Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy
Differences in Complication Rate and Diagnostic Performance

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Background—Endomyocardial biopsy (EMB) represents the gold standard for diagnosing myocarditis and nonischemic cardiomyopathies. This study focuses on the risk of complications and the respective diagnostic performance of left ventricular (LV), right ventricular (RV), or biventricular EMB in patients with suspected myocarditis and/or cardiomyopathy of unknown origin.

Methods and Results—In this 2-center study, 755 patients with clinically suspected myocarditis (n=481) and/or cardiomyopathy of nonischemic origin including those with infiltrative or connective tissue disease (n=274) underwent either selective LV-EMB (n=265; 35.1%), selective RV-EMB (n=133; 17.6%), or biventricular EMB (n=357; 47.3%) after coronary angiography and exclusion of significant coronary artery disease. Cardiovascular magnetic resonance, including late gadolinium enhancement, imaging was performed in 540 patients (71.5%). The major complication rate for LV-EMB was 0.64% and for RV-EMB, 0.82%. Considering postprocedural pericardial effusion that occurred after biventricular EMB, the minor complication rate for LV-EMB varied between 0.64% to 2.89% and for RV-EMB, between 2.24% and 5.10%. Diagnostic EMB results were achieved significantly more often in those patients who underwent biventricular EMBS (79.3%) compared to those who underwent either selective LV-EMB or selective RV-EMB (67.3%; P<0.001). In patients with biventricular EMB, myocarditis was diagnosed in LV-EMB samples in 18.7% and in RV-EMB samples in 7.9% (P=0.002), and it was diagnosed in both ventricles in 73.4%. There were no differences in the number of positive LV-EMB, RV-EMB, or LV- and RV-EMB findings when related to the site of cardiovascular magnetic resonance–based late gadolinium enhancement.

Conclusions—Both LV-EMB and RV-EMB are safe procedures if performed by experienced interventionalists. The diagnostic yield of EMB may be optimized when samples from both ventricles are available. Preferential biopsy in regions showing late gadolinium enhancement on cardiovascular magnetic resonance does not increase the number of positive diagnoses of myocarditis. (Circulation. 2010;122:900-909.)

Key Words: endomyocardial fibrosis • biopsy • magnetic resonance imaging • myocarditis • cardiomyopathy

Clinical Perspective on p 909
Recently, the role of EMB in the management of cardiovascular disease was described for the first time in a joint scientific statement from the American Heart Association (AHA), the American College of Cardiology, and the European Society of Cardiology.10 A group of experts identified several clinical scenarios in which the value of EMB was weighed against the procedural risks. These experts felt that

Endomyocardial biopsy (EMB) is still the gold standard for in vivo diagnosis of myocarditis or other noninflammatory cardiovascular diseases such as amyloidosis, sarcoidosis, and Morbus Fabry.1–6 The therapeutic and prognostic benefits of EMB-based diagnoses have been demonstrated recently in several clinical trials.1,6–9 Nevertheless, the EMB procedure is still controversial because of concerns about the invasive nature of the procedure and the risk of complications.

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further investigations were necessary to prove the procedural risk and diagnostic value of left versus right ventricular biopsy. They also pointed out that new techniques, such as guidance by cardiovascular magnetic resonance imaging (CMR), might be helpful to improve the accuracy and safety of this invasive procedure.

The present study is the first to investigate the procedural safety and diagnostic performance of selective LV-EMB, selective RV-EMB, or biventricular EMB in patients with suspected myocarditis or nonischemic cardiomyopathy, using state-of-the-art techniques for sampling of biopsies as well as postprocedural histological, immunohistochemical, and molecular pathological analyses of the myocardial specimens. Furthermore, the role of CMR as a noninvasive tool in diagnosing inflammatory3,11 and several noninflammatory cardiomyopathies12,13 as well as in guiding EMB was evaluated.

Methods

Patient Population

This retrospective 2-center study includes 755 patients who presented either to the Division of Cardiology at the Robert-Bosch-Krankenhaus in Stuttgart (n = 529) between 2006 and 2008 or to the Department of Cardiology at the University Hospital of the Saarland in Homburg (n = 226) between 1995 and 2008 with clinically suspected myocarditis (n = 481) and/or for further evaluation of cardiomyopathy of nonischemic origin including those with infiltrative or connective tissue disease (n = 274). Myocarditis was clinically suspected when at least 2 of the following criteria were present in addition to an impaired LV function and/or a CMR study result indicative of myocarditis: (1) clinical symptoms of chest pain, dyspnea, or palpitation; (2) history of malaise for more than 1 week and/or the history of respiratory and/or gastrointestinal infection, both within 6 months preceding admission; (3) ECG signs such as ST-wave abnormalities, T-wave inversions, new onset of conduction blocks, and supraventricular tachycardia as well as sustained or nonsustained ventricular tachycardia; (4) an increase in serum concentrations of myocardial necrosis markers; or (5) presence of pericardial effusion. Patients with suspected infiltrative or connective tissue diseases including amyloidosis, sarcoidosis, Morbus Fabry, dystrophinopathy, Wegener granulomatosis, and systemic lupus erythematoses also underwent EMB as part of the diagnostic procedure. Follow-up biopsies, which were performed in some patients with rapidly worsening LV function in spite of appropriate heart failure treatment or in patients receiving immunomodulatory therapy, are not included in this analysis. None of the 755 patients underwent biopsy to monitor potential heart transplant rejection. All patients included in this study underwent a clinical examination followed by laboratory studies, a resting 12-lead ECG, a chest x-ray, and either echocardiography or a CMR study preceding cardiac catheterization. EMBs were only taken in those patients with significant coronary artery disease defined as coronary artery stenosis (in at least 1 coronary artery segment) of ≥50% and without severe valvular disease. After the EMB procedure, echocardiography was performed in every patient in order to assess whether a new or larger pericardial effusion was present after biopsy. Written informed consent was obtained from every patient before his or her respective procedure (CMR, coronary angiography, or EMB).

CMR: Protocol and Data Analysis

ECG-gated CMR imaging was performed in breath-hold with the use of a 1.5-T Magnetom Sonata (Siemens Medical Solutions, Erlangen, Germany) and comprised both cine and LGE, as described previously.1,13 Hyperemia- and edema-detecting sequences14 did not work on the scanners of both study centers at the time when the majority of this patient group was examined. Image analyses were performed as described in detail previously.3,13

Cardiac Catheterization and EMB

Coronary angiography was performed before the EMB procedure. EMBs were performed by experienced interventionalists with ≥3 years of experience in taking EMBs. A detailed description of the EMB procedure is provided in the online-only Data Supplement. EMBs were taken under fluoroscopic control from the right (septum) and/or left ventricle (free wall) with a total of 4 to 6 samples per ventricle being collected from 2 to 3 different sites of each ventricle in order to reduce sampling error. EMBs were preferentially taken from the ventricle demonstrating LGE. Those patients demonstrating unequivocal presence of LGE exclusively in the LV free lateral wall underwent, at a minimum, selective LV biopsies, whereas those patients demonstrating LGE in the septal wall or having no LGE at all underwent either biventricular or selective RV biopsies. Definition and assessment of major and minor biopsy complications were in accordance with previous studies.15,16 In brief, major complications included pericardial tamponade with need for pericardiocentesis, hemo- and pneumopericardium, permanent AV block requiring permanent pacemaker implantation, myocardial infarction, transient cerebral ischemic attack and stroke, severe valvular damage, and death, whereas minor complications included transient chest pain, transient ECG abnormalities, transient arrhythmias, transient hypotension, and small pericardial effusions.

Histopathological Analysis and Detection of Viral Genomes

Histopathological and molecular pathological workup of biopsy samples were performed as described in detail previously.3,13

Diagnostic Categories by EMB

Biopsy results were used for diagnosis according to the World Health Organization/International Society and Federation of Cardiology Task Force Report.17 Myocardial inflammation indicative of myocarditis was defined on the basis of immunohistochemical analyses as ≥14 infiltrating leukocytes/mm² (CD3+ T-lymphocytes and/or CD68+ macrophages), with further differentiation between active myocarditis requiring additional myocyte damage and borderline myocarditis (without myocyte damage) based on hematoxylin/eosin and Masson trichrome stainings, respectively. In addition, expression of human leukocyte antigen class II molecules in professional antigen-presenting immune cells18 and endothelium was visually assessed after immunohistochemical staining.19 Because previous studies showed a relationship between virus genome presence in myocardial specimens and patient symptoms as well as outcomes,9,18,20,21 the presence of a virus genome was carefully evaluated. Furthermore, Masson trichrome and hematoxylin/eosin staining allowed diagnoses of hypertrophic cardiomyopathy,22,23 myocardial infarction,13 and amyloidosis,24 respectively, and was supplemented by Congo red staining and electron microscopy. The diagnosis of dilated cardiomyopathy was primarily made in association with additional angiographic and CMR data, especially when histopathological data were ambiguous for dilated cardiomyopathy. Takotsubo cardiomyopathy was diagnosed on the basis of clinical, angiographic, and CMR results. As of this date, there is no consensus on pathognomonic histological findings.

Statistical Analysis

Data for continuous variables are expressed as mean±SD for normally distributed values and median and range for nonnormally distributed values. Categorical variables are expressed as the number and percentage, respectively. Comparisons between groups were done by use of Mann-Whitney U test for nonnormally distributed continuous variables and Student t test for normally distributed variables. The χ²-square test and Fisher exact test were used for comparison of categorical variables. A 2-tailed P value <0.05 was considered statistically significant.
Results

Patient Characteristics
EMBs were performed in 755 patients with a mean age of 53.7±17.3 years and a mean LV ejection fraction of 43.1±20.8% (Table 1). Leading clinical symptoms were resting and/or exercise-induced chest pain in 275 of 755 (36.4%) patients and resting and/or exercise-induced dyspnea in 612 of 755 (81.1%) patients. New onset of or worsening clinical symptoms (chest pain and/or dyspnea) within 2 weeks before hospital admission was documented in 228 of 755 (30.2%) patients. Most patients underwent biventricular EMBs (n=357; 47.3%) whereas selective LV-EMB only was performed in another 133 (17.6%). Additional CMR performed in 265 patients (35.1%) and selective RV-EMB was performed in 490. On the average, 8.4±3.5 samples were taken per patient without significant numeric differences between LV- (5.8±1.5 samples) and RV-EMB (5.6±1.5 samples). During LV-EMB, 4 major complications (2 perforations and 2 peri-/postinterventional strokes) were observed, whereas during RV-EMB, 4 perforations leading to hemopericardium and pericardial tamponade with need for pericardiocentesis occurred (Table 2). In 1 patient with postinterventional stroke, a complex coagulation disorder (heterozygous factor V Leiden, methylenetetrahydrofolate reductase mutation, factor XII–, and protein S-deficit) was diagnosed after the complication had occurred. After intracerebral lysis and physiotherapy, the patient recovered nearly completely. In the second patient with periinterventional stroke, lysis therapy was performed after cerebral angiography was done in the catheterization laboratory with documented thrombus in the A. cerebri media and anterior. The patient recovered within a few hours without sequelae. Thus, the major complication rate for LV-EMB was 0.64% and for RV-EMB, 0.82%. The major complication rate was 0.56% (2 of 357) for biventricular EMB and 1.51% (6 of 398) for univentricular EMB.

Observed minor complications included transient chest pain (1× LV-EMB and 3× RV-EMB), nonsustained ventricular tachycardia (defined as ≥10 ventricular complexes), LV-EMB, and 3× RV-EMB), transient hypotension (4× RV-EMB), and an AV block III° requiring a temporary pacemaker in 1 patient during RV-EMB (Table 2). After 3 days of monitoring, the AV block had subsided and the temporary pacemaker was removed. There were no long-term sequelae after this complication. Echocardiography was performed immediately after the EMB procedure in all patients and revealed small asymptomatic pericardial effusions in 14 patients that were not present before the procedure (in 9 by preinterventional CMR study and in 5 by echocardiography). All of these 14 patients had undergone biventricular EMBs that precluded an appropriate assignment of this complication to either ventricle. Thus, depending on the assignment of those pericardial effusions, the minor complication rate for LV-EMB was either 0.64% (minimal) or 2.89% (maximal), whereas this rate for RV-EMB was either 2.24% (minimal) or 5.10% (maximal).

Spectrum of Histopathological Findings
The results of histopathologic workup are demonstrated in Table 3. Unequivocal pathological diagnoses based on histological, immunohistochemical, and molecular pathological

### Table 1. Baseline Patient Characteristics (n=755)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±17</td>
<td>...</td>
</tr>
<tr>
<td>No. of male patients</td>
<td>487</td>
<td>65</td>
</tr>
<tr>
<td>No. of patients with selective LV-EMB only</td>
<td>265</td>
<td>35</td>
</tr>
<tr>
<td>No. of patients with selective RV-EMB only</td>
<td>133</td>
<td>18</td>
</tr>
<tr>
<td>No. of patients with combined LV- and RV-EMB</td>
<td>357</td>
<td>47</td>
</tr>
<tr>
<td>No. of myocardial samples taken per patient from the LV</td>
<td>5.8±1.5</td>
<td>...</td>
</tr>
<tr>
<td>No. of myocardial samples taken per patient from the RV</td>
<td>5.6±1.5</td>
<td>...</td>
</tr>
<tr>
<td>No. of myocardial samples taken per patient during all EMB procedures</td>
<td>8.4±3.5</td>
<td>...</td>
</tr>
<tr>
<td>No. of patients with NYHA class III</td>
<td>277</td>
<td>37</td>
</tr>
<tr>
<td>No. of patients with NYHA class IV</td>
<td>81</td>
<td>11</td>
</tr>
<tr>
<td>Mean left ventricular EF, %</td>
<td>43±21</td>
<td>...</td>
</tr>
<tr>
<td>No. of patients with additional CMR study</td>
<td>540</td>
<td>72</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean±SD. EF indicates ejection fraction; NYHA, New York Heart Association.

### Table 2. Major and Minor Complications (n=755)

<table>
<thead>
<tr>
<th>Complication</th>
<th>LV-EMB (n=622)</th>
<th>RV-EMB (n=490)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemopericardium/tamponade with pericardiocentesis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total percentage of major complications</td>
<td>0.64</td>
<td>0.82</td>
</tr>
<tr>
<td>Minor complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient chest pain</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nonsustained VT (≥10 ventricular complexes)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Transient hypotension</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>AV block III° temporarily requiring pacemaker</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Small pericardial effusion*</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Total percentage of minor complications, minimal to maximal†</td>
<td>0.64 to 2.89</td>
<td>2.24 to 5.10</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia.
*All 14 observed pericardial effusions occurred in patients with combined LV- and RV-EMB preventing an assignment of the complication to 1 ventricle.
†Minimal value if complication “small pericardial effusion” assigned to the other ventricle vs maximal value if complication “small pericardial effusion” assigned to the same ventricle.
Table 3. Spectrum of Biopsy Diagnoses (n=755)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Value (%) in All Patients With EMB (n=755)</th>
<th>Value (%) in Those With Combined EMB (n=357)</th>
<th>Value (%) in Those With Selective EMB (n=398)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis and/or virus genome presence</td>
<td>458 (60.7)</td>
<td>254 (71.1)</td>
<td>204 (51.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocarditis (≥14 leukocytes/mm³)</td>
<td>329 (43.6)</td>
<td>203 (56.9)</td>
<td>126 (31.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Active myocarditis</td>
<td>10 (3.0)</td>
<td>4</td>
<td>6</td>
<td>...</td>
</tr>
<tr>
<td>Borderline myocarditis</td>
<td>319 (70.0)</td>
<td>199</td>
<td>120</td>
<td>...</td>
</tr>
<tr>
<td>Virus genome presence</td>
<td>318 (42.1)</td>
<td>181 (50.7)</td>
<td>137 (34.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVB19</td>
<td>163 (51.2)</td>
<td>87 (48.1)</td>
<td>76 (55.5)</td>
<td>...</td>
</tr>
<tr>
<td>HHV6</td>
<td>74 (23.3)</td>
<td>49 (27.1)</td>
<td>25 (18.2)</td>
<td>...</td>
</tr>
<tr>
<td>PVB19 + HHV6</td>
<td>46 (14.5)</td>
<td>30 (16.6)</td>
<td>16 (11.7)</td>
<td>...</td>
</tr>
<tr>
<td>EBV</td>
<td>14 (4.4)</td>
<td>6 (3.3)</td>
<td>8 (5.8)</td>
<td>...</td>
</tr>
<tr>
<td>Others</td>
<td>21 (6.6)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>27 (3.6)</td>
<td>16 (4.5)</td>
<td>11 (2.8)</td>
<td>...</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>27 (3.6)</td>
<td>4 (1.1)</td>
<td>23 (5.8)</td>
<td>...</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>16 (2.1)</td>
<td>3 (0.8)</td>
<td>13 (3.3)</td>
<td>...</td>
</tr>
<tr>
<td>Sarcoidiosis</td>
<td>3 (0.4)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>...</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>...</td>
</tr>
<tr>
<td>Morbus Fabry</td>
<td>1 (0.1)</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Dystrophinopathy</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>...</td>
</tr>
<tr>
<td>Takotsubo cardiomyopathy</td>
<td>8 (1.1)</td>
<td>3 (0.8)</td>
<td>5 (1.3)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Diagnosis was made considering additional clinical and CMR data.

PVB19 indicates parvovirus B19; HHV6, human herpes virus 6; and EBV, Epstein-Barr Virus.

examinations of EMBs were made in 542 patients (71.8%). The diagnoses based on EMB comprised myocarditis, sarcoidosis, amyloidosis, hypertrophic cardiomyopathy, restrictive CMP, myocardial infarction, Morbus Fabry, and dystrophinopathy (Figure 1). Myocarditis was the most frequent diagnosis in our study group and was found in 329 (43.6%) patients. Significant myocardial inflammation with signs of cardiomyocyte damage (= active myocarditis) was detected in 10 (3.0%) and without (=borderline myocarditis) in 319 (97.0%) patients. As shown in Table 3, polymerase chain reaction analyses revealed the presence of PVB19 in 163 (51.2%), HHV6 in 74 (23.3%), both PVB19 and HHV6 in 46 (14.5%), and EBV in 14 (4.4%), as well as other combinations and viruses (comprising mainly adenoviruses and enteroviruses) in 21 (6.6%) patients. In 213 (28.2%) patients, there were no unequivocal diagnostic histopathological findings for the above-mentioned diseases. However, in 112 (14.8%) of these patients, histopathological findings in association with clinical data (increased LV diameters and reduced LV ejection fraction with diffuse impairment) were suggestive of (nonischemic) dilated cardiomyopathy.

Positive diagnostic EMB results were obtained significantly more often in those patients who underwent biventricular EMBs (79.3%), as compared to those who underwent either selective LV-EMB or selective RV-EMB (both 67.3%; P<0.001). This resulted mainly from a more frequent diagnosis of myocarditis and/or virus genome presence in biventricular EMBs (71.1%), compared to either selective LV-EMB or selective RV-EMB (51.3%; P<0.001). In the average, 11.4±2.3 samples were taken per patient in those who underwent biventricular EMBs as compared to only 5.7±1.6 samples in those who underwent either selective LV-EMB or selective RV-EMB (P<0.001).

In patients with selective LV-EMB only (n=265), ≥5 LV samples were taken in 127 of 265 (47.9%), whereas ≥5 LV samples were obtained in the remaining 138 of 265 (52.1%). A final histopathological diagnosis was obtained in LV biopsies in 95 of 127 (74.8%) of those patients with ≥5 LV samples and in 89 of 138 (64.5%) of those with ≥5 LV samples (P=0.08). In the patients who underwent selective RV-EMB only (n=133), ≥5 RV samples were taken in 56 of 133 (42.1%) patients, whereas ≥5 RV samples were obtained in the remaining 77 of 133 (57.9%). Diagnostic information was given from RV biopsy results in 32 of 56 (57.1%) of those patients with ≥5 RV samples and in 43 of 77 (55.8%) of those with ≥5 RV samples (P=1).

Ventricle-Based Analysis of Patients With Biventricular EMB

In order to compare the value of LV-EMB to that of RV-EMB or biventricular EMB to diagnose myocarditis and/or virus genome presence, we further concentrated on those 254 of 357 patients who received an EMB-based diagnosis of myocarditis and/or virus genome presence and had undergone biventricular EMBs (Table 4). The diagnosis of myocarditis and/or virus genome presence in these 254 patients was based on the results of LV-EMB only in 12.6% and of RV-EMB only in 7.1%, whereas myocarditis was observed in both ventricles in 80.3%. Thus, omitting the LV-EMB in these patients would have resulted in missing 12.6% of cases with...
myocarditis and/or virus genome presence, whereas in the case of omitting the RV-EMB, this value would only be 7.1% ($P=0.05$).

In more detail, the presence of myocarditis (203 of 254 patients) was diagnosed only in LV-EMBs in 18.7%, only in RV-EMBs in 7.9%, and consistently in both (LV- and RV-EMB) in 73.4%. Thus, omitting the LV-EMB in these patients would have resulted in missing 18.7% of cases with myocardial inflammation whereas if RV-EMB had been dispensed with, this value would only be 7.9% ($P=0.002$). The presence of virus genomes in the myocardium (181/254 patients) was diagnosed only in LV-EMBs in 16.6%, only in RV-EMBs in 17.1% and consistently in both (LV- and RV-EMB) in 66.3%.

### Presence of LGE in Relation to Histopathological Results

In order to assess the value of LGE in relation to ventricle-based EMB results, we focused on those patients who had undergone biventricular EMBs and in whom CMR data were available ($n=292$; Table 5). CMR-based contrast imaging revealed the presence of LGE in at least 1 myocardial segment in 155 (53.1%) of these 292 patients. The diagnosis of myocarditis and/or virus genome presence based on either LV-EMB and/or RV-EMB results was made in 116 (74.8%) of those 155 patients with any positive LGE. There was no substantial difference in the percentage of biopsy-based diagnoses of myocarditis and/or virus genome presence when patients with LGE in the septal wall were compared to those

### Table 4. Focus on Patients With Histopathological Myocarditis and/or Virus Genome Presence and Combined LV- and RV-EMB ($n=254$)

<table>
<thead>
<tr>
<th>Histopathological Diagnosis Based On</th>
<th>Either Positive LV- or Positive RV-EMB</th>
<th>Only Positive LV-EMB</th>
<th>Only Positive RV-EMB</th>
<th>Positive LV- and RV-EMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis and/or virus genome presence</td>
<td>254 (100)</td>
<td>32 (12.6)</td>
<td>18 (7.1)</td>
<td>204 (80.3)</td>
</tr>
<tr>
<td>Myocarditis ($\geq14$ leukocytes/mm$^2$)</td>
<td>203 (80.0)</td>
<td>38 (18.7)</td>
<td>16 (7.9)</td>
<td>149 (73.4)</td>
</tr>
<tr>
<td>Virus genome presence</td>
<td>181 (71.3)</td>
<td>30 (16.6)</td>
<td>31 (17.1)</td>
<td>120 (66.3)</td>
</tr>
</tbody>
</table>

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**Figure 1.** Examples of histopathological EMB findings in some of our study patients: A, Normal myocardium; B, cardiomyocyte hypertrophy, myofiber disarray and fibrosis indicative of hypertrophic cardiomyopathy; C, cardiomyocyte necrosis and lymphocyte infiltrations indicative of active myocarditis; and D, granulomatous inflammation indicative of cardiac sarcoidosis (A through D, Masson trichrome stain). E, Accumulation of amyloid fibers indicative of cardiac amyloidosis (Congor red staining). F, Electron microscopy demonstrating characteristic concentric lamellar bodies indicative of Morbus Fabry.
with LGE in the free LV wall (78.0% versus 70.1%). We further assessed whether the percentage of diagnostic LV-EMB or RV-EMB results was associated with the distribution pattern of LGE (septal wall versus free LV wall). However, there were no substantial differences in the number of positive diagnostic LV-EMBs, RV-EMBs, or LV- and RV-EMBs when related to the site of LGE (Figure 2).

Biopsy workup led to the diagnosis of myocarditis in 214 out of the 292 patients who had undergone biventricular EMBs and in whom CMR data were available. In 116 out of these 214 patients with biopsy-proven myocarditis, LGE-CMR was positive, indicating a sensitivity of LGE-CMR for the noninvasive diagnosis of myocarditis of only 54.2%. In 56 patients, EMB workup was without a pathological finding. LGE-CMR was negative in 36 of these 56 patients, indicating a specificity of 64.3%.

### Discussion

To the best of our knowledge, this is the first study in which the procedural safety and diagnostic performance of selective LV-EMB, selective RV-EMB, and biventricular EMB were comparatively evaluated in patients with suspected myocarditis or nonischemic cardiomyopathy using state-of-the-art biopsy and pathology analysis techniques. Analyses of LV- and/or RV-EMBs in 755 patients (with 6361 biopsy samples taken in all EMB procedures) revealed a major complication rate for LV-EMB of 0.64% and for RV-EMB of only 0.82%. Thus, both LV-EMB and RV-EMB turned out to be safe procedures. Another major finding of this study was that diagnostic EMB results were obtained significantly more often in those patients who underwent biventricular EMBs (79.3%), compared to those who underwent either selective LV-EMB or selective RV-EMB (67.3%; P<0.001). Finally, there were no substantial differences in the number of positive diagnostic LV-EMBs, RV-EMBs, or biventricular EMBs when related to the site of CMR-based LGE.

### Safety of EMB

It is known that the feasibility and safety of a medical procedure depends, apart from the complexity of the procedure itself and the clinical status of the patient, primarily on the expertise of the conducting institution or person. Therefore, when addressing the feasibility and safety issues of a certain procedure, local experiences have to be compared with appropriate reference institutions. Reported data on the complication risks of EMBs are exclusively based on single-center experiences. The overall complication rate varies between 1% and up to 6% for individual centers taking EMBs mainly from the RV septum, including sometimes large numbers of repetitive procedures in patients after heart transplantation. In these studies, the complication rate associated directly with the biopsy procedure itself varied between 0.28% and 3.3%. The largest series reported today by Holzmann et al comprised 3048 RV-EMB procedures. They found major complications in only 0.12% in the retrospective part of their study and 0% in the prospective part whereas minor complications were observed in 0.20%/5.5% (retrospective/prospective study part) of patients.16 When the study of Holzmann et al is excluded, complication rates published for LV-EMB were considerably lower than for RV-EMB; eg, Mason27 performed 161 LV-EMBs and Frustaci et al5 took 1144 LV-EMBs, and both groups documented a major complication rate of 0% for LV-EMB. These investigators therefore suggested that retrograde LV-EMB might be a safe and reliable alternative to RV-EMB. Moreover, the recently published guidelines of the AHA, the American College of Cardiology, and the European Society of Cardiology also describe LV-EMB as an apros-
appropriate technique in patients with suspected myocarditis. The results of our analysis, which directly compares the safety of both procedures in the same patients, are in line with these aforementioned studies: Both LV- and RV-EMB turned out to be safe procedures, with LV-EMB being slightly safer than RV-EMB with respect to minor complications.

**Diagnostic Performance of EMB**

With this study, we also addressed some other important and so far not sufficiently elucidated issues: (1) Which EMB approach (only RV-EMB versus only LV-EMB versus biventricular EMB) is more appropriate and gives the highest number of diagnostic results? (2) Is the diagnostic performance of EMB improved in EMBs taken from the ventricle demonstrating LGE?

Although both LV- and RV-EMB are safe procedures, both have a nonnegligible complication risk. Obviously, one would prefer to biopsy just 1 ventricle if the diagnostic yield were sufficient and if omitting biopsy of the other ventricle would not result in missing diagnoses. However, the data of the present study suggest that diagnostic EMB results are obtained significantly more often in those patients who undergo biventricular EMBs (79.3%) as compared to those who undergo only selective LV-EMB or selective RV-EMB (67.3%; \(P<0.001\)). This finding may be due to a significantly higher number of biopsy samples taken in patients undergoing biventricular EMBs (11.4±2.3 versus 5.7±1.6 samples; \(P<0.001\)), thereby increasing the diagnostic yield of the procedure.

If one considers only those patients who underwent biventricular biopsy with a similar number of samples taken from both ventricles, myocarditis and/or virus genome presence were found only in the LV in 12.6% and only in the RV in 7.1% (\(P=0.05\)). Thus, 7.1% more diagnoses were obtained by biventricular biopsy as compared to LV biopsy alone, whereas biventricular biopsy yielded 12.6% more diagnoses than RV biopsy alone. The difference in favor of biventricular biopsy was even larger when the detection of myocardial inflammation alone is considered. Omitting the LV-EMB would have resulted in missing 18.7% of cases with myocardial inflammation, whereas leaving out the RV-EMB would have missed 7.9% of patients with inflammatory disease (\(P=0.002\)). Considering the therapeutic and prognostic relevance of myocardial inflammation in EMBs as recently demonstrated by Frustaci et al and Kindermann et al, valuable diagnostic EMB data will be missed if biopsies are taken only from 1 ventricle and particularly if taken only from the RV. Therefore, we suggest that (1) biventricular

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**Figure 2.** Examples of 3 patients with clinical suspicion of myocarditis are shown in comparison. CMR images show a long-axis late LGE image whereas biopsy images include histological (Masson trichrome stain) as well as immunohistochemical (CD68+ macrophages and CD3+ T-lymphocytes) results of each patient. Patient A shows a rim pattern of LGE in the anteroseptal segment and a subepicardial pattern in the inferolateral wall indicative of myocarditis. However, Masson trichrome and CD68+ staining do not show any significant pathological findings. In contrast, patient B shows no LGE at all. However, Masson trichrome staining reveals irregularly sized cardiomyocytes with diffuse interstitial fibrosis, and CD68+ and CD3+ staining demonstrates the presence of inflammatory cells (red arrows) indicative of myocarditis. Patient C demonstrates scarce focal areas of LGE in the apical free lateral wall and severe active myocarditis with cardiomyocyte damage and accumulation of inflammatory cells.
biopsies have a higher diagnostic yield compared to selective biopsies and (2) LV-EMB should be preferred if minimizing the length of the procedure is a consideration, given that LV-EMB gives a higher diagnostic yield as compared to RV-EMB while having a lower risk for minor complications.

**Diagnostic Relevance of a CMR-Guided Biopsy**

The aforementioned conclusions with respect to the ideal biopsy approach were made without considering additionally available CMR data. CMR is now widely used for workup of ischemic and nonischemic cardiomyopathy and particularly for evaluation of myocarditis, as it is a completely noninvasive tool. CMR was also shown to yield similar results as EMB in patients with troponin-positive acute chest pain in the absence of significant coronary artery disease. Moreover, CMR has been proposed as a tool to direct EMB. A small study from Stuttgart suggested that the diagnostic performance of EMB might be increased when biopsies were obtained from the region of LGE. Most often, LGE is found either in the interventricular septum, which is best reached by the bioprome from the right side, or in the posterolateral LV wall to which the bioprome is automatically directed after its passage through the aortic valve in case of LV-EMB. Although obtaining EMBs exactly from the region of LGE could indeed result in an even higher number of positive diagnoses of myocarditis, an important caveat has to be remembered: The area of LGE may be small and consequently cannot exactly be reached by the bioprome because of the limited steerability of the bioprome. Therefore, obtaining EMBs exactly from the region of LGE may sometimes be a nonachievable goal. Consequently, our current routine clinical approach is to preferentially take EMBs in a standardized procedure from the ventricle demonstrating LGE but not only from the “area” of LGE.

It was hypothesized, on the basis of results of an earlier study, that the diagnostic yield of EMB might be increased if EMBs were obtained from the ventricle demonstrating LGE. Because data from 116 patients who had undergone biventricular EMBs (with histopathological diagnosis of myocarditis) in addition to a CMR study (showing LGE) were available in the current study, we were able to analyze the distribution of LGE (in the septal or LV free wall) in relation to the EMB results in a larger number of patients than previously studied. Surprisingly, there were no substantial differences in the number of diagnostic LV-EMBs, RV-EMBs, or LV- and RV-EMBs when related to the site of LGE, disproving our hypothesis.

Because LGE is a nonspecific sign of myocardial damage and only indicates an increase in extracellular space (which may be due to acute necrosis as well as chronic fibrosis), the lack of diagnostic improvement in biopsies obtained from the ventricle showing LGE may be due to the potential detection of LGE in patients with already healed myocarditis (without any inflammatory infiltrates left). Thus, EMB workup focusing on the presence of inflammatory cells (the presence of fibrosis was noted but not quantified) may result in nonpathological or nondiagnostic findings in such patients, whereas CMR may be indicative of myocarditis because of the presence of LGE. Consequently, a CMR-guided biopsy in such patients would not increase the diagnostic yield but would decrease the specificity of the CMR procedure for the diagnosis of myocarditis when the EMB procedure is considered the gold standard.

In addition to our inability to confirm the value of LGE-CMR for guiding EMB to areas with a higher inflammatory activity, we also found a limited diagnostic accuracy for LGE-CMR in the present study. The sensitivity of LGE-CMR for the noninvasive diagnosis of myocarditis was only 54.2% in this study and the specificity of LGE-CMR was only 64.3%. This is in line with the recently published consensus article for CMR-based diagnosis of myocarditis stating that “LGE showed a variable sensitivity to detect active or chronic inflammation” and also that “active myocarditis may not always lead to large enough regions of necrotic myocytes to be visually detectable” with LGE-CMR. Therefore, our results support the combined use of different CMR protocols for an improved CMR evaluation of myocarditis.

**Study Limitations**

Obviously, this was a retrospective analysis of 755 patients who underwent EMB at 2 centers for different clinical indications. However, the EMB procedure was performed in the same way in all of these patients, and 357 (47.3%) patients underwent standardized biventricular EMBs. Therefore, this is the first study enabling a direct comparison of procedural safety between LV-EMB and RV-EMB.

When comparing the risk for complications between different studies, the average disease severity of the studied population and the technique applied for sampling of biopsies have to be carefully considered. In this regard, the patient population in our study was probably on average less ill than, for example, those patients who were enrolled in the multicenter Myocarditis Treatment trial because of our broader inclusion criteria (in particular before the publication of the scientific statement from the AHA, the American College of Cardiology, and the European Society of Cardiology on the role of EMB in the management of cardiovascular disease in 2007). In addition, as described in detail in the online-only Data Supplement, our methodological approach in collecting EMBs was different compared to the techniques applied in previous studies (eg, those performed in the United States), with respect in particular to the bioprome used for sampling EMBs.

We would like to emphasize that our study group included a nonnegligible fraction (~30%) of patients with relatively recent onset of or worsening symptoms, whereas the recently published Tailored Immunosuppression in Inflammatory Cardiomyopathy study, which suggested the high efficacy of immunosuppressive therapy in patients with biopsy-proven inflammatory cardiomyopathy, included only patients with chronic stable heart failure (lasting ≥6 months). Thus, it has to be carefully evaluated whether the convincing therapeutic implementations of the Tailored Immunosuppression in Inflammatory Cardiomyopathy study will also be appropriate in patients with relatively recent onset of symptoms.

Another potential limitation of this study is the fact that our CMR workup of myocarditis and/or cardiomyopathy was solely based on LGE imaging. As stated previously, hyper-
emia- and edema-detecting sequences did not work on the scanners of both study centers at the time when the majority of this patient group was examined. Theoretically, the additional application of such sequences should increase the sensitivity and specificity of CMR, and in particular enable the differentiation between acute and chronic myocardial damage. It will be worthwhile to evaluate in future studies whether CMR-guided biopsy results in an increased diagnostic yield if one focuses only on patients with CMR results suggestive of acute myocardial damage.

Conclusions

Both LV-EMB and RV-EMB are safe procedures with a low complication rate if performed by experienced interventionists. On the basis of our experience, LV-EMB was safer than RV-EMB because more minor complications were observed in RV-EMB. In this population, the diagnostic yield of EMB was higher in biventricular EMB compared to selective univentricular EMB and was higher in LV samples in patients with biventricular biopsy than in RV samples. The number of positive diagnoses of myocarditis was not higher in samples from the ventricle exhibiting LGE by CMR.

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Disclosures

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References


CLINICAL PERSPECTIVE

Several recent clinical trials have demonstrated the therapeutic and prognostic benefits of EMB-based diagnoses such as myocarditis and other nonischemic cardiomyopathies. However, EMB is an invasive procedure with a nonnegligible risk of complications, and therefore its clinical use has been controversial. In the present study, the procedural safety and diagnostic performance of selective LV-EMB, selective RV-EMB, or biventricular EMB were comparatively investigated for the first time in patients with suspected myocarditis or nonischemic cardiomyopathy, using state-of-the-art techniques for sampling of biopsies as well as postprocedural histopathological workup of specimens. In addition, the role of CMR as a noninvasive tool in diagnosing inflammatory and several noninflammatory cardiomyopathies as well as in guiding EMB was evaluated. Analyses of LV- and/or RV-EMBs in 755 patients revealed a major complication rate for LV-EMB of 0.64% and for RV-EMB of only 0.82%. Thus, both LV-EMB and RV-EMB turned out to be safe procedures. Moreover, on the basis of the results of this study, (1) biventricular biopsies have a higher diagnostic yield compared to selective biopsies and (2) LV-EMB gives a higher diagnostic yield compared to RV-EMB while having a lower risk for minor complications. Finally, there were no substantial differences in the number of positive diagnostic LV-EMBs, RV-EMBs, or biventricular EMBs when related to the site of CMR-based LGE. As suggested by a recently published consensus article for CMR-based diagnosis of myocarditis, the combined use of different CMR protocols for an improved CMR evaluation of myocarditis is recommended.

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Comparative Evaluation of Left and Right Ventricular Endomyocardial Biopsy: Differences in Complication Rate and Diagnostic Performance

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**Technical Description:**

**Description of catheter-based endomyocardial biopsy approach in the left and right ventricles**

For sampling of biopsy specimens, a right or left femoral access was used to introduce a guiding sheath (7F, Cordis, The Netherlands in Stuttgart) or a guiding catheter (7F, LA7-JR40/AL10/JL40, Medtronic, Danvers, Mass in Homburg) after intravenous infusion of 2.500 IE heparin. A long sheath with angulated tip was introduced through the femoral vein and used for RV-EMB while a long sheath with straight tip was introduced through the femoral artery and used for LV-EMB.

Biopsy specimens were taken using a disposable dedicated cardiac bioptomes (either a Meiners™ bioptome (B-18110, Meiners Medical Systems, Germany) in Stuttgart or a Maslanka bioptome (EH1518.01-A, H. + H. Maslanka, Tuttlingen, Germany) in Homburg; see attached image of different bioptomes for comparison below). The cardiac biopsy forceps Maslanka bioptome which is used in Homburg has a pliable shaft with a length of 120 cm and two cutting jaws with a cup diameter of 1.8 mm each. In contrast to the modified Stanford Caves-Schultz bioptome which has a single cutting jaw and circular cups (available diameters 2.0-2.8mm) the Maslanka bioptome has dual moving jaws and cups with a superelliptic cutting profile. The shaft of the Maslanka bioptome shows full flexibility over the whole length while the Stanford Caves-Schultz bioptome is formable only at the distal curve. The single moving jaw of the Stanford Caves-Schultz bioptome is actuated by a surgical forceps which is affixed to its proximal end while the Maslanka bioptome is operated by a handle consisting of a thumb ring and slider. There are no major differences between the Meiners™ bioptome and the Maslanka bioptome.

Left ventricular biopsy is performed under heparinization with UFH and an activated clotting time (ACT) target level of 150sec which is usually accomplished by a single bolus of 2.500 IE of UFH. In Homburg, the EMB procedure starts with a 7F JR4 coronary guiding catheter which is passed retrogradely through the aortic valve into the left ventricle using a standard J tip guide wire whereas in Stuttgart a long guiding sheath (7F, Cordis, The Netherlands) with a straight tip is introduced into the left ventricle in the same way. With the JR4 guiding catheter the inferior, posterior, lateral and apical
segments of the left ventricle can be reached. For biopsy of the anterior segments an AL1 guiding catheter is sometimes more helpful. In order to reach the left ventricular septum, in most cases a JL4 guiding catheter must be chosen. Before insertion the bioptome is bent smoothly in its distal part to enhance flexibility and to decrease the risk of perforation. Then the bioptome is advanced through the guiding catheter (or guiding sheath in Stuttgart) into the left ventricle under biplane fluoroscopic control (30° RAO and 60° LAO) which helps to guide the tip of the catheter to the target area. Care is taken that the jaws of the bioptome are opened within the left ventricular cavity before close wall contact is reached. Upon reaching wall contact with the opened jaws we exert as much pressure as needed to produce a smooth curve at the end of the guiding catheter and the bioptome. Usually close wall contact is accompanied by a series of ventricular premature beats. Then the biopsy specimen is taken from the wall region of interest. After each biopsy aspiration of blood from the guiding catheter and rinsing with heparinised sodium chloride solution is performed to prevent clotting.

For right ventricular biopsy, a 7F JR4 guiding catheter is advanced over a J tip guide wire into the right ventricle in Homburg whereas a long sheath with angulated tip is used in Stuttgart. Under fluoroscopic control at 60° LAO the tip of the guiding catheter or guiding sheath is steered backwards to the spine in order to reach a septal position. Then the bioptome is advanced and the biopsies are taken from the septum.
Supplemental Figure Legend:

Upper image shows the Maslanka bioptome (EH1518.01-A, H. + H. Maslanka, Tuttlingen, Germany) which is used in Homburg for invasive sampling of endomyocardial biopsies (EMB). Lower image shows the Meiners™ bioptome (B-18110, Meiners Medical Systems, Germany) which is used in Stuttgart for sampling of EMBs.