Complication Rate of Right Ventricular Endomyocardial Biopsy via the Femoral Approach
A Retrospective and Prospective Study Analyzing 3048 Diagnostic Procedures Over an 11-Year Period

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Background—An unequivocal diagnosis of myocarditis and cardiac virus persistence is based on histological, immunohistological, and molecular biological analyses of endomyocardial biopsies (EMBs). Biopsy-based diagnosis of myocarditis has become increasingly important because recent studies have demonstrated the beneficial effects of biopsy-based causal treatment strategies (immunosuppressive or antiviral). Because the risks of major complications caused by EMB procedures have not yet been well defined, we evaluated the incidence of major and minor complications of right ventricular EMB procedures in this retrospective and prospective single-center study.

Methods and Results—With the use of a modified Cordis bioptome, 1919 patients underwent 2505 EMB procedures retrospectively over a 9-year period (January 1995 to December 2003), and 496 patients underwent 543 EMB procedures prospectively between January 2004 and December 2005. A total of 2415 patients had 3048 EMB procedures via the right femoral vein approach under biplane fluoroscopic control to evaluate unexplained left ventricular dysfunction (retrospective left ventricular ejection fraction, 49.8±18.8%; prospective, 48.8±19.7%) after exclusion of secondary causes. During each EMB procedure, an average of 8.2±0.8 EMBs were obtained retrospectively and 10.1±0.6 specimens prospectively for a total of 26 025 specimens. No patient died or required emergency cardiac surgery. Other major complications like cardiac tamponade requiring pericardiocentesis or complete atrioventricular block requiring permanent pacing were very rare: 0.12% in the retrospective study and 0% in the prospective study. Minor complications such as pericardial effusion, conduction abnormalities, or arrhythmias occurred in 0.20% of the EMB procedures in the retrospective study and 5.5% in the prospective study.

Conclusions—The EMB procedure via the femoral vein approach under fluoroscopic guidance has a very low complication rate when performed by experienced operators. (Circulation. 2008;118:1722-1728.)

Key Words: biopsy ■ cardiomyopathy ■ complications ■ heart failure ■ myocarditis

Endomyocardial biopsies (EMBs) are still the gold standard for establishing the diagnosis of myocarditis and cardiac virus persistence because anamnestic data and noninvasive diagnostic tools are not specific enough to ascertain myocardial virus persistence or inflammation. EMB-based diagnosis of myocarditis or cardiac virus persistence is gaining increasing relevance in clinical practice because controlled clinical trials have recently demonstrated beneficial effects of immunomodulatory therapies. EMBs are also useful for assessing the clinical course and outcome of patients with impaired left ventricular (LV) function. Nevertheless, EMB procedures have not yet gained widespread acceptance because of concerns about possible complications associated with EMB procedures. Only small studies have been performed thus far on this topic; therefore, the risks of major complications caused by EMB procedures (eg, emergency cardiac surgery, cardiac tamponade requiring pericardiocentesis, or death) are still not well defined.

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The first report of a catheter-based bioptome was published in 1962. It was inserted through a peripheral vein (left basilic/axillary vein) or an artery (left axillary/common carotid artery) and advanced into the apex of the right ventricle.
Over the years, the most common approach for EMB procedures has been through the right internal jugular vein, and the most common biopsy site was the RV side of the septum (interventricular septum [IVS]) under fluoroscopic guidance, even if some groups used the LV as another biopsy site according to their personal experience. Our single-center study analyzed the incidence of major and minor EMB procedure–related complications in a large database of 1919 retrospective and 496 prospective patients over an 11-year period. EMB procedures were performed by inserting a modified Cordis biop tome via the right femoral vein and taking EMBs from the RV septum under plane fluoroscopic guidance without any additional echocardiographic control.

Methods

**Patient Selection**

In the retrospective part of our study, 1919 consecutive adult patients were enrolled over a period of 9 years (January 1995 to December 2003). In the prospective part, 496 patients were evaluated over a period of 2 years (January 2004 to December 2005). None of the patients was in a posttransplant setting. These patients underwent a total of 3048 EMB procedures over 11 years. An average of 8.2 ± 0.8 EMBS were obtained retrospectively and 10.1 ± 0.6 EMBS were obtained prospectively during each EMB procedure, yielding a total of 26 025 EMBS. EMB procedures were indicated for the evaluation of unexplained LV dysfunction, particularly in cases of clinically suspected myocarditis with progressive LV dysfunction, and for the evaluation of immunomodulatory treatment effects in viral myocarditis and inflammatory cardiomyopathy. EMBs were also taken from patients with unexplained ventricular arrhythmias, neoplastic heart disease, and systemic diseases with possible cardiac involvement according to the published recommendations. Infiltrative or connective tissue disorders included amyloidosis, sarcoidosis, hemochromatosis, scleroderma, systemic lupus erythematosus, polymyositis, mixed connective-tissue disease, and Wegener’s granulomatosis.

After the clinical history and physical examination, we performed a 12-lead ECG, transthoracic echocardiography, chest x-ray, and selected laboratory tests (including liver and thyroid function tests and antinuclear antibodies measurement if indicated by the initial assessment) in all patients. All patients underwent coronary angiography to exclude coronary heart disease as a frequent cause of impaired LV function. LV dysfunction was evaluated by echocardiography and LV angiography, and LV end-diastolic pressure (LVEDP) was measured routinely. Patients with LV dysfunction and an identified secondary cause (ischemic or valvular heart disease, hypertension, peripartum cardiomyopathy, drug abuse, endocrine diseases like thyroid disease, diabetes, pheochromocytoma, or neuromuscular disease) were excluded from further EMB procedure diagnostics.

In patients with myocardial virus genomes or inflammation proven by EMB diagnostics, follow-up biopsies were obtained to evaluate the course and the effect of immunomodulatory treatment strategies (interferon-β, prednisone, and azathioprine).

**Definition of Major Complications and Minor Complications**

**Major Complications**

Major complications included death, urgent cardiac surgery, advanced cardiac life support, pericardiocentesis in cardiac tamponade, permanent complete atrioventricular (AV) block requiring permanent pacing, hemotherax, and pneumotherax.

**Minor Complications**

Minor complications included pericardial effusion without pericardiocentesis, temporary (lasting <24 hours) or permanent right bundle-branch block (RBBB), temporary Mobitz type II AV block with AV conduction 2:1 requiring medical treatment with atropine, complete AV block requiring medical treatment with atropine or additive temporary pacing, nonsustained ventricular tachycardia with long runs of >10 ventricular complexes, and an episode of atrial fibrillation lasting <12 hours or cardiovascular of atrial fibrillation.

**EMB, Right Heart Catheterization, and Echocardiography**

EMB procedures were limited to 4 highly experienced operators with >800 invasive procedures a year over a period of at least 5 years. Interventional fellows performed at least 50 EMB procedures per year, and senior clinicians performed >100. Operators were only allowed to perform EMB procedures alone if a minimum of 50 procedures had been previously supervised by a senior operator. Patients had to have an international normalized ratio of <1.5 at the time of EMB procedures, and antiocoagulant therapy with phenprocoumon or heparin was discontinued for 16 hours before and 12 hours after EMB procedures. EMB procedures were performed with the use of a modified Cordis biop tome. This biop tome (B-18110; Medizintechnik Meiners, Monheim, Germany) has been used in clinical practice since 1985. It has a 6F diameter and a total length of 1100 mm. The 2 closed biop tome jaws have a total diameter of 1.8 mm, a length of 2.8 mm, and a volume of 4.5 mm³. Compared with the Cordis biop tome, it has a more flexible polytetrafluoroethylene (Teflon) tube instead of an inflexible steel spiral as well as smaller jaws at the biop tome head.

Vascular access was obtained via the right femoral vein under local anesthesia with 2% lidocaine. The biop tome was advanced slowly up to the middle to apical segment of the right IVS under plane fluoroscopic guidance. Once contact with the IVS was confirmed by premature ventricular complexes, the biop tome was withdrawn 1 to 2 cm, and its jaws were opened and slowly advanced to engage the IVS. Gentle forward pressure was maintained while the jaws were closed. The biop tome containing the specimen was removed by gentle traction on the shaft. Right heart filling pressures (including RV end-diastolic pressure [RVEDP]) were measured with a pigtail catheter before and after EMB procedures for the early detection of an incipient cardiac tamponade. A 12-lead ECG and a standard transthoracic 2-dimensional and M-mode echocardiography were performed in all patients before EMB procedures. LV diastolic (LVEDD) and systolic (LVESD) dimensions were measured by M-mode echocardiography by the leading-edge method in the parasternal long-axis view. In the retrospective trial, all patients developing chest pain, dyspnea, or ECG changes after the EMB procedures received a control echocardiography to detect pericardial effusion or incipient cardiac tamponade. In the prospective trial, all patients underwent a 12-lead ECG and a transthoracic echocardiography after EMB procedures to obtain a detailed evaluation of the incidence of conduction abnormalities, arrhythmias, and pericardial effusions. In addition, a detailed worksheet was filled out for all patients for every examination during their further clinical workup, on which all adverse EMB procedure–related events were immediately recorded. Abnormalities and respective changes before and after EMB procedures were documented by ECG and echocardiography findings. Such findings included a new onset of atrial fibrillation, ventricular tachycardia, RBBB, left bundle-branch block (LBBB), conduction abnormalities requiring atropine, other antiarrhythmic agents administered intravenously, and temporary versus permanent pacing. Correspondingly, a new onset of pericardial effusion was documented after echocardiography. Complications like death, urgent cardiac surgery, advanced cardiac life support, pericardiocentesis, hemotherax, and pneumotherax were also documented.
Cardiac perforation was seen in 2 cases (0.08%) (Table 2). These 2 patients developed symptoms of chest pain, dyspnea, bradycardia, and a decrease in systolic pressure to <70 mm Hg accompanied by an increase in right heart filling pressures during myocardial biopsy. Echocardiography revealed the presence of pericardial effusion with RV collapse indicating cardiac tamponade due to RV free wall perforation. Immediate pericardiocentesis with the standard subxiphoid percutaneous access rapidly improved the hemodynamic status of both patients. The pigtail catheter placed in the pericardial space was removed after 18 or 26 hours, respectively, when there was no further drainage. One of these 2 patients with a final diagnosis of dilated cardiomyopathy developed hemodynamically relevant bradycardia requiring temporary pacing before pericardiocentesis was started. In this case, the pacemaker could be removed after 7 minutes. The second patient had a final diagnosis of an angiosarcoma with diffuse pleural, pericardial, epicardial, and myocardial metastases. The clinical follow-up of both patients showed no long-term sequelae. Interestingly, both cases of cardiac tamponade during EMB procedures occurred in patients with normal LV dimensions (LVEDD ≤65 mm).

**Conduction Abnormalities**

Only 1 (0.04%) of the 5 patients requiring temporary pacing (see Minor Complications) needed a permanent pacemaker because of persistent conduction abnormalities (Table 2). She had a preexisting LBBB and known scleroderma with predominant dermatological and limited pulmonary manifestations. The EMBs demonstrated significant interstitial and subendocardial fibrosis and degenerative atrophy with consecutive hypertrophy of heart muscle cell groups. Hence, the EMBs confirmed the diagnosis of a cardiac manifestation of scleroderma, and specific therapy was started with D-penicillamine in addition to an angiotensin-converting enzyme inhibitor. This patient also had no relevant LV enlargement (LVEDD ≤65 mm).

**Other Major Complications**

There was no EMB procedure–related death, no case requiring emergency cardiac surgery, and no case of pneumothorax or hemothorax (Table 2).

**Minor Complications in 2505 Retrospective EMB Procedures**

**Conduction Abnormalities**

Altogether, 5 cases (0.20%) developed complete AV block during the EMB procedures, which required temporary pacing because of hemodynamic instability (Table 3). The aforementioned patient with cardiac perforation developed bradycardia with hemodynamic instability before pericardiocentesis. Another patient developed complete AV block...
during cannulation of the femoral vein before the bioprobe was inserted, suggesting a pronounced vasovagal reaction. The other 3 patients had preexisting LBBB before EMB procedures and developed complete AV block as a direct result of EMB procedures, 1 of them during bioprobe positioning because of contact with the proximal IVS and the other 2 during EMBs. The period of temporary pacing ranged from 7 to 31 minutes, with a mean pacing time of 18.0 ± 8.8 minutes.

In all performed EMB procedures, patients with preexisting LBBB had a significantly higher risk of developing a temporary complete AV block requiring temporary pacing than those without LBBB (Fisher exact test, P = 0.02; Table 4). Subgroup analyses demonstrated an increased incidence of temporary pacing in patients with normal LV dimensions (LVEDD ≥ 65 mm, 0.21% versus 0.17%).

**Major Complications in 543 Prospective EMB Procedures**

There was no case of EMB procedure–related pericardial tamponade requiring pericardiocentesis, no pneumothorax or hemothorax, no permanent pacemaker support, no death, and no case requiring emergency cardiac surgery (Table 2).

**Minor Complications in 543 Prospective EMB Procedures**

**Pericardial Effusions**

There were 4 cases (0.74%) of EMB procedure–induced small pericardial effusions, 3 with de novo onset after EMB procedures and 1 with an increase of the preexisting effusion (Table 2). None of the patients experienced hemodynamic impairment, and all cases resolved spontaneously within 4 days. There was no evidence of microperforation in any EMB by histological assessment; in particular, no mesothelial cells or nerve tissues were detected.

**Conduction Abnormalities**

Conduction abnormalities such as RBBB induced during the EMB procedures were temporary (lasting <24 hours after EMB procedures) in 6 cases (1.10%) and sustained (>24 hours) in 2 cases (0.37%). Furthermore, we documented periprocedural Mobitz type II AV block with 2:1 AV conduction in 2 cases (0.37%) and complete AV block in 2 cases (0.37%), all requiring atropine 0.5 to 1 mg and resolving spontaneously within 10 minutes. Temporary AV block III requiring injection of atropine 0.5 to 1 mg and temporary pacemaker support occurred in 8 cases (1.47%), with the period of temporary pacing ranging from 22 seconds to 4 hours (mean pacing time of 66.3 ± 8.8 minutes).

All of these 8 patients had preexisting LBBB. Patients with preexisting LBBB had a significantly higher risk of developing temporary complete AV block requiring temporary pacing (9.64%) than those without LBBB (Fisher exact test, P < 0.01; Table 4).

Subgroup analysis demonstrated an increased incidence of temporary pacing in patients with normal LV dimensions (LVEDD ≥ 65 mm, 1.7% versus 0.78%).

**Arrhythmias**

There were no cases of complex ventricular arrhythmias such as nonsustained ventricular tachycardia with long runs of ≥ 10 ventricular complexes, 5 (0.92%) episodes of atrial fibrillation (lasting <12 hours), and 1 case (0.18%) of persistent atrial fibrillation (lasting >12 hours) with subsequent successful cardioversion. The clinical follow-up of all these patients showed no long-term sequelae.

**Discussion**

This is the largest report of 3048 EMB procedures, analyzing major and minor complications of this invasive procedure.

### Table 3. Minor Complications of 2505 Retrospective and 543 Prospective EMB Procedures

<table>
<thead>
<tr>
<th>Minor Complications of EMB Procedures</th>
<th>Retrospective, Absolute/%</th>
<th>Prospective, Absolute/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small pericardial effusions</td>
<td>4/0.74</td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>3/0.55</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>1/0.18</td>
<td></td>
</tr>
<tr>
<td>Conduction abnormalities</td>
<td>5/0.20</td>
<td>20/3.7</td>
</tr>
<tr>
<td>RBBB sustained (&gt;24 h)</td>
<td>2/0.37</td>
<td></td>
</tr>
<tr>
<td>RBBB temporary (&lt;24 h)</td>
<td>6/1.10</td>
<td></td>
</tr>
<tr>
<td>AV block II Mobitz, 2:1</td>
<td>2/0.37</td>
<td></td>
</tr>
<tr>
<td>periprocedural (&lt;10 min) requiring 0.5 to 1 mg atropine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block III periprocedural (&lt;10 min) requiring 0.5 to 1 mg atropine</td>
<td>2/0.37</td>
<td></td>
</tr>
<tr>
<td>AV block III temporary (&lt;24 h) requiring atropine + temporary pacemaker</td>
<td>5/0.20</td>
<td>8/1.47</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>6/1.10</td>
<td></td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia (≥10 ventricular complexes)</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Episode (&lt;12 h) of atrial fibrillation</td>
<td>5/0.92</td>
<td></td>
</tr>
<tr>
<td>Persistent atrial fibrillation with cardioversion</td>
<td>1/0.18</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Subgroups of EMB Procedures in Patients With Versus Without Preexisting LBBB**

<table>
<thead>
<tr>
<th>EMB Procedures</th>
<th>Retrospective (n = 2505)</th>
<th>Prospective (n = 543)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary Pacemaker</td>
<td>No Temporary Pacemaker</td>
<td>P</td>
</tr>
<tr>
<td>LBBB</td>
<td>3</td>
<td>353</td>
</tr>
<tr>
<td>No LBBB</td>
<td>2</td>
<td>2147</td>
</tr>
</tbody>
</table>

*P* values calculated with Fisher exact test.
The patients (1919 retrospectively and 496 prospectively investigated) were unselected adults in a nontransplant setting, and all RV EMB procedures were performed by the right femoral vein approach with a modified Cordis bioprobe.

The risk of major complications in this single-center study was very low: 0.12% when analyzed retrospectively and 0% prospectively. In the retrospective trial, 2 patients required pericardiocentesis because of cardiac tamponade (0.08%), and 1 patient required a permanent pacemaker because of persistent complete AV block after the EMB procedures (0.04%). When we compared these data with the major complication rates of EMB procedures reported by 2 earlier monocentric studies, the rate of major complications in our study was lower. Deckers et al24 performed a prospective study on the complication rate of 546 EMB procedures in 464 patients between 1982 and 1989. They reported a major complication rate including death of 0.37%, caused by cardiac tamponade despite pericardiocentesis. Patients in this study had a lower mean LVEF and higher filling pressures compared with the patients in our study. The difference in major complications (death, urgent cardiac surgery, advanced cardiac life support, pericardiocentesis, permanent pacemaker implantation, hemotherax, and pneumothorax) despite similar perforation rates in both studies (0.7% small pericardial effusion in this prospective analysis and 0.5% in the Deckers analysis) may arise from the fact that seriously ill patients have only a small margin for further hemodynamic problems due to perforation. From the same center, Felker et al23 reported on a prospective analysis of 323 EMB procedures between January 1996 and September 1998 with an incidence of 0.31% of cardiac tamponade requiring urgent cardiac surgery. A similar rate of emergency surgery of 0.27% was reported by Frustaci et al2 in a subanalysis of RV free wall perforations occurring during 1481 RV EMB procedures.

There are several possible reasons for this difference in the major complication rate between our study and the 2 earlier ones. We exclusively used the right femoral vein for vascular access instead of the right internal jugular vein as in the other studies, and EMBs were only obtained from the RV septum. An obvious advantage of the femoral approach is the absence of subjective complaints or hemodynamic measurements. Despite this very detailed documentation of all possible complications in the prospective trial, we observed no complication with severe sequelae for the patients. The studies of Deckers et al24 and Felker et al23 used a similarly detailed worksheet for documentation of adverse effects in their prospective report of EMB procedure complications. Their rate of minor complications of rhythm disturbances (nonsustained ventricular tachycardia, atrial fibrillation [either episodic or persistent with cardioversion]) was similar to ours: 1.1% in this study versus 1.1% reported by Deckers et al24 and 1.5% by Felker et al.23 In our study, the rate of pericardial effusion resolving spontaneously was 0.7%, which is similar to the rates reported by Frustaci et al2 (0.4%) and Deckers et al24 (0.5%). Conduction abnormalities (RBBB, temporary Mobitz type II AV block, or temporary AV block III, treated medically or additionally requiring temporary pacing) were more frequent in our study (3.7%) than in the studies of Deckers (0.9%) and Felker (0.6%).

Possible explanations for the increased incidence of conduction abnormalities in our prospective study include the different right femoral vein approach and the fact that our patients had only mildly reduced EF and near-normal cardiac dimensions. Under these conditions involving a more acute angle between the inferior vena cava and the longitudinal axis of the tricuspid valve, it is sometimes more difficult to advance the bioprobe via the femoral approach through the relatively small cardiac spaces to an adequate position for EMBS in the middle to apical region of the IVS. The occasional need to more intensely manipulate the bioprobe under these conditions may cause increased irritation at the basal IVS close to the right bundle branch and AV node and thus induce conduction abnormalities more frequently.

To test this hypothesis, we analyzed subgroups of our patients with major LV dilation (LVEDD >65 mm). The risk of conduction abnormalities requiring temporary pacing was linked in both the retrospective and the prospective studies to normal LV dimensions (LVEDD ≤65 mm; 0.21%/1.7%). Patients with LV dilation showed a trend toward a lower incidence of temporary pacing requirement (0.17%/0.78%), which was, however, not significant.

To evaluate the impact of preexisting LBBB as a risk factor for developing conduction abnormalities during EMB procedures, we performed an analysis of a patient subgroup with preexisting LBBB (Table 4). The risk of developing complete AV block requiring temporary pacing induced by EMB procedures was significantly increased by preexisting LBBB, with 0.84% in the retrospective and 9.64% in the prospective part of our study (P<0.01). Mechanical irritation of the right bundle branch is apparently sufficient to induce temporary complete AV block in patients with a preexisting LBBB.
Holmman et al

Conclusions
When performed by experienced operators, the EMB procedure from the RV septum via the right femoral vein approach under biplane fluoroscopic guidance is a safe procedure for evaluating patients with unexplained LV dysfunction. Major complications were very low in both the retrospective and prospective trials (0.12% versus 0%). Patients with pre-existing LBBB had a significantly higher risk of developing complete AV block requiring temporary pacing. Patients with LV enlargement had no increased risk of conduction abnormalities requiring temporary pacemaker support.

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Disclosures
None.

References

Complication Rate in Endomyocardial Biopsy

The diagnosis of myocarditis and viral persistence, based on histological, immunohistological, and molecular biological analyses of endomyocardial biopsies (EMBs), has prognostic and crucial therapeutic implications for the selection of immunosuppressive or antiviral treatment in patients with unexplained left ventricular dysfunction. Nevertheless, EMB procedures have not yet gained widespread acceptance because of concerns about possible complications, which are still not well defined. Therefore, this retrospective and prospective single-center study, the largest of its kind with 2415 patients subjected to 3048 EMB procedures, evaluated the incidence of major and minor complications associated with right ventricular EMB procedures to assess unexplained left ventricular dysfunction. EMB procedures were performed via the right femoral approach under biplane fluoroscopic guidance by senior cardiologists and 4 interventional fellows using a flexible modified Cordis bioptome. No patient died or required emergency cardiac surgery. Other major complications like cardiac tamponade requiring pericardiocentesis or complete atrioventricular block requiring permanent pacing were very rare: 0.12% in the retrospective and 0% in the prospective trial. Minor complications such as pericardial effusion, conduction abnormalities, or arrhythmias occurred in 0.20% of the EMB procedures in the retrospective trial and 5.5% in the prospective trial. Patients with preexisting left bundle-branch block had a higher risk for complete atrioventricular block requiring temporary pacing, whereas patients with left ventricular enlargement had no increased risk of conduction abnormalities. In summary, the femoral approach to EMB procedures with a modified Cordis biopette enables the safe utilization of recent knowledge about the clinical benefit arising from EMB-based differential therapies of heart failure.
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