viral myocarditis. For transmission electron microscopy, pieces are fixed in 4% glutaraldehyde at room temperature at the time of EMB.<sup>22</sup> One or more pieces may be frozen for molecular studies, immunofluorescence, or immunohistochemistry that may be required for suspected myocarditis, storage diseases, tumor typing, amyloid classification, or viral genome analysis.<sup>26</sup> Pieces of myocardium can be snap-frozen in OCT-embedding medium and stored at -80°F for immunohistochemical or liquid nitrogen molecular studies. Flash-freezing is suitable for culture, polymerase chain reaction (PCR), or reverse transcriptase PCR (rtPCR) for the identification of viruses, but flash-freezing is not ideal for standard histological preparation because of ice crystal artifacts and cell culture.

### Light microscopic examination and stains

For routine light microscopy examination, EMB tissue is embedded in paraffin, and serial sections are obtained and sequentially numbered.<sup>23</sup> For suspected myocarditis, many laboratories will stain every third piece for hematoxylin

**Table 1** Risks associated with endomyocardial biopsy in 546 procedures

Overall 33 complications (6%)
Sheath insertion 15 (2.7%)
12 (2.0%) arterial puncture during local anesthesia
2 (0.4%) vasovagal reaction
1 (0.2%) prolonged venous oozing after sheath removal
Biopsy procedure 18 (3.3%)
6 (1.1%) arrhythmia
5 (1.0%) conduction abnormalities
4 (0.7%) possible perforation (pain)
3 (0.5%) definite perforation (pericardial fluid)
2 of 3 patients with definite perforation died

Data derived from Deckers *et al.*<sup>20</sup>

and eosin and the middle 2 pieces for Movat or elastic trichrome stain to visualize collagen and elastic tissue. Many laboratories also routinely stain 1 slide for iron on men and all postmenopausal women, regardless of the indication for EMB.<sup>23</sup> Congo red staining may be performed on 10- to 15- $\mu$ m sections to rule out amyloidosis. The remaining slides are usually preserved for immunohistochemistry.

### Molecular biological detection of viral genomes

Recent advances in quantitative (qPCR) and qualitative (nested PCR) molecular techniques can detect fewer than 10 gene copies of viral pathogens in the myocardium. These highly sensitive techniques provide both challenges and opportunities. The clinical impact on prognosis and treatment largely depends on establishing a standardized set of diagnostic methods. PCR analysis for viral genomes can yield false results if the sample is not rapidly and properly transported from the catheterization laboratory to the laboratory bench. To prevent sample degradation and contamination, the use of pathogen-free biopsy devices and storage vials is required. New fixatives such as RNAlater (Ambion, Austin, Tex) allow PCR and rtPCR to be performed on samples transported on dry ice at room temperature without loss of sensitivity compared with frozen tissue that is transported on ice.

Over the past 2 decades, the use of nested PCR has substantially increased the information about possible cardiotropic viruses in patients with acquired heart disease. Multiple studies of patients with myocarditis or dilated cardiomyopathy (DCM) reported a wide range of viruses, including enteroviruses, adenoviruses, parvovirus B19, cytomegalovirus, influenza and respiratory syncytial virus, herpes simplex virus, Epstein-Barr virus, human herpesvirus 6, HIV, and hepatitis C.<sup>27–36</sup> In a comprehensive study by Bowles *et al.*<sup>31</sup> nested PCR amplified a viral product in 40% of 773 samples primarily from patients <18 years of age with myocarditis ( $n = 624$ ) or DCM ( $n = 149$ ). In this study, adenovirus and enterovirus genomes were the most frequent.<sup>31</sup> In adults with DCM or unexplained global or regional left ventricular dysfunction, enterovirus, parvovirus B19, human herpes virus 6, or multiple genomes were frequently detected in EMB of consecutively analyzed patients.<sup>34</sup>

Specialized virological laboratories also use real-time PCR, a more quantitative approach, to estimate viral loads in the majority of cardiotropic viruses. Virus loads have been reported to be between 50 and 500 000 copies/ $\mu$ g in parvovirus B19-positive patients.<sup>37</sup> Unfortunately, the clinical application of real-time PCR is also hampered by sampling error in focal disease and the frequent late timing of EMB after disease onset. Indeed, no published data exist on real-time PCR sampling error or associations of viral loads with clinical outcomes.

Therefore, a limitation for the interpretation of viral genome data remains uncertain sensitivity. Because the number of pieces needed to attain a clinically acceptable sensitivity for cardiotropic viruses is not known, only a positive PCR result is diagnostic, whereas a negative PCR does not exclude viral disease. Because of uncertainties in the methods and interpretation at centers not experienced in these techniques, the Writing Group consensus is that routine testing for viral genomes in EMB specimens is not recommended at this time outside of centers with extensive experience in viral genome analysis.

### When should EMB be performed?

Most publications on the use of EMB are only accessible through multiple literature searches by specific pathological diseases, such as lymphocytic myocarditis or giant cell myocarditis (GCM). The Writing Group recognized that a major obstacle to the clinical use of these data is that decisions to proceed with EMB are made on the basis of clinical presentations, not of pathological diagnoses, which are known only after the procedure. To create a set of clinically useful recommendations, the writing group members extracted and synthesized the presenting scenarios from pathology-focused publications in which EMB was used to obtain tissue. The novel result of this effort is a set of distinct clinical scenarios from which a practical decision to proceed with EMB can be made.

One broad conclusion of the committee members is that EMB is not commonly indicated in the evaluation of heart disease. In this regard, the results presented in this Scientific Statement are in agreement with the recommendations for EMB from the current AHA/ACC guideline on the Diagnosis and Management of Chronic Heart Failure in the Adult,<sup>38</sup> the Heart Failure Society of America Heart Failure Practice Guideline,<sup>39</sup> and the ESC Heart Failure guidelines.<sup>40</sup> However, there are specific clinical circumstances in which EMB results may meaningfully estimate prognosis or guide treatment. The present Scientific Statement also explores the indications for EMB besides unexplained cardiomyopathy. Because no randomized, controlled treatment data exist on the utility of biopsy, the recommendations of this writing group are based on case-control series and expert opinion, which are summarized in *Table 2*.

The definitions of key terms relevant to the clinical scenarios that follow are provided to clarify the interpretation of the committee's recommendations. Unexplained heart failure refers to a clinical setting where appropriate tests to exclude common forms of cardiomyopathy have been performed and fail to reveal the diagnosis. These tests usually include an ECG, chest radiograph, and echocardiography to identify valvular, congenital, or pericardial causes for heart failure and coronary angiography for the evaluation of coronary artery disease. Other tests may include CT or magnetic resonance imaging, depending on the clinical setting. Throughout this document, "ventricular arrhythmia" refers to ventricular fibrillation or sustained and non-sustained ventricular tachycardia usually associated with hemodynamic compromise.

#### Clinical scenario 1

**EMB should be performed in the setting of unexplained, new-onset heart failure of < 2 weeks' duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise. Class of Recommendation I, Level of Evidence B.**

Adult and pediatric patients who present with the sudden onset of severe left ventricular failure within 2 weeks of a distinct viral illness and who have typical lymphocytic myocarditis on EMB have an excellent prognosis.<sup>41,42</sup> These patients often are in cardiogenic shock and require intravenous inotropic agents or mechanical assistance for circulatory support. The left ventricle is often thick but not dilated, and the ejection fraction (EF) is markedly depressed.<sup>43</sup> Patients of this type who have lymphocytic myocarditis on EMB are uncommon and poorly represented

**Table 2** The role of endomyocardial biopsy in 14 clinical scenarios

Scenario number	Clinical scenario	Class of recommendation (I, IIa, IIb, III)	Level of evidence (A, B, C)
1	New-onset heart failure of < 2 weeks' duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I	B
2	New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	I	B
3	Heart failure of > 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks	IIa	C
4	Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa	C
5	Heart failure associated with suspected anthracycline cardiomyopathy	IIa	C
6	Heart failure associated with unexplained restrictive cardiomyopathy	IIa	C
7	Suspected cardiac tumors	IIa	C
8	Unexplained cardiomyopathy in children	IIa	C
9	New-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	B
10	Heart failure of > 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks	IIb	C
11	Heart failure associated with unexplained HCM	IIb	C
12	Suspected ARVD/C	IIb	C
13	Unexplained ventricular arrhythmias	IIb	C
14	Unexplained atrial fibrillation	III	C

in the randomized trials of acute myocarditis and cardiomyopathy.<sup>44,45</sup> Therefore, there are too few data on immunosuppressive treatment of fulminant myocarditis in the adult population to assess the efficacy or safety of intravenous immunoglobulin or corticosteroids in this disorder. However, if other causes of heart failure (such as coronary artery disease) are excluded, EMB can provide unique prognostic information and exclude clinically more aggressive disorders.

GCM and necrotizing eosinophilic myocarditis may present with a fulminant clinical course, but unlike fulminant lymphocytic myocarditis, both disorders have a poor prognosis.<sup>46</sup> Necrotizing eosinophilic myocarditis is a rare condition known only from small case series and case reports. The prognosis is poor, with most cases diagnosed at autopsy.<sup>47</sup> This form of eosinophilic heart disease is characterized by an acute onset and rapid progression of hemodynamic compromise. Histologically, necrotizing eosinophilic myocarditis may be identified by a diffuse inflammatory infiltrate with predominant eosinophils associated with extensive myocyte necrosis.<sup>48</sup> Necrotizing eosinophilic myocarditis differs from typical hypersensitivity myocarditis (HSM) in that the lesions are diffuse rather than perivascular and interstitial, and myocyte necrosis is prominent. A histological diagnosis on EMB alters prognosis and would lead to immunosuppressive treatment.

Therapy with combinations of immunosuppressive agents has been associated with improved outcome in GCM and necrotizing eosinophilic myocarditis.<sup>46,49</sup> The sensitivity of EMB for lymphocytic myocarditis is variable and depends on the duration of illness. In subjects with symptom duration of <4 weeks, up to 89% may have lymphocytic myocarditis,<sup>50</sup> but generally the yield is lower, between 10% and 35% depending on the "gold standard" used.<sup>1,51</sup> In contrast, the

sensitivity of EMB for GCM is 80% to 85% in subjects who subsequently die or undergo heart transplantation.<sup>52</sup> In the setting of anticipated mechanical circulatory device support, a pathological diagnosis of GCM may lead to use of a biventricular device because of the likelihood of progressive right ventricular failure. Thus, EMB may provide unique and clinically meaningful information and should be performed in the setting of unexplained, new-onset heart failure of <2 weeks' duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise.

## Clinical Scenario 2

**EMB should be performed in the setting of unexplained new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular (AV) heart block, or failure to respond to usual care within 1 to 2 weeks. Class of Recommendation I, Level of Evidence B.**

Although most cases of acute DCM are relatively mild and resolve with few short-term sequelae, certain signs and symptoms predict GCM, a disorder with a mean transplantation-free survival duration of only 5.5 months.<sup>46</sup> GCM is associated with a variety of autoimmune disorders, thymoma,<sup>53</sup> and drug hypersensitivity.<sup>54</sup> At presentation, ventricular tachycardia is present in 15% of cases, complete heart block in 5%, and an acute coronary syndrome in 6%—rates higher than are typically seen in noninflammatory DCM. In follow-up, 29% of GCM patients developed ventricular tachycardia and 15% developed AV block (8% complete).<sup>55</sup> Thus, clinical clues to suggest GCM and prompt an EMB include association with other autoimmune disorders or thymoma, failure to respond

to usual care, and the presence of complete heart block or ventricular tachycardia.

Patients with acute heart failure due to GCM respond well to heart transplantation. Alternatively, treatment with combination immunosuppression may improve transplantation-free survival duration compared with patients with GCM not receiving immunosuppressive treatment. Patients treated without immunosuppressive therapy had a median transplantation-free survival duration of 3.0 months, compared with a 12.3-month ( $P = 0.003$ ) median transplantation-free survival duration for patients treated with cyclosporine-based immunosuppression. Therefore, a diagnosis of GCM will affect prognosis and treatment. A comparison of survival between patients in the multicenter Giant Cell Myocarditis Registry and those from the Myocarditis Treatment Trial (lymphocytic myocarditis) showed that patients with GCM had a significantly poorer prognosis. At 4 years, only 11% of patients with GCM were alive without transplantation, compared with 44% of patients with lymphocytic myocarditis.

On the basis of these reports, the Writing Group recommends that EMB be performed in the setting of unexplained, new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree AV heart block, or failure to respond to usual care within 1 to 2 weeks.

### Clinical scenario 3

**EMB is reasonable in the clinical setting of unexplained heart failure of >3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree AV heart block, or failure to respond to usual care within 1 to 2 weeks. Class of Recommendation IIa, Level of Evidence C.**

Patients who present with heart failure of >3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks are at risk for cardiac sarcoidosis or idiopathic granulomatous myocarditis. Cardiac sarcoidosis is present in  $\approx 25\%$  of patients with systemic sarcoidosis,<sup>56</sup> but symptoms referable to cardiac sarcoidosis occur in only 5% of sarcoid patients,<sup>55,57</sup> and up to 50% of patients with granulomatous inflammation in the heart have no evidence of extracardiac disease. Patients with cardiac sarcoidosis sometimes may be distinguished from those with DCM by a high rate of heart block (8% to 67%) and ventricular arrhythmias (29%).<sup>58-61</sup> The rates of ventricular tachycardia and heart block are therefore similar in cardiac sarcoidosis and GCM, but cardiac sarcoidosis generally has a more chronic course.

Histologically, sarcoidosis consists of noncaseating granulomas with fibrosis, few eosinophils, and little myocyte necrosis.<sup>62</sup> In a study of 26 patients in whom cardiac sarcoidosis was strongly suspected on the basis of clinical diagnostic criteria for sarcoidosis, ECG abnormalities, or noninvasive imaging,<sup>63</sup> noncaseating granulomata were found in only 19.2% of the patients, which confirmed earlier reports that the sensitivity of EMB for sarcoidosis is  $\approx 20\%$  to 30%.<sup>64</sup> Thus, the heterogeneous myocardial distribution of sarcoid heart disease may lead to sampling error and decrease the diagnostic rate of the EMB. In patients with biopsy-proven pulmonary sarcoid, CMR has been used to infer cardiac involvement and localize disease activity.<sup>65</sup>

Even though the diagnostic rate of the EMB in cardiac sarcoidosis is low, a histological distinction between cardiac sarcoidosis and GCM (both of which have giant cells) is important for therapeutic decisions and prognosis. The rate of transplantation-free survival at 1 year is significantly worse in patients diagnosed by EMB with idiopathic GCM than in patients with cardiac sarcoidosis (21.9% versus 69.8%;  $P < 0.0001$ ).<sup>61</sup> Reports differ as to whether survival rate in cardiac sarcoidosis is similar to or worse than in DCM.<sup>1,58,66</sup>

Sarcoidosis may respond to treatment with corticosteroids. Rate of survival was better in those who received corticosteroids than in those who received usual care (64% versus 40%;  $P = 0.048$ ) in one retrospective study.<sup>67</sup> Small case series and case reports also suggest that corticosteroids may improve clinical status and ventricular function, particularly if used early in the course of disease, but their benefit on ventricular arrhythmias is less certain.<sup>64,68,69</sup> Implantable cardiac defibrillators may be effective in treating arrhythmias in patients with ventricular tachycardia related to sarcoidosis.<sup>70,71</sup> After extensive fibrosis of the left ventricle, steroid use is probably of little benefit. Therefore, EMB is reasonable in the clinical setting of unexplained heart failure of >3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree AV heart block, or failure to respond to usual care within 1 to 2 weeks.

### Clinical scenario 4

**EMB is reasonable in the setting of unexplained heart failure associated with a DCM of any duration that is associated with suspected allergic reaction in addition to eosinophilia. Class of Recommendation IIa, Level of Evidence C.**

HSM is an uncommon disorder with a wide range of presentations, including sudden death, rapidly progressive heart failure, or more chronic DCM. Clinical clues that are reported in a minority of cases include rash, fever, and peripheral eosinophilia. A temporal relation with recently initiated medications or the use of multiple medications is usually present.<sup>72</sup> The ECG is often abnormal, with nonspecific ST-segment changes or infarct patterns similar to other forms of acute myocarditis. The prevalence of clinically undetected HSM in explanted hearts ranges from 2.4% to 7%<sup>73</sup> and has been associated with dobutamine.<sup>74</sup>

Early suspicion and recognition of HSM may lead to withdrawal of offending medications and administration of high-dose corticosteroids. The hallmark histological findings of HSM include an interstitial infiltrate with prominent eosinophils with little myocyte necrosis; however, GCM, granulomatous myocarditis, or necrotizing eosinophilic myocarditis may also be a manifestation of drug hypersensitivity<sup>54</sup> and may be distinguished from common forms of HSM only by EMB.

Eosinophilic myocarditis associated with the hypereosinophilic syndrome is a form of eosinophilic myocarditis that typically evolves over weeks to months. The presentation is usually biventricular heart failure, although arrhythmias may lead to sudden death. Usually hypereosinophilia precedes or coincides with the onset of cardiac symptoms, but the eosinophilia may be delayed.<sup>75</sup> Eosinophilic myocarditis may also occur in the setting of malignancy or parasite infection and early in the course of endocardial fibrosis. Because EMB may distinguish HSM from GCM or necrotizing eosinophilic myocarditis, EMB is reasonable in the setting of unexplained

heart failure associated with a DCM of any duration associated with suspected allergic reaction in addition to eosinophilia.

### Clinical scenario 5

**EMB is reasonable in the setting of unexplained heart failure associated with suspected anthracycline cardiomyopathy. Class of Recommendation IIa, Level of Evidence C.**

Certain chemotherapeutic agents, particularly anthracyclines, are known to be cardiotoxic, particularly at higher cumulative doses. Although cardiotoxicity may be monitored by several modalities, including echocardiographic or radionuclide angiography assessment of EF, fractional shortening, or parameters of diastolic dysfunction, these modalities are generally regarded as capable of detecting more advanced stages of cardiotoxicity rather than earlier degrees of cardiotoxicity. Nevertheless, these techniques are noninvasive and thus widely used in routine clinical practice. EMB, though an invasive procedure, is considered to be the most sensitive and specific means of evaluating cardiotoxicity.

Examination of biopsy specimens in anthracycline-induced cardiomyopathy with electron microscopy demonstrates characteristic changes, including extensive depletion of myofibrillary bundles, myofibrillar lysis, distortion and disruption of the Z-lines, mitochondrial disruption, and intramyocyte vacuolization.<sup>76</sup> A grading system is used to score toxicity on the basis of the percentage of biopsy specimen cells that demonstrate associated toxicity, with a score of 1 indicating <5% biopsy specimen cell involvement and 3 representing >35% involvement.<sup>76,77</sup>

Early study of the procedure demonstrated that in patients with risk factors, the use of EMB, along with hemodynamic data, reduced the rate of doxorubin-induced heart failure when compared with monitoring without invasive studies.<sup>78</sup> A good correlation was found between cumulative adriamycin dose and EMB grade (although the correlation between changes in biopsy grade and EF was poor).<sup>79</sup> In one series, patients with a biopsy grade  $\geq 1.5$  had a >20% chance of cardiac failure with continued therapy.<sup>80</sup> With its ability to detect earlier stages of cardiac toxicity, as well as its sensitivity and specificity, EMB has been used in studies of newer chemotherapeutic agents and regimens.<sup>81–84</sup> The threshold to perform biopsy may also be influenced by the prior use of concomitant therapies known to potentiate anthracycline-induced cardiotoxicity, including radiation, herceptin, and cyclophosphamide.

Given its invasive nature, EMB in patients treated with chemotherapeutic agents may be best suited for situations in which there is question as to the cause of cardiac dysfunction,<sup>76</sup> as well as in select cases in which ultimate administration of greater than the usual upper limit of an agent is believed to be desirable, and in clinical studies of chemotherapeutic-related toxicity of newer agents and regimens.<sup>85,86</sup>

### Clinical scenario 6

**EMB is reasonable in the setting of heart failure associated with unexplained restrictive cardiomyopathy. Class of Recommendation IIa, Level of Evidence C.**

Of the 3 major functional categories of the cardiomyopathies (dilated, hypertrophic, and restrictive), restrictive cardiomyopathy is the least common form in adults and in children. Typically, a patient presents with symptoms of

heart failure and on echocardiogram is found to have normal or decreased volume of both ventricles, biatrial enlargement, normal or minimally increased wall thickness with no valvular abnormality, or normal or near-normal systolic function with impaired diastolic filling, for example, restrictive physiology. As shown in Table 3, this category of cardiomyopathy has been further classified into noninfiltrative processes, infiltrative disorders, and storage diseases that cause characteristic ventricular filling abnormalities, as well as the endomyocardial diseases that have many of the same clinical manifestations.<sup>87</sup> Thus, a variety of pathological processes may result in restrictive cardiomyopathy, although the cause often remains unknown. More importantly, the clinical and hemodynamic features of many types of restrictive cardiomyopathy may mimic those of constrictive pericarditis.<sup>88,89</sup> EMB, in combination with either CT or CMR, can be helpful in differentiating the 2 clinical entities restrictive cardiomyopathy and constrictive pericarditis. EMB may reveal either a specific infiltrative disorder, for example, amyloidosis or hemochromatosis, or myocardial fibrosis and myocyte hypertrophy consistent with idiopathic restrictive cardiomyopathy. However, if pericardial thickening is noted on CT or CMR and the physiology is most consistent with constrictive pericarditis, EMB is often not needed. Because of the frequency of treatable disorders, EMB is reasonable in the setting of heart failure associated with unexplained restrictive cardiomyopathy.

**Table 3** Classification of types of restrictive cardiomyopathy according to cause

Myocardial
Noninfiltrative
Idiopathic cardiomyopathy*
Familial cardiomyopathy
Hypertrophic cardiomyopathy
Scleroderma
Pseudoxanthoma elasticum
Diabetic cardiomyopathy
Infiltrative
Amyloidosis*
Sarcoidosis*
Gaucher's disease
Hurler's disease
Fatty infiltration
Storage diseases
Hemochromatosis
Fabry's disease
Glycogen storage disease
Endomyocardial
Endomyocardial fibrosis*
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic cancers
Radiation*
Toxic effects of anthracycline*
Drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

\*This condition is more likely than the others to be encountered in clinical practice.

Adapted from Kushwaha *et al.*<sup>87</sup> with permission from the Massachusetts Medical Society. Copyright 1997, The Massachusetts Medical Society.

### Clinical scenario 7

**EMB is reasonable in the setting of suspected cardiac tumors, with the exception of typical myxomas. Class of Recommendation IIa, Level of Evidence C.**

There are several dozen case reports and one small series of EMB being used for the tissue diagnosis of cardiac tumors.<sup>14,90-106</sup> Over the past decade, such biopsy usually has been performed with the aid of transesophageal echocardiography. Lesions have been biopsied in all 4 cardiac chambers, though most reports are of right-sided tumors. Biopsy has resulted in diagnoses such as primary cardiac lymphoma, non-Hodgkin's lymphoma, cardiac sarcoma, cervical carcinoma, melanoma, hepatocellular carcinoma, and pulmonary microcytoma; lymphoma is the most commonly reported tumor. Most tumors were suspected, although several have been serendipitously discovered during biopsy for other indications. The actual yield of EMB for suspected cardiac tumor cannot be defined because the number of non-diagnostic and unpublished procedures could never be determined. Similarly, the complication rate of such procedures cannot be definitively determined, although none of the published reports of EMB for suspected tumor note any major complications. Because right heart myxomas can embolize to the lungs with manipulation, EMB is not usually warranted if the appearance is typical on noninvasive imaging.

Therefore, EMB for suspected cardiac tumor seems a reasonable procedure if (1) the diagnosis cannot be established by noninvasive modalities (such as cardiac CMR) or less invasive (noncardiac) biopsy; (2) tissue diagnosis can be expected to influence the course of therapy; (3) the chances of successful biopsy are believed to be reasonably high; and (4) the procedure is performed by an experienced operator. Guidance with transesophageal echocardiography or CMR is advised when possible.

### Clinical scenario 8

**EMB is reasonable in the setting of unexplained cardiomyopathy in children. Class of Recommendation IIa, Level of Evidence C.**

As in adults, the major indications for EMB in children include fulminant or acute unexplained heart failure, cardiac transplant surveillance or rejection evaluation, unexplained arrhythmias, and idiopathic forms of DCM. Rarely, patients with other forms of cardiomyopathy, including arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), restrictive cardiomyopathy, and hypertrophic cardiomyopathy (HCM), undergo EMB. In nearly all instances, the biopsies are performed in the right ventricle under sedation or anesthesia.<sup>107</sup> The reported experience with EMB in children consists of case reports and case series, and therefore the recommendations of this Writing Group are based on expert opinion.

Most cases of myocarditis in children are viral induced, have acute onset, and present with heart failure, cardiovascular collapse, or unexplained arrhythmias (usually ventricular tachycardia)<sup>107,108</sup> or conduction disease (typically AV block). The histopathologic picture is similar to that seen in adults, although it appears to be virus specific. For instance, enteroviruses such as coxsackievirus are consistently associated with classic frank myocarditis by histology, whereas adenovirus is most commonly associated with histological features of borderline myocarditis. Parvovirus,

Epstein-Barr virus, and cytomegalovirus appear to have variable histological features.<sup>31,109</sup>

Outcomes of young children (<1 year of age) with myocarditis appear to be worse than those of older children and also appear to be associated with viral pathogenesis, with adenovirus having the worst prognosis.<sup>31</sup> However, the underlying viruses have changed over the decades, with coxsackievirus common in the 1980s through 1990s, followed by a predominance of adenovirus in the 1990s, and now replaced by parvovirus B19. Similar data have been noted in children after transplantation. Shirali *et al.*<sup>110</sup> demonstrated that children with PCR evidence of adenovirus in EMB samples have a 5-year survival rate of 66%, whereas PCR-negative patients had a 5-year survival rate of 95%. The present Writing Group's assessment is that EMB is reasonable in the setting of unexplained cardiomyopathy in children (Class of Recommendation IIa, Level of Evidence C).

### Clinical scenario 9

**EMB may be considered in the setting of unexplained, new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks. Class of Recommendation IIb, Level of Evidence B.**

The utility of EMB in patients with DCM of 2 weeks' to 3 months' duration is less certain than in patients with <2 weeks of symptoms because most patients with uncomplicated acute idiopathic dilated cardiomyopathy improve with standard heart failure care. Furthermore, several studies have demonstrated a wide variation in the incidence in which the pathological diagnosis of lymphocytic myocarditis is made, ranging from 0% to 63%.<sup>111</sup> This can be attributed to variation in the patient populations studied, sampling error, and variability in pathological interpretation. In cases in which EMB is positive, lymphocytic myocarditis is the most frequent form of myocarditis seen. Studies with a high incidence rate of lymphocytic myocarditis found on biopsy usually involved patients with acute heart failure with symptom onset within 1 month,<sup>50</sup> rather than patients who had had symptoms for months to years.

Lack of a consensus definition for diagnosing lymphocytic myocarditis on EMB also contributed to the variation. Formal criteria, called the Dallas criteria, were established in 1986<sup>112</sup> and were used in the National Heart, Lung, and Blood Institute-sponsored Myocarditis Treatment Trial.<sup>44</sup> The Dallas criteria have been questioned as the gold standard for diagnosis of myocarditis because of sampling error, inter-observer variability in histopathologic interpretation, and lack of correlation between Dallas criteria myocarditis and demonstration of viral genomes in heart tissue.<sup>113</sup>

Prognosis varies with results of EMB because the risk of death or heart transplantation in lymphocytic myocarditis with 2 weeks or more of symptoms and lack of a distinct viral prodrome is greater than in fulminant lymphocytic myocarditis described in clinical scenario 1; however, the presence of lymphocytic myocarditis on EMB in this clinical setting rarely affects treatment. For example, in the Myocarditis Treatment Trial, 111 patients with active or borderline myocarditis on EMB and left ventricular EF of <45% were randomized to conventional therapy or a 24-week



immunosuppressive regimen consisting of either prednisone and azathioprine or prednisone and cyclosporine.<sup>44</sup> The average symptom duration before treatment was 4 weeks, and the primary end point was the change in EF after 28 weeks. The average EF and the median transplantation-free survival duration were similar in the immunosuppression and conventional therapy groups. The risk of death or transplantation was 56% at 4 years. Similarly, in the Immunoglobulin for Myocarditis and Acute Cardiomyopathy (IMAC-1) trial of intravenous immunoglobulin for acute nonischemic DCM, at 2 years the risk of death or transplantation was 12%. Sixteen percent of patients in the IMAC-1 study had borderline or active myocarditis.<sup>45</sup> Grogan *et al.*<sup>114</sup> compared the prognosis of patients with acute DCM with and without myocarditis and found that the survival rate in patients with Dallas criteria myocarditis was the same as in those with no inflammation. From these 3 studies, subjects with acute DCM who also have myocarditis as defined by the Dallas criteria do not seem to respond to immunosuppressive therapies, including intravenous immunoglobulin. Therefore, the information gained from the Dallas criteria does not alter prognosis or therapy in most patients. On the basis of these reports, the Writing Group does not recommend performing EMB for the routine evaluation of new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks. Immunoperoxidase stains, including novel immune markers such as human leukocyte antigen (HLA)-ABC and HLA-DR, may affect prognosis and guide therapy in the future, but these are not in routine clinical use at the present time.<sup>113,115-117</sup>

### Clinical scenario 10

**EMB may be considered in the setting of unexplained heart failure of >3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks. Class of Recommendation IIb, Level of Evidence C.**

The role of EMB in chronic, symptomatic DCM has been the focus of recent research articles, particularly in viral-associated cardiomyopathy. Some patients who have symptomatic heart failure and DCM after 6 months of optimal therapy may benefit from immunomodulation or antiviral therapy. Two recent trials examined patients with DCM, symptom duration of >6 months, and cardiomyocyte HLA-ABC and HLA-DR antigen expression on EMB. Treatment with atorvastatin<sup>117</sup> or azathioprine and prednisone<sup>115</sup> resulted in improved EF. In both trials, the test used to classify these patients as having persistent immune activation was an immunoperoxidase stain for HLA-ABC or HLA-DR, a more sensitive marker of cardiac inflammation than lymphocyte infiltration.<sup>118</sup> If these data are confirmed in a larger trial with clinically meaningful end points, EMB may have a greater role in the evaluation of chronic DCM.<sup>119</sup>

Another group of patients who may present with chronic DCM are individuals with hereditary or acquired hemochromatosis. Cardiac involvement in hemochromatosis usually can be diagnosed on the basis of history, clinical examination, and echocardiography or CMR demonstrating DCM in the setting of laboratory abnormalities such as elevated

serum iron and HFE gene mutation. In the event that findings are equivocal and the possibility of cardiac hemochromatosis still exists, EMB can be useful for diagnosis and to guide treatment. Iron deposition is seen within the sarcoplasm.<sup>120</sup> Treatment with phlebotomy or iron chelation therapy can reverse the ventricular dysfunction.<sup>121</sup>

On the basis of these reports, the Writing Group recognizes that divergent evidence exists with regard to the utility of EMB in this clinical scenario. The Writing Group recommends that EMB may be considered in the setting of unexplained heart failure of >3 months' duration associated with a dilated left ventricle, without new ventricular arrhythmias, or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (Class of Recommendation IIb, Level of Evidence C).

### Clinical scenario 11

**EMB may be considered in the setting of heart failure associated with unexplained HCM. Class of Recommendation IIb, Level of Evidence C.**

HCM occurs in an autosomal dominant pattern in 1:500 of the general population recognized to have the clinical phenotype,<sup>122</sup> which makes it the most frequently occurring cardiomyopathy. HCM may present as sudden cardiac death in the young and may also cause heart failure at any age. HCM is defined by a hypertrophied, nondilated left ventricle in the absence of other systemic or cardiac disease that might result in left ventricular wall thickening to the magnitude that is seen in HCM, eg, systemic hypertension or aortic stenosis.

The diagnosis is made by echocardiography or magnetic resonance imaging, which shows left ventricular wall thickening, small left ventricular cavity, and sometimes a dynamic outflow obstruction. EMB is not usually needed in the evaluation of HCM but may be considered in those cases in which unexplained wall thickening prompts an effort to exclude infiltrative disorders such as Pompe's or Fabry's diseases and noninvasive tests are inconclusive. Occasional patients being considered for surgical myomectomy may benefit from EMB before surgery to exclude Fabry's disease, which may respond to enzyme replacement therapy.<sup>123</sup>

Senile, transthyretin-associated, and primary (AL) amyloidosis may have cardiac involvement that results in a dilated, restrictive, or hypertrophic pattern of cardiomyopathy.<sup>124</sup> When cardiac amyloidosis is present, low voltage on ECG and left ventricular hypertrophy on echocardiogram strongly support the diagnosis.<sup>125</sup> Prognosis in cardiac amyloidosis is much worse if either histological evidence of myocarditis or elevated serum troponin are present.<sup>125,126</sup> Immunohistochemistry performed on heart tissue can distinguish among types of amyloidosis, which have specific therapies. Often the diagnosis can be established from less invasive procedures, such as fat pad or bone marrow biopsies; however, in patients in whom clinical evaluation is equivocal, EMB can be used to establish the diagnosis and guide treatment.<sup>127</sup>

### Clinical scenario 12

**EMB may be considered in the setting of suspected ARVD/C. Class of Recommendation IIb, Level of Evidence C.**

ARVD/C, an inherited or sporadic form of right and left ventricular cardiomyopathy, is estimated to occur in 1:5000 persons. The disorder involves predominantly the right ventricle, with progressive loss of myocytes that are replaced by fibrofatty tissue, resulting in ventricular dysfunction and tachyarrhythmias, typically monomorphic ventricular tachycardia.<sup>128–130</sup> Noninvasive tests, including echocardiography, right ventricular angiography, cardiac CMR, and cardiac CT imaging, often establishes the diagnosis. In a study of the use of CMR in 40 patients with ARVD/C and 20 normal subjects, the sensitivity of fat infiltration, right ventricular enlargement, and regional right ventricular dysfunction for diagnosing ARVD/C was 84%, 68%, and 78%, and specificity was 79%, 96%, and 94%, respectively.<sup>131</sup>

The use of EMB for ARVD/C has been controversial because of the perceived risk of perforation of the thin-walled right ventricle with fibrofatty replacement, but the few reports of EMB for ARVD/C do not report a high rate of complications.<sup>132,133</sup> Within the pediatric population, this disease occurs nearly exclusively in adolescents and young adults, who have a lower risk than infants. Nonetheless, experts in this field disagree as to the risks of the procedure. The histopathologic findings from EMB may be diagnostic of ARVD/C if performed in the appropriate position in the right ventricle.<sup>134</sup> Diagnosis relies on the finding of fibrofatty replacement of sufficient degree. Bowles and colleagues<sup>135</sup> also demonstrated that some cases are associated with viral genome in the myocardium. A high percentage of biopsy and autopsy studies in patients with ARVD/C have associated inflammatory infiltrates, but the prognostic relevance of these lesions is uncertain. Recognizing that there is a wide spectrum of clinical practice in the use of EMB in the management of suspected ARVD/C and scarce data to inform this practice, the Writing Group recommends that EMB may be considered in the setting of suspected ARVD/C (Class IIb, Level of Evidence C).

### Clinical scenario 13

**EMB may be considered in the setting of unexplained ventricular arrhythmias. Class of Recommendation IIb, Level of Evidence C.**

There is modest published literature on the use of EMB in patients with primary or idiopathic (eg, without known structural heart disease or predisposing disease) arrhythmias and primary conduction abnormalities. Many of these studies were conducted in the 1980s, and most involve only modest numbers of patients (Table 4).<sup>144,157–162</sup>

Most studies reported a high incidence of abnormal findings, although these were usually nonspecific findings; the incidence of histologically diagnosed myocarditis varied widely in these reports, and only rarely were other specific disease entities diagnosed. One authoritative review questioned the “strikingly high” incidence of reported histological myocardial abnormalities in the literature, and the review authors comment that they suspect the true incidence of abnormalities described in these reports to be lower.<sup>136</sup> Notably, biopsy is not believed to be able to detect abnormalities that are present in only the conduction system.<sup>137</sup>

Hosenpud *et al.*<sup>138</sup> reported that in 10 patients with life-threatening arrhythmias in the absence of structural heart disease, EMB demonstrated lymphocytic myocarditis in 2

patients, granulomatous myocarditis in 2 patients, and small-vessel vasculitis in 1 patient. In another series of 14 patients with high-grade ventricular arrhythmias and no structural heart disease, EMB was normal in 6 patients and demonstrated nonspecific abnormalities, predominantly fibrosis, in the other patients. In this series, abnormal biopsy findings did not correlate with induced arrhythmias or prognosis. No specific treatable diagnoses were revealed by biopsy in this series.<sup>139</sup> In a third case series, EMB in 12 patients with serious ventricular arrhythmias and structurally normal hearts demonstrated nonspecific abnormalities in 11 patients and acute lymphocytic myocarditis in 1 patient.<sup>140</sup> Vignola *et al.*<sup>141</sup> reported that in 12 patients with high-grade ventricular arrhythmias and without overt cardiac disease, EMB led to a diagnosis of clinically unsuspected lymphocytic myocarditis in 6 patients. After 6 months of immunosuppressive therapy, ventricular arrhythmia could not be provoked in 5 of the 6 patients.<sup>141</sup> Frustaci and colleagues<sup>142</sup> reported on the results of noninvasive and invasive evaluation, including right and left heart biopsy, of 17 young patients without overt organic heart disease who were resuscitated from sudden cardiac arrest, 9 of whom were subsequently classified as having structurally normal hearts. Six of these 9 patients appear to have been classified with histological evidence of myocarditis. Interestingly, left ventricular biopsy allowed the diagnoses of myocarditis in 3 patients in whom the diagnosis would not have been made by right ventricular biopsy.<sup>142</sup>

EMB results in 11 children with paroxysmal or incessant supraventricular tachycardia, the majority of whom had grossly structurally normal hearts, yielded a high incidence of nonspecific histopathologic abnormalities, including hypertrophy and interstitial fibrosis or disarray. Additionally, it was speculated that the arrhythmia may have led to the myocardial damage, rather than vice versa.<sup>143</sup> Teragaki and coworkers<sup>144</sup> examined the results of EMB in 10 patients with documented AV block without apparent heart disease who also underwent electrophysiological testing. Seven of the 10 patients were found to have evidence of myocardial fibrosis, with either myocyte hypertrophy or disarray. The results of electrophysiological testing did not correlate with the histopathologic findings or severity.<sup>144</sup> In another report, 19 of 32 patients with various forms of supraventricular tachycardia and without other clinical abnormalities were found to have some form of myocardial changes, including 6 with myocarditic changes.<sup>145</sup>

Uemura and colleagues<sup>146</sup> also reported on the results of EMB in 50 patients with second- or third-degree AV block in whom the cause of the heart block was not clear. Patients with known coronary artery disease, DCM, cardiac sarcoidosis, or “obvious” acute myocarditis were excluded from the study. The results in these patients were also compared with the findings from 12 normal hearts. Biopsy specimens in those with AV block revealed more myocyte hypertrophy, greater fibrosis, and higher lymphocyte counts than in biopsy specimens from normal hearts. In addition, specimens from the group with AV block had variable degrees of myocyte disorganization and disarrangement, myocytolysis, and nuclear deformity. Myocarditis was diagnosed in 3 of the 50 patients (6%).<sup>146</sup>

Thus, EMB in patients with primary (idiopathic) rhythm abnormalities can be expected to often yield abnormal but nondiagnostic findings. Although EMB may detect otherwise

**Table 4** Findings in reports of endomyocardial biopsy in patients with primary (idiopathic) arrhythmias and conduction abnormalities

Author	Date of publication	Abnormality	Patients, <i>n</i>	Findings
Strain <i>et al.</i> <sup>157</sup>	1983	Ventricular tachycardia or ventricular fibrillation	18	16 of 18 patients (89%) with abnormal findings Nonspecific myocellular hypertrophy, interstitial and perivascular fibrosis, and vascular sclerosis in 9 of 18 patients, subacute inflammatory myocarditis in 3 of 18 patients, diffuse abnormalities of the intramyocardial arteries in 2 of 18 patients, and changes consistent with ARVD/C in 2 of 18 patients
Vignola <i>et al.</i> <sup>141</sup>	1984	Malignant ventricular arrhythmias	12	'Clinically unsuspected myocarditis' in 6 of 12 cases and 'early cardiomyopathy' in 3 of 12 cases
Sugrue <i>et al.</i> <sup>140</sup>	1984	Ventricular arrhythmias	12	11 of 12 patients with histological abnormalities
Morgera <i>et al.</i> <sup>158</sup>	1985	Ventricular tachycardia	10	1 of 12 patients with acute lymphocytic myocarditis 1 of 6 patients without echocardiographic evidence of ARVD/C or right ventricular cardiomyopathy had evidence of myocarditis
Hosenpud <i>et al.</i> <sup>138</sup>	1986	Life-threatening arrhythmias	12	Various forms of myocarditis in 4 of 12 patients, vasculitis in 1 of 12 patients, and 'cardiomyopathic changes' in 6 of 12 patients
Dunnigan <i>et al.</i> <sup>159</sup>	1987	Ventricular tachycardia	11	Various nonspecific abnormalities in all 11 of 11 patients
Kobayashi <i>et al.</i> <sup>145</sup>	1988	Various supraventricular tachycardias	50	Myocarditis changes in 6 of 50 patients, postmyocarditic changes in 15 of 50 patients, and nonspecific abnormalities in 9 of 50 patients
Nishikawa <i>et al.</i> <sup>160</sup>	1990	Various arrhythmias or AV block	23 (pediatric)	Myocyte hypertrophy, disarrangement of muscle bundles, and/or interstitial fibrosis with or without myocyte degeneration in 7 of 11 atrioventricular block cases, 1 of 6 premature ventricular contraction cases, and 0 of 3 sick sinus syndrome cases
Frustaci <i>et al.</i> <sup>147</sup>	1991	Lone atrial fibrillation	14	'Cardiomyopathic' changes in 3 of 14 patients, active myocarditis in 3 of 14 patients, and 'nonspecific necrosis and/or fibrosis' in 8 of 14 patients
Sekiguchi <i>et al.</i> <sup>161</sup>	1992	Ventricular tachycardia or premature ventricular contractions	43	'Active myocarditis' in 1 patient and 'postmyocarditic' changes in 9 patients
Oakes <i>et al.</i> <sup>139</sup>	1992	Ventricular arrhythmias	14	Fibrosis in 6 of 14 patients and monocytes containing aminosalicic acid-positive vacuoles in 1 of 14 patients
Thongtang <i>et al.</i> <sup>162</sup>	1993	Various dysrhythmias	53	No specific treatable diagnosis present in any biopsy
Frustaci <i>et al.</i> <sup>142</sup>	1994	Young sudden cardiac death survivors	17 (9 of whom had structurally normal hearts)	Myocarditis diagnosed in 18 of 53 patients Histological diagnosis of myocarditis in 6 of 9 patients with macroscopically structurally normal hearts Left ventricular biopsy revealed a diagnosis of myocarditis in 3 of 7 total study patients with normal right ventricular histology
Yonesaka <i>et al.</i> <sup>143</sup>	1996	Children with supraventricular tachycardia	11 (4 of whom had cardiomyopathy)	Frequent nonspecific hypertrophy, degeneration, disarray, and endomyocardial changes Speculated that the supraventricular tachycardia causes the histological changes rather than vice versa
Teragaki <i>et al.</i> <sup>144</sup>	1999	AV block	10	Myocardial fibrosis with hypertrophy and/or disarray in 7 of 10 patients
Uemura <i>et al.</i> <sup>146</sup>	2001	Second- or third-degree AV block	50	Frequent myocyte hypertrophy, lymphocytic infiltration, myocyte disarrangement, myocytolysis, and nuclear deformity
Uemura <i>et al.</i> <sup>148</sup>	2004	Sick sinus syndrome	25	Myocarditis diagnosed in 6% of patients Frequent myocyte hypertrophy, myocyte size variation, myocyte disorganization, myocytolysis, and interstitial large mononuclear cell proliferation

clinically unsuspected myocarditis, the value of this finding in clinical decision making remains controversial. The detection of active myocarditis in a patient with malignant ventricular arrhythmia might theoretically lead to a decision to defer implantation of a defibrillator until the myocarditis has subsided, but such an approach is more theoretical than tested. Eighteen years ago, Mason and O'Connell<sup>136</sup> classified the indication for EMB in unexplained, life-threatening ventricular tachyarrhythmias as "uncertain," and it seems there has been little published literature since to change this classification. Therefore, the Writing Group recommends that EMB may be considered in the setting of unexplained ventricular arrhythmias only in exceptional cases in which the perceived likelihood of meaningful prognostic and therapeutic benefit outweighs the procedural risks.

#### Clinical scenario 14

**EMB should not be performed in the setting of unexplained atrial fibrillation. Class of Recommendation III, Level of Evidence C.**

Frustaci and colleagues<sup>147</sup> reported on 14 patients with lone atrial fibrillation unresponsive to usual antiarrhythmic therapy who underwent extensive evaluation, including EMB. Some degree of histological abnormalities was present in all patients, with 3 patients showing cardiomyopathic changes, 3 other patients showing active myocarditis (lymphocytic in 2 and eosinophilic in 1), and 8 patients showing nonspecific necrosis and/or fibrosis. The addition of steroid therapy to the patients diagnosed with myocarditis reportedly resulted in reversion to sinus rhythm. The other patients continued to have atrial fibrillation.<sup>147</sup>

Uemura and colleagues<sup>148</sup> reported on the results of right ventricular EMB in 25 patients admitted for diagnostic evaluation of "sick sinus syndrome" who did not have underlying cardiac disease such as cardiomyopathy or valvular disease. These results were compared with biopsies from 12 normal autopsied hearts. Compared with normal hearts, biopsies from those with sick sinus syndrome demonstrated a larger mean myocyte transverse diameter, greater myocyte size variation, similar degrees of fibrosis, and similar lymphocyte counts. Histologically abnormal findings such as myocyte

disorganization, interstitial mononuclear cells, and endocardial lesions were only seen in those biopsy specimens from patients with sick sinus syndrome. No mention is made of how these findings might have related to clinical management.<sup>148</sup> On the basis of these reports, the Writing Group recommends that EMB not be performed in the setting of unexplained atrial fibrillation.

#### EMB as a research tool

In addition to its clinical roles, EMB may be used to better understand the cellular and molecular pathophysiology of cardiovascular disease. For example, the development of techniques for quantifying gene expression in small amounts of EMB tissue using PCR<sup>149</sup> led to the finding that recapitulation of the "fetal gene program" that accompanied the development of heart failure could be reversed with normalization of left ventricular function<sup>150</sup> and that changes in gene expression could be correlated with biochemical and physiological changes in the failing heart.<sup>151</sup> In addition, serial measures of gene expression are useful in documenting the relationship between biochemical and phenotypic changes in the failing heart in response to either treatment or disease progression.<sup>152</sup>

More recently, silicon chip-based technology or mRNA expression arrays and protein expression through mass spectroscopy have also been used to assess the biochemistry of the failing heart *in vivo*. Several reviews on microarrays in cardiovascular diseases have been published.<sup>153,154</sup> Various studies have identified differentially expressed genes<sup>155</sup> and clustering gene expression profiles to find functional groupings of genes.<sup>156</sup>

The Writing Group's review of several hundred reports involving the use of EMB in cardiovascular disease also revealed a number of clinically relevant and unanswered questions. The utility of novel histological markers of inflammation to define myocarditis and improve on the standard Dallas criteria has only been explored in preliminary studies. The sensitivity of EMB for viral-associated cardiomyopathy is also a key unanswered question. Notably, the relative risks and diagnostic yield of left versus right ventricular biopsy as well as techniques to improve the safety of EMB have not been investigated.

## Disclosures Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Leslie T. Cooper	Mayo Clinic	None	None	None	None	None	None	None
Kenneth L. Baughman	Brigham and Women's Hospital	NIH <sup>†</sup>	None	None	None	None	None	None
Arthur Feldman	Thomas Jefferson University Hospital	None	None	None	None	None	None	None
Andrea Frustaci	La Sapienza University	None	None	None	None	None	None	None
Mariell Jessup	University of Pennsylvania	None	None	AstraZeneca*; Medtronic*; ACORN*; GlaxoSmithKline*	None	None	ACORN*; Medtronic*; GlaxoSmithKline*; Ventracor*	None
Uwe Kuhl	Charite University	None	None	None	None	None	None	None
Glenn N. Levine	Baylor College of Medicine	None	None	Sanofi-Aventis*; Medicines Company*	None	None	None	None
Jagat Narula	University of California, Irvine	None	None	GlaxoSmithKline <sup>†</sup>	None	None	None	None
Randall C. Starling	Cleveland Clinic Foundation	NIH <sup>†</sup>	Novartis*; Orquis*; Johnson & Johnson*	None	None	None	Acorn Cardiovascular Inc*; Cardiomems*; Myocor*; Medtronic*; World Heart*	None
Jeffrey Towbin	Baylor College of Medicine	None	None	None	None	None	None	None
Renu Virmani	CV Path	None	None	None	None	None	Medtronic <sup>†</sup> ; Guidant <sup>†</sup> ; Abbott Laboratories <sup>†</sup> ; W.L. Gore <sup>†</sup> ; CryoVascular Systems, Inc <sup>†</sup> ; Volcano Therapeutics Inc <sup>†</sup> ; Precient Medical <sup>†</sup> ; Medicon <sup>†</sup> ; Cardiomind, Inc <sup>†</sup> ; Direct Flow <sup>†</sup> ;	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

<sup>†</sup>Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Mazen Abu-Fadel	Ponca City Medical Center	None	None	None	None	None	None	None
Jeffrey Anderson	LDS Hospital	None	None	None	None	None	None	None
Eloisa Arbustini	I.R.C.C.S. Policlinico San Matteo, Pavia, Italy	None	None	None	None	None	None	None
Eric Bates	University of Michigan	None	None	None	None	None	None	None
Fred Bove	Temple University	Penn Dept of Health	None	None	None	None	Insight Telehealth Systems*	None
Rihal Charanjit	Mayo Clinic	None	None	None	None	None	None	None
G. William Dec	Massachusetts General Hospital	None	None	None	None	None	None	None
Jose Diez	Baylor College of Medicine	None	None	None	None	None	Sanofi-Aventis*	None
Mark Eisenberg	McGill University	None	None	None	None	None	None	None
Gerasimos Filippatos	Evangelismos Hospital, Athens, Greece	None	None	None	None	None	None	None
Robert Harrington	Duke University	None	None	None	None	None	None	None
Mark Hlatky	Stanford University	None	None	None	None	None	None	None
Maryl Johnson	University of Wisconsin	None	None	None	None	None	None	None
Jay Mason	Covance Central Diagnostics	None	None	None	None	None	None	None
Walter Paulus	VU University Medical Center, Netherlands	None	None	None	None	None	None	None
Richard Schofield	University of Florida	None	None	AstraZeneca*; AtCor Medical*; Novartis*; Pfizer*; Scios*	None	None	Pfizer	None
Udo Sechtem	Robert-Bosch-Medical Center, Stuttgart, Germany	None	None	None	None	None	None	None
Ajay Shah	King's College London	None	None	None	None	None	None	None
Samuel J. Shubrooks, Jr	Beth Israel Deaconess Medical Center	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

\*Modest.

†Significant.

## References

- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077-1084.
- Weinberg M, Fell EH, Lynfield J. Diagnostic biopsy of the pericardium and myocardium. *AMA Arch Surg*. 1958;76:825-829.
- Bulloch RT, Murphy ML, Pearce MB. Intracardiac needle biopsy of the ventricular septum. *Am J Cardiol*. 1965;16:227-233.
- Sakakibara S, Konno S. Endomyocardial biopsy. *Jpn Heart J*. 1962;3:537-543.
- Caves PK, Stinson EB, Graham AF, Billingham ME, Grehl TM, Shumway NE. Percutaneous transvenous endomyocardial biopsy. *JAMA*. 1973;225:288-291.
- Richardson PJ. King's endomyocardial biopsies. *Lancet*. 1974;1:660-661.
- Kawai C, Kitaura Y. New endomyocardial biopsy catheter for the left ventricle. *Am J Cardiol*. 1977;40:63-65.
- Anderson JL, Marshall HW. The femoral venous approach to endomyocardial biopsy: comparison with internal jugular and transarterial approaches. *Am J Cardiol*. 1984;53:833-837.
- Denys BG, Uretsky BF, Reddy PS, Ruffner RJ, Sandhu JS, Breishlatt WM. An ultrasound method for safe and rapid central venous access. *N Engl J Med*. 1991;324:566.
- Denys BG, Uretsky BF, Reddy PS. Ultrasound-assisted cannulation of the internal jugular vein: a prospective comparison to the external landmark-guided technique. *Circulation*. 1993;87:1557-1562.
- Brooksby IA, Jenkins BS, Coltart DJ, Webb-Peploe MM, Davies MJ. Left-ventricular endomyocardial biopsy. *Lancet*. 1974;2:1222-1225.
- Rios B, Nihill MR, Mullins CE. Left ventricular endomyocardial biopsy in children with the transeptal long sheath technique. *Cathet Cardiovasc Diagn*. 1984;10:417-423.
- Mahrholdt H, Goedecke C, Wagner A, Meinhardt G, Athanasiadis A, Vogelsberg H, Fritz P, Klingel K, Kandolf R, Sechtem U. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation*. 2004;109:1250-1258.
- Copeland JG, Valdes-Cruz L, Sahn DJ. Endomyocardial biopsy with fluoroscopic and two-dimensional echocardiographic guidance: case report of a patient suspected of having multiple cardiac tumors. *Clin Cardiol*. 1984;7:449-452.
- Miller LW, Labovitz AJ, McBride LA, Pennington DG, Kanter K. Echocardiography-guided endomyocardial biopsy: a 5-year experience. *Circulation*. 1988;78(5 pt 2):III-99-III-102.
- Mavrogeni SI, Markussis V, Kaklamanis L, Tsiapras D, Paraskevidis I, Karavolias G, Karagiorga M, Douskou M, Cokkinos DV, Kremastinos DT. A comparison of magnetic resonance imaging and cardiac biopsy in the evaluation of heart iron overload in patients with beta-thalassemia major. *Eur J Haematol*. 2005;75:241-247.
- Amitai ME, Schnittger I, Popp RL, Chow J, Brown P, Liang DH. Comparison of three-dimensional echocardiography to two-dimensional echocardiography and fluoroscopy for monitoring of endomyocardial biopsy. *Am J Cardiol*. 2007;99:864-866.
- Fowles RE, Mason JW. Endomyocardial biopsy. *Ann Intern Med*. 1982;97:885-894.
- Sekiguchi M, Take M. World survey of catheter biopsy of the heart. In: Sekiguchi M, Olsen EGJ, eds. *Cardiomyopathy: Clinical, Pathological and Theoretical Aspects*. Baltimore, Md: University Park Press; 1980:217-225.
- Deckers JW, Hare JM, Baughman KL. Complications of transvenous right ventricular endomyocardial biopsy in adult patients with cardiomyopathy: a seven-year survey of 546 consecutive diagnostic procedures in a tertiary referral center. *J Am Coll Cardiol*. 1992;19:43-47.
- Veinot JP, Ghadially FN, Walley VM. Light microscopy and ultrastructure of the blood vessel and heart. In: Silver MD, Gotlieb AI, Schoen FJ, eds. *Cardiovascular Pathology*. 3rd ed. New York, NY: Churchill Livingstone; 2001:30-53.
- Virmani R, Burke A, Farb A, Atkinson J. *Cardiovascular Pathology*. 2nd ed. Philadelphia, Pa: Saunders; 2001.
- Cunningham KS, Veinot JP, Butany J. An approach to endomyocardial biopsy interpretation. *J Clin Pathol*. 2006;59:121-129.
- Billingham ME, Mason JW, Bristow MR, Daniels JR. Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer Treat Rep*. 1978;62:865-872.
- Torti FM, Bristow MR, Howes AE, Aston D, Stockdale FE, Carter SK, Kohler M, Brown BW Jr, Billingham ME. Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule: assessment by endomyocardial biopsy. *Ann Intern Med*. 1983;99:745-749.
- Veinot JP. Diagnostic endomyocardial biopsy pathology: general biopsy considerations, and its use for myocarditis and cardiomyopathy: a review. *Can J Cardiol*. 2002;18:55-65.
- Jin O, Sole MJ, Butany JW, Chia WK, McLaughlin PR, Liu P, Liew CC. Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and cardiomyopathy using gene amplification by polymerase chain reaction. *Circulation*. 1990;82:8-16.
- Grasso M, Arbustini E, Silini E, Diegoli M, Percivalle E, Ratti G, Bramero M, Gavazzi A, Vigano M, Milanese G. Search for Coxsackievirus B3 RNA in idiopathic dilated cardiomyopathy using gene amplification by polymerase chain reaction. *Am J Cardiol*. 1992;69:658-664.
- Weiss LM, Movahed LA, Billingham ME, Cleary ML. Detection of Coxsackievirus B3 RNA in myocardial tissues by the polymerase chain reaction. *Am J Pathol*. 1991;138:497-503.
- Muir P, Nicholson F, Jhetam M, Neogi S, Banatvala JE. Rapid diagnosis of enterovirus infection by magnetic bead extraction and polymerase chain reaction detection of enterovirus RNA in clinical specimens. *J Clin Microbiol*. 1993;31:31-38.
- Bowles NE, Ni J, Kearney DL, Pauschinger M, Schultheiss HP, McCarthy R, Hare J, Bricker JT, Bowles KR, Towbin JA. Detection of viruses in myocardial tissues by polymerase chain reaction: evidence of adenovirus as a common cause of myocarditis in children and adults. *J Am Coll Cardiol*. 2003;42:466-472.
- Bowles NE, Bayston TA, Zhang HY, Doyle D, Lane RJ, Cunningham L, Archard LC. Persistence of enterovirus RNA in muscle biopsy samples suggests that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy. *J Med*. 1993;24:145-160.
- Pauschinger M, Bowles NE, Fuentes-Garcia FJ, Pham V, Kuhl U, Schwimmbeck PL, Schultheiss HP, Towbin JA. Detection of adenoviral genome in the myocardium of adult patients with idiopathic left ventricular dysfunction. *Circulation*. 1999;99:1348-1354.
- Kuhl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, Poller W, Kandolf R, Schultheiss HP. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation*. 2005;111:887-893.
- Tschope C, Bock CT, Kasner M, Noutsias M, Westermann D, Schwimmbeck PL, Pauschinger M, Poller WC, Kuhl U, Kandolf R, Schultheiss HP. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. *Circulation*. 2005;111:879-886.
- Matsumori A. Hepatitis C virus infection and cardiomyopathies. *Circ Res*. 2005;96:144-147.
- Klein RM, Jiang H, Niederacher D, Adams O, Du M, Horlitz M, Schley P, Marx R, Lankisch MR, Brehm MU, Strauer BE, Gabbert HE, Scheffold T, Gulker H. Frequency and quantity of the parvovirus B19 genome in endomyocardial biopsies from patients with suspected myocarditis or idiopathic left ventricular dysfunction. *Z Kardiol*. 2004;93:300-309.
- Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure) [published correction appears in *J Am Coll Cardiol*. 2006;47:1503-1505]. *J Am Coll Cardiol*. 2005;46:e1-e82.
- Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail*. 2006;12:10-38.
- Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ; Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:1115-1140.
- McCarthy RE 3rd, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Hare JM, Baughman KL. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med*. 2000;342:690-695.

42. Amabile N, Fraisse A, Bouvenot J, Chetaille P, Ovaert C. Outcome of acute fulminant myocarditis in children. *Heart*. 2006;**92**:1269–1273.
43. Felker GM, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Baughman KL, Hare JM. Echocardiographic findings in fulminant and acute myocarditis. *J Am Coll Cardiol*. 2000;**36**:227–232.
44. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, Moon TE. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;**333**:269–275.
45. McNamara DM, Holubkov R, Starling RC, Dec GW, Loh E, Torre-Amione G, Gass A, Janosko K, Tokarczyk T, Kessler P, Mann DL, Feldman AM. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;**103**:2254–2259.
46. Cooper LT Jr, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis: natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. *N Engl J Med*. 1997;**336**:1860–1866.
47. Herzog CA, Snover DC, Staley NA. Acute necrotizing eosinophilic myocarditis. *Br Heart J*. 1984;**52**:343–348.
48. deMello DE, Liapis H, Jureidini S, Nouri S, Kephart GM, Gleich GJ. Cardiac localization of eosinophil-granule major basic protein in acute necrotizing myocarditis. *N Engl J Med*. 1990;**323**:1542–1545.
49. Cooper LT, Zehr KJ. Biventricular assist device placement and immunosuppression as therapy for necrotizing eosinophilic myocarditis. *Nat Clin Pract Cardiovasc Med*. 2005;**2**:544–548.
50. Dec GW Jr, Palacios IF, Fallon JT, Aretz HT, Mills J, Lee DC, Johnson RA. Active myocarditis in the spectrum of acute dilated cardiomyopathies: clinical features, histologic correlates, and clinical outcome. *N Engl J Med*. 1985;**312**:885–890.
51. Narula J, Khaw BA, Dec GW, Palacios IF, Newell JB, Southern JF, Fallon JT, Strauss HW, Haber E, Yasuda T. Diagnostic accuracy of anti-myosin scintigraphy in suspected myocarditis. *J Nucl Cardiol*. 1996;**3**:371–381.
52. Shields RC, Tazelaar HD, Berry GJ, Cooper LT Jr. The role of right ventricular endomyocardial biopsy for idiopathic giant cell myocarditis. *J Card Fail*. 2002;**8**:74–78.
53. Kilgallen CM, Jackson E, Bankoff M, Salomon RN, Surks HK. A case of giant cell myocarditis and malignant thymoma: a postmortem diagnosis by needle biopsy. *Clin Cardiol*. 1998;**21**:48–51.
54. Daniels PR, Berry GJ, Tazelaar HD, Cooper LT. Giant cell myocarditis as a manifestation of drug hypersensitivity. *Cardiovasc Pathol*. 2000;**9**:287–291.
55. Okura Y, Dec GW, Hare JM, Berry GR, Tazelaar HD, Cooper LT. A multicenter registry comparison of cardiac sarcoidosis and idiopathic giant-cell myocarditis. *Circulation*. 2000;**102**(18 suppl II):II-788. Abstract 3807.
56. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation*. 1978;**58**:1204–1211.
57. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic considerations. *Cardiovasc Drugs Ther*. 1996;**10**:495–510.
58. Yazaki Y, Isobe M, Hiramitsu S, Morimoto S, Hiroe M, Omichi C, Nakano T, Saeki M, Izumi T, Sekiguchi M. Comparison of clinical features and prognosis of cardiac sarcoidosis and idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1998;**82**:537–540.
59. Fleming HA, Bailey SM. Sarcoid heart disease. *J R Coll Physicians Lond*. 1981;**15**:245–246, 249–253.
60. Cooper L, Okura Y, Hare J, Grogan M. Survival in biopsy-proven cardiac sarcoidosis is similar to survival in lymphocytic myocarditis and dilated cardiomyopathy. In: Kimchi A, ed. *Heart Disease: New Trends in Research, Diagnosis, and Treatment: Proceedings of the 2nd International Congress on Heart Disease*. Englewood, NJ: Medimond Medical Publications; 2001:491–496.
61. Okura Y, Dec GW, Hare JM, Kodama M, Berry GJ, Tazelaar HD, Bailey KR, Cooper LT. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *J Am Coll Cardiol*. 2003;**41**:322–329.
62. Litovsky SH, Burke AP, Virmani R. Giant cell myocarditis: an entity distinct from sarcoidosis characterized by multiphasic myocyte destruction by cytotoxic T cells and histiocytic giant cells. *Mod Pathol*. 1996;**9**:1126–1134.
63. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999;**138**(2 pt 1):299–302.
64. Sekiguchi M, Numao Y, Imai M, Furuie T, Mikami R. Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis: concepts through a study employing endomyocardial biopsy, I: sarcoidosis. *Jpn Circ J*. 1980;**44**:249–263.
65. Schulz-Menger J, Wassmuth J, Abdel-Aty H, Siegel I, Franke A, Dietz R, Friedrich MG. Patterns of myocardial inflammation and scarring in sarcoidosis as assessed by cardiovascular magnetic resonance. *Heart*. 2006;**92**:399–400.
66. Ardehali H, Howard DL, Hariri A, Qasim A, Hare JM, Baughman KL, Kasper EK. A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. *Am Heart J*. 2005;**150**:459–463.
67. Takada K, Ina Y, Yamamoto M, Satoh T, Morishita M. Prognosis after pacemaker implantation in cardiac sarcoidosis in Japan: clinical evaluation of corticosteroid therapy. *Sarcoidosis*. 1994;**11**:113–117.
68. Bellhassen B, Pines A, Laniado S. Failure of corticosteroids to prevent induction of ventricular tachycardia in sarcoidosis. *Chest*. 1989;**95**:918–920.
69. Johns CJ, Michele TM. The clinical management of sarcoidosis: a 50-year experience at the Johns Hopkins Hospital. *Medicine (Baltimore)*. 1999;**78**:65–111.
70. Bajaj AK, Kopelman HA, Echt DS. Cardiac sarcoidosis with sudden death: treatment with the automatic implantable cardioverter defibrillator. *Am Heart J*. 1988;**116**(2 pt 1):557–560.
71. Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E, Gomes JA. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. *J Am Coll Cardiol*. 1991;**18**:937–943.
72. Taliercio CP, Olney BA, Lie JT. Myocarditis related to drug hypersensitivity. *Mayo Clin Proc*. 1985;**60**:463–468.
73. Hawkins ET, Levine TB, Goss SJ, Moosvi A, Levine AB. Hypersensitivity myocarditis in the explanted hearts of transplant recipients: reappraisal of pathologic criteria and their clinical implications. *Pathol Annual*. 1995;**30**(pt 1):287–304.
74. Spear GS. Eosinophilic explant carditis with eosinophilia: hypersensitivity to dobutamine infusion. *J Heart Lung Transplant*. 1995;**14**:755–760.
75. Morimoto S, Kato S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, Sugiura A, Miyagishima K, Iwase M, Ito T, Hishida H. Narrowing of the left ventricular cavity associated with transient ventricular wall thickening reduces stroke volume in patients with acute myocarditis. *Circ J*. 2003;**67**:490–494.
76. Meinardi MT, van der Graaf WT, van Veldhuisen DJ, Gietema JA, de Vries EG, Sleijfer DT. Detection of anthracycline-induced cardiotoxicity. *Cancer Treat Rev*. 1999;**25**:237–247.
77. Mason JW. Techniques for right and left ventricular endomyocardial biopsy. *Am J Cardiol*. 1978;**41**:887–892.
78. Bristow MR, Lopez MB, Mason JW, Billingham ME, Winchester MA. Efficacy and cost of cardiac monitoring in patients receiving doxorubicin. *Cancer*. 1982;**50**:32–41.
79. Ewer MS, Ali MK, Mackay B, Wallace S, Valdivieso M, Legha SS, Benjamin RS, Haynie TP. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving adriamycin. *J Clin Oncol*. 1984;**2**:112–117.
80. Mackay B, Ewer MS, Carrasco CH, Benjamin RS. Assessment of anthracycline cardiomyopathy by endomyocardial biopsy. *Ultrastruct Pathol*. 1994;**18**:203–211.
81. Torti FM, Bristow MM, Lum BL, Carter SK, Howes AE, Aston DA, Brown BW Jr, Hannigan JF Jr, Meyers FJ, Mitchell EP *et al*. Cardiotoxicity of epirubicin and doxorubicin: assessment by endomyocardial biopsy. *Cancer Res*. 1986;**46**:3722–3727.
82. Umsawasdi T, Valdivieso M, Booser DJ, Barkley HT Jr, Ewer M, MacKay B, Dhingra HM, Murphy WK, Spitzer G, Chiuten DF *et al*. Weekly doxorubicin versus doxorubicin every 3 weeks in cyclophosphamide, doxorubicin, and cisplatin chemotherapy for non-small cell lung cancer. *Cancer*. 1989;**64**:1995–2000.
83. Valero V, Buzdar AU, Theriault RL, Azarnia N, Fonseca GA, Willey J, Ewer M, Walters RS, Mackay B, Podoloff D, Booser D, Lee LW, Hortobagyi GN. Phase II trial of liposome-encapsulated doxorubicin, cyclophosphamide, and fluorouracil as first-line therapy in patients with metastatic breast cancer. *J Clin Oncol*. 1999;**17**:1425–1434.
84. Hortobagyi GN, Willey J, Rahman Z, Holmes FA, Theriault RL, Buzdar AU. Prospective assessment of cardiac toxicity during a randomized phase II trial of doxorubicin and paclitaxel in metastatic breast cancer. *Semin Oncol* 1997;**24**(5 suppl 17):S17-65–S17-68.
85. Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, Walters B, Shevtsov S, Pesant S, Clubb FJ, Rosenzweig A, Salomon RN, Van



- Etten RA, Alroy J, Durand JB, Force T. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12:908-916.
86. Feldman AM, Lorell BH, Reis SE. Trastuzumab in the treatment of metastatic breast cancer: anticancer therapy versus cardiotoxicity. *Circulation*. 2000;102:272-274.
  87. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med*. 1997;336:267-276.
  88. Asher CR, Klein AL. Diastolic heart failure: restrictive cardiomyopathy, constrictive pericarditis, and cardiac tamponade: clinical and echocardiographic evaluation. *Cardiol Rev*. 2002;10:218-229.
  89. Yazdani K, Maraj S, Amanullah AM. Differentiating constrictive pericarditis from restrictive cardiomyopathy. *Rev Cardiovasc Med*. 2005;6:61-71.
  90. Alter P, Grimm W, Tontsch D, Maisch B. Diagnosis of primary cardiac lymphoma by endomyocardial biopsy. *Am J Med*. 2001;110:593-594.
  91. Iwaki T, Kanaya H, Namura M, Ikeda M, Uno Y, Terashima N, Ohka T, Miura Y, Shimizu M, Mabuchi H. Right ventricular metastasis from a primary cervical carcinoma. *Jpn Circ J*. 2001;65:761-763.
  92. Malouf JF, Thompson RC, Maples WJ, Wolfe JT. Diagnosis of right atrial metastatic melanoma by transesophageal echocardiography-guided transvenous biopsy. *Mayo Clin Proc*. 1996;71:1167-1170.
  93. Flipse TR, Tazelaar HD, Holmes DR Jr. Diagnosis of malignant cardiac disease by endomyocardial biopsy. *Mayo Clin Proc*. 1990;65:1415-1422.
  94. Scott PJ, Ettles DF, Rees MR, Williams GJ. The use of combined transesophageal echocardiography and fluoroscopy in the biopsy of a right atrial mass. *Br J Radiol*. 1990;63:222-224.
  95. Burling F, Devlin G, Heald S. Primary cardiac lymphoma diagnosed with transesophageal echocardiography-guided endomyocardial biopsy. *Circulation*. 2000;101:e179-e181.
  96. Savoia MT, Liguori C, Nahar T, Marboe C, Weinberger J, Di Tullio MR, Homma S. Transesophageal echocardiography-guided transvenous biopsy of a cardiac sarcoma. *J Am Soc Echocardiogr*. 1997;10:752-755.
  97. Hanley PC, Shub C, Seward JB, Wold LE. Intracavitary cardiac melanoma diagnosed by endomyocardial left ventricular biopsy. *Chest*. 1983;84:195-198.
  98. Hausheer FH, Josephson RA, Grochow LB, Weissman D, Brinker JA, Weisman HF. Intracardiac sarcoma diagnosed by left ventricular endomyocardial biopsy. *Chest*. 1987;92:177-179.
  99. Morrone A, Gaglione A, Bortone A, Iliceto S, Caruso G, Calabrese P, Chiddo A. Endomyocardial biopsy diagnosis of a pulmonary microcytoma metastasized to the atrium. *Cardiologia*. 1988;33:419-421. Italian.
  100. Hammoudeh AJ, Chaaban F, Watson RM, Millman A. Transesophageal echocardiography-guided transvenous endomyocardial biopsy used to diagnose primary cardiac angiosarcoma. *Cathet Cardiovasc Diagn*. 1996;37:347-349.
  101. Gosalakal JA, Sugrue DD. Malignant melanoma of the right atrium, antemortem diagnosis by transvenous biopsy. *Br Heart J*. 1989;62:159-160.
  102. Miyashita T, Miyazawa I, Kawaguchi T, Kasai T, Yamaura T, Ito T, Takei M, Kiyosawa K. A case of primary cardiac B cell lymphoma associated with ventricular tachycardia, successfully treated with systemic chemotherapy and radiotherapy: a long-term survival case. *Jpn Circ J*. 2000;64:135-138.
  103. Cooper DL, Sinard JH, Edelson RL, Flynn SD. Cardiogenic shock due to progression of cutaneous T-cell lymphoma. *South Med J*. 1994;87:89-94.
  104. Starr SK, Pugh DM, O'Brien-Ladner A, Stites S, Wilson DB. Right atrial mass biopsy guided by transesophageal echocardiography. *Chest*. 1993;104:969-970.
  105. Chan KL, Veinot J, Leach A, Bedard P, Smith S, Marquis JF. Diagnosis of left atrial sarcoma by transvenous endocardial biopsy. *Can J Cardiol*. 2001;17:206-208.
  106. Medolago G, Virota G, Piti A, Tsepili M, D'Adda F, Rottoli MR, Comotti B, Motta T, Orlandi C, Bertocchi C. Abnormal uptake of technetium-99 m hexakis-2-methoxyisobutylisonitrile in a primary cardiac lymphoma. *Eur J Nucl Med*. 1992;19:222-225.
  107. Towbin J. Cardiomyopathy and heart transplantation in children. *Curr Opin Cardiol*. 2002;17:274-279.
  108. Shmorhun D, Fenrich A, Cecchin F *et al*. Identification of viral causes for ventricular arrhythmia in children using PCR analysis. *Pacing Clin Electrophysiol*. 1996;19:588.
  109. Martin AB, Webber S, Fricker FJ, Jaffe R, Demmler G, Kearney D, Zhang YH, Bodurtha J, Gelb B, Ni J *et al*. Acute myocarditis: rapid diagnosis by PCR in children. *Circulation*. 1994;90:330-339.
  110. Shirali GS, Ni J, Chinnock RE, Johnston JK, Rosenthal GL, Bowles NE, Towbin JA. Association of viral genome with graft loss in children after cardiac transplantation. *N Engl J Med*. 2001;344:1498-1503.
  111. Dec GW. Introduction to clinical myocarditis. In: Cooper LT, ed. *Myocarditis From Bench to Bedside*. Totowa, NJ: Humana Press; 2003:257-281.
  112. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, Olsen EG, Schoen FJ. Myocarditis: a histopathologic definition and classification. *Am J Cardiovasc Pathol*. 1987;1:3-14.
  113. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation*. 2006;113:593-595.
  114. Grogan M, Redfield MM, Bailey KR, Reeder GS, Gersh BJ, Edwards WD, Rodeheffer RJ. Long-term outcome of patients with biopsy-proved myocarditis: comparison with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 1995;26:80-84.
  115. Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, Glanowska G, Wilczewski P, Niklewski T, Zembala M, Polonski L, Rozek MM, Wodniecki J. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. *Circulation*. 2001;104:39-45.
  116. Staudt A, Schaper F, Stangl V, Plagemann A, Bohm M, Merkel K, Wallukat G, Wernecke KD, Stangl K, Baumann G, Felix SB. Immunohistological changes in dilated cardiomyopathy induced by immunoadsorption therapy and subsequent immunoglobulin substitution. *Circulation*. 2001;103:2681-2686.
  117. Wojnicz R, Wilczek K, Nowalany-Kozielska E, Szygula-Jurkiewicz B, Nowak J, Polonski L, Dyrbus K, Badzinski A, Mercik G, Zembala M, Wodniecki J, Rozek MM. Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. *Am J Cardiol*. 2006;97:899-904.
  118. Herskowitz A, Ahmed-Ansari A, Neumann DA, Beschoner WE, Rose NR, Soule LM, Burek CL, Sell KW, Baughman KL. Induction of major histocompatibility complex antigens within the myocardium of patients with active myocarditis: a nonhistologic marker of myocarditis. *J Am Coll Cardiol*. 1990;15:624-632.
  119. Parrillo JE. Inflammatory cardiomyopathy (myocarditis): which patients should be treated with anti-inflammatory therapy? *Circulation*. 2001;104:4-6.
  120. Olson LJ, Edwards WD, McCall JT, Ilstrup DM, Gersh BJ. Cardiac iron deposition in idiopathic hemochromatosis: histologic and analytic assessment of 14 hearts from autopsy. *J Am Coll Cardiol*. 1987;10:1239-1243.
  121. Rahko PS, Salerni R, Uretsky BF. Successful reversal by chelation therapy of congestive cardiomyopathy due to iron overload. *J Am Coll Cardiol*. 1986;8:436-440.
  122. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113:1807-1816.
  123. Frustaci A, Chimenti C, Ricci R, Natale L, Russo MA, Pieroni M, Eng CM, Desnick RJ. Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. *N Engl J Med*. 2001;345:25-32.
  124. Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005;112:2047-2060.
  125. Rahman JE, Helou EF, Gelzer-Bell R, Thompson RE, Kuo C, Rodriguez ER, Hare JM, Baughman KL, Kasper EK. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. *J Am Coll Cardiol*. 2004;43:410-415.
  126. Dispenzieri A, Kyle RA, Gertz MA, Therneau TM, Miller WL, Chandrasekaran K, McConnell JP, Burritt MF, Jaffe AS. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. *Lancet*. 2003;361:1787-1789.
  127. Pellikka PA, Holmes DR Jr, Edwards WD, Nishimura RA, Tajik AJ, Kyle RA. Endomyocardial biopsy in 30 patients with primary amyloidosis and suspected cardiac involvement. *Arch Intern Med*. 1988;148:662-666.
  128. Kies P, Bootsma M, Bax J, Schalijs MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. *Heart Rhythm*. 2006;3:225-234.

129. Basso C, Thiene G. Adipositas cordis, fatty infiltration of the right ventricle, and arrhythmogenic right ventricular cardiomyopathy: just a matter of fat? *Cardiovasc Pathol*. 2005;14:37-41.
130. Hulot JS, Jouven X, Empana JP, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation*. 2004;110:1879-1884.
131. Tandri H, Castillo E, Ferrari VA, Nasir K, Dalal D, Bomma C, Calkins H, Bluemke DA. Magnetic resonance imaging of arrhythmogenic right ventricular dysplasia: sensitivity, specificity, and observer variability of fat detection versus functional analysis of the right ventricle. *J Am Coll Cardiol*. 2006;48:2277-2284.
132. Wichter T, Hindricks G, Lerch H, Bartenstein P, Borggrefe M, Schober O, Breithardt G. Regional myocardial sympathetic dysinnervation in arrhythmogenic right ventricular cardiomyopathy: an analysis using 123I-meta-iodobenzylguanidine scintigraphy. *Circulation*. 1994;89:667-683.
133. Chimenti C, Pieroni M, Maseri A, Frustaci A. Histologic findings in patients with clinical and instrumental diagnosis of sporadic arrhythmogenic right ventricular dysplasia. *J Am Coll Cardiol*. 2004;43:2305-2313.
134. Basso C, Ronco F, Abudurehman A, Thiene G. In vitro validation of endomyocardial biopsy for the in vivo diagnosis of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2006;27(suppl):960. Abstract.
135. Bowles NE, Ni J, Marcus F, Towbin JA. The detection of cardiotropic viruses in the myocardium of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2002;39:892-895.
136. Mason JW, O'Connell JB. Clinical merit of endomyocardial biopsy. *Circulation*. 1989;79:971-979.
137. Veinot JP. Diagnostic endomyocardial biopsy pathology: secondary myocardial diseases and other clinical indications: a review. *Can J Cardiol*. 2002;18:287-296.
138. Hosenpud JD, McAnulty JH, Niles NR. Unexpected myocardial disease in patients with life threatening arrhythmias. *Br Heart J*. 1986;56:55-61.
139. Oakes DF, Manolis AS, Estes NA 3rd. Limited clinical utility of endomyocardial biopsy in patients presenting with ventricular tachycardia without apparent structural heart disease. *Clin Cardiol*. 1992;15:24-28.
140. Segrue DD, Holmes DR Jr, Gersh BJ, Edwards WD, McLaran CJ, Wood DL, Osborn MJ, Hammill SC. Cardiac histologic findings in patients with life-threatening ventricular arrhythmias of unknown origin. *J Am Coll Cardiol*. 1984;4:952-957.
141. Vignola PA, Aonuma K, Swaye PS, Rozanski JJ, Blankstein RL, Benson J, Gosselin AJ, Lister JW. Lymphocytic myocarditis presenting as unexplained ventricular arrhythmias: diagnosis with endomyocardial biopsy and response to immunosuppression. *J Am Coll Cardiol*. 1984;4:812-819.
142. Frustaci A, Bellocci F, Olsen EG. Results of biventricular endomyocardial biopsy in survivors of cardiac arrest with apparently normal hearts. *Am J Cardiol*. 1994;74:890-895.
143. Yonesaka S, Takahashi T, Tomimoto K, Kinjo M, Sunagawa Y, Sato S, Nakada T, Matubara T, Oura H, Koda M, Furukawa H. Clinical and histopathological studies in children with supraventricular tachycardia. *Jpn Circ J*. 1996;60:560-566.
144. Teragaki M, Toda I, Sakamoto K, Shimada K, Yamagishi H, Yoshiyama M, Akioka K, Kawase Y, Nishimoto M, Takeuchi K, Yoshikawa J. Endomyocardial biopsy findings in patients with atrioventricular block in the absence of apparent heart disease. *Heart Vessels*. 1999;14:170-176.
145. Kobayashi Y, Yazawa T, Baba T, Mukai H, Inoue S, Takeyama Y, Niitani H. Clinical, electrophysiological, and histopathological observations in supraventricular tachycardia. *Pacing Clin Electrophysiol*. 1988;11:1154-1167.
146. Uemura A, Morimoto S, Hiramitsu S, Hishida H. Endomyocardial biopsy findings in 50 patients with idiopathic atrioventricular block: presence of myocarditis. *Jpn Heart J*. 2001;42:691-700.
147. Frustaci A, Caldarulo M, Buffon A, Bellocci F, Fenici R, Melina D. Cardiac biopsy in patients with "primary" atrial fibrillation: histologic evidence of occult myocardial diseases. *Chest*. 1991;100:303-306.
148. Uemura A, Morimoto S, Hiramitsu S, Ohtsuki M, Kato S, Kato Y, Sugiura A, Miyagishima K, Hishida H. Right ventricular endomyocardial biopsy findings in 25 patients with sick sinus syndrome. *Jpn Heart J*. 2004;45:73-80.
149. Feldman AM, Ray PE, Silan CM, Mercer JA, Minobe W, Bristow MR. Selective gene expression in failing human heart: quantification of steady-state levels of messenger RNA in endomyocardial biopsies using the polymerase chain reaction. *Circulation*. 1991;83:1866-1872.
150. Ladenson PW, Sherman SI, Baughman KL, Ray PE, Feldman AM. Reversible alterations in myocardial gene expression in a young man with dilated cardiomyopathy and hypothyroidism [published correction appears in *Proc Natl Acad Sci U S A*. 1992;89:8856]. *Proc Natl Acad Sci U S A*. 1992;89:5251-5255.
151. Bristow MR, Minobe WA, Reynolds MV, Port JD, Rasmussen R, Ray PE, Feldman AM. Reduced beta 1 receptor messenger RNA abundance in the failing human heart. *J Clin Invest*. 1993;92:2737-2745.
152. Lowes BD, Zolty R, Minobe WA, Robertson AD, Leach S, Hunter L, Bristow MR. Serial gene expression profiling in the intact human heart. *J Heart Lung Transplant*. 2006;25:579-588.
153. Cook SA, Rosenzweig A. DNA microarrays: implications for cardiovascular medicine. *Circ Res*. 2002;91:559-564.
154. Napoli C, Lerman LO, Sica V, Lerman A, Tajana G, de Nigris F. Microarray analysis: a novel research tool for cardiovascular scientists and physicians. *Heart*. 2003;89:597-604.
155. Henriksen PA, Kotelevtsev Y. Application of gene expression profiling to cardiovascular disease. *Cardiovasc Res*. 2002;54:16-24.
156. Slonim DK. From patterns to pathways: gene expression data analysis comes of age. *Nat Genet*. 2002;32(suppl):502-508.
157. Strain JE, Grose RM, Factor SM, Fisher JD. Results of endomyocardial biopsy in patients with spontaneous ventricular tachycardia but without apparent structural heart disease. *Circulation*. 1983;68:1171-1181.
158. Morgera T, Salvi A, Alberti E, Silvestri F, Camerini F. Morphological findings in apparently idiopathic ventricular tachycardia: an echocardiographic haemodynamic and histologic study. *Eur Heart J*. 1985;6:323-334.
159. Dunnigan A, Staley NA, Smith SA, Pierpont ME, Judd D, Benditt DG, Benson DW Jr. Cardiac and skeletal muscle abnormalities in cardiomyopathy: comparison of patients with ventricular tachycardia or congestive heart failure. *J Am Coll Cardiol*. 1987;10:608-618.
160. Nishikawa T, Sekiguchi M, Hasumi M, Kasajima T, Nakazawa M, Ando M, Takao A. Histopathologic findings of endomyocardial biopsies in pediatric patients with arrhythmias or conduction disturbances. *Heart Vessels Suppl*. 1990;5:24-27.
161. Sekiguchi M, Nishizawa M, Nunoda S, Hiroe M, Hosoda S. Endomyocardial biopsy approach in cases with ventricular arrhythmias. *Postgrad Med J*. 1991;68(suppl 1):S40-S43.
162. Thongtang V, Chiathiraphan S, Ratanarapee S, Panchavinnin P, Srivanasont N, Jootar P, Sahasakul Y, Charoenchob N, Tresukosol D. Prevalence of myocarditis in idiopathic dysrhythmias: role of endomyocardial biopsy and efficacy of steroid therapy. *J Med Assoc Thai*. 1993;76:368-373.