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Safety of Endomyocardial Biopsy in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

A Study Analyzing 161 Diagnostic Procedures

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Objectives The aim of the present study was to assess the feasibility and safety of target-directed sampling of right ventricular (RV) endomyocardial biopsies (EMB) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Background EMB is an integral part of the diagnostic evaluation of ARVC. Due to safety concerns, EMB are often obtained from the RV septum, which is usually spared from characteristic alterations. At our institution, EMB in ARVC patients were sampled target-directed from predilection areas and areas with abnormal contraction.

Methods Under fluoroscopic guidance, 3,777 EMB samples from 6 different RV sites were obtained in 482 patients who were evaluated for unclear cardiomyopathy (n = 280; 58%), assumed myocarditis (n = 59; 12%), or unexplained ventricular tachyarrhythmias (n = 143; 30%). Complication rates were compared with those from exclusively septal EMB procedures (n = 2,321) in 271 patients after heart transplantation (HTx).

Results Overall, no procedure-related deaths or sustained ventricular tachyarrhythmias occurred. A pericardial effusion was reported in 6 of 161 patients with the final diagnosis of ARVC (3.7%) needing no further intervention in all but 1 patient (0.6%) who required pericardiocentesis. Among the non-ARVC patients (n = 321), the incidence of a minor pericardial effusion (3.9%) and cardiac tamponade (2.2%) was comparable to that in ARVC (p = NS) but was higher when compared with HTx ($p < 0.001$). A transient complete atrioventricular block occurred in 1 of 321 non-ARVC (0.3%) and 2 of 271 HTx patients (0.1%).

Conclusions Multisite target-directed EMB sampling in ARVC is a safe procedure when performed by experienced interventionalists. The procedure-related complication rates were low and comparable to those in other cardiomyopathies. (J Am Coll Cardiol Intv 2011;4:1142–8) © 2011 by the American College of Cardiology Foundation

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inheritable disease accounting for ventricular tachyarrhythmias and sudden cardiac death in a young population (1). Localized rather than diffuse atrophy, predominantly of the right ventricular (RV) free wall myocardium, with subsequent replacement by fibrous and fatty tissue mainly of the RV outflow tract, the right ventricular apex, and the inflow tract (subtricuspid region) represent the histopathological hallmarks of ARVC. The RV septum is usually spared. A left ventricular involvement is frequent but clinically unapparent until advanced stages of the disease.

Despite the proposed list of major and minor criteria (2), clinical diagnosis of ARVC in the absence of 1 single diagnostic test (3) remains a true challenge. In the modified version of the Task Force criteria, evidence of fibrofatty replacement on endomyocardial biopsies (EMB) still is considered as a major criterion (4). Target-directed EMB sampling from predilection areas of the RV as well as from areas with regional RV wall motion abnormalities in patients with ARVC is yet perceived to carry an increased risk of perforation, given the reduced thickness of the RV free wall with additional structural alterations due to fibrofatty replacement and only scarce residual viable myocardium. However, histological confirmation of ARVC is crucial in patients with suspected ARVC in whom noninvasive evaluation remains inconclusive. Therefore, we analyzed the procedure-related complications in a large cohort of ARVC patients who were studied at our institution.

Methods

Study patients. The EMB procedures were performed according to current guidelines in patients who were transferred to our institution for diagnostic evaluation of unclear cardiomyopathy (n = 280; 58%), assumed myocarditis (n = 59; 12%) (Table 1) (5–8), or unexplained ventricular tachyarrhythmias (n = 143; 30%). Written informed consent was obtained before EMB sampling in all patients.

After careful and detailed investigations, diagnosis of ARVC was made in 161 patients. All non-ARVC patients were subsumed under control Group-1 (control-1) (Table 1). We analyzed the procedure-related in-hospital complications in this patient cohort and compared the results with those that occurred in the course of exclusively septal EMB procedures in 271 heart-transplant recipients (HTx) (mean age 51 ± 13 years) (Table 1). These patients served as a second control group (control-2), because septal EMB in HTx patients are considered to carry a lower risk of major complications (9).

A major EMB-related complication was defined as periprocedural death, sustained ventricular tachyarrhythmias (i.e., lasting >30 s or requiring cardioversion for hemodynamic instability), complete atrioventricular (AV) block, or pericardiocentesis due to cardiac tamponade. Pericardial effusion (PE) with no need for further intervention/treatment was defined as a minor complication.

RV EMB. Right ventricular EMB was performed under fluoroscopic guidance during diagnostic right heart catheterization (5). For femoral vein approach, a 7-F long sheath (96 cm; Cordis, Haan, Germany) was placed in the RV and a 1.8 × 1,000 mm bioptome (Pilling Weck, Karlstein am Rhein, Germany) was used for EMB sampling. For jugular vein approach, an 8-F introducer sheath (11 cm, diameter 2.7 mm; Cordis) with a 1.8 × 510 mm bioptome (Teleflex Medical, Tuttlingen, Germany) was employed. In ARVC (99%) and in control-1 patients (96%), the right femoral vein was the most commonly used access site, in contrast to the predominantly internal jugular vein approach in HTx patients (91%).

To ensure target-directed positioning of the bioptome, standard fluoroscopic view angles of 30° right anterior oblique and 60° left anterior oblique projection were adjusted for the EMB procedure. The integrated information from all available imaging techniques (cardiac magnetic resonance imaging and 2-dimensional transthoracic echocardiography) was used for the planning of target-directed RV biopsy sampling.

Besides continuous electrocardiographic recording, right atrial as well as RV pressure were recorded before and immediately after biopsy sampling to detect a potentially impending cardiac tamponade. A transthoracic 2-dimensional echocardiogram was additionally performed after the biopsy procedure and before discharge.

Abbreviations and Acronyms

ARVC = arrhythmogenic right ventricular cardiomyopathy
AV = atrioventricular
EMB = endomyocardial biopsy
HTx = heart transplantation
PE = pericardial effusion
RV = right ventricle/ventricular

Technique of RV EMB sampling. The bioptome jaws were opened just outside the long sheath, and the RV wall was approached with jaws open to avoid both distension and perforation of the trabecular system and of the RV free wall (Fig. 1). The jaws were closed after stable contact with the RV wall was established; EMB samples were retrieved. Finally, the bioptome and the long sheath were removed from the RV. This protocol was developed by our group and applied in 2 large multicenter, multinational registries and studies funded by the European Union and the National Institute of Health (10,11). Biopsies were fixed in prespecified media according to the destined further analyses. These included formalin (histology), glutaraldehyde (electron microscopy), and liquid nitrogen (molecular biology).

Results of histological semiquantitative analyses of biopsy specimen were defined as "normal" in case they did not reveal any pathological alterations, "unspecific" if abnormal histological findings—such as isolated fatty replacement, mild interstitial fibrosis, or lymphocytic cell infiltration, which are considered compatible but nonspecific for the

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Table 1. Clinical and Procedural Characteristics of Study Patients

	All Patients	ARVC	RV Diseases/CMP (Control-1)	HTx (Control-2)	p Value
Demographic data					
Male	753 (68)	161 (71)	321 (56)	271 (81)	
Age, yrs	46 ± 15	45 ± 14	43 ± 15	51 ± 13	<0.001
EMB sampling					
EMB procedures	2,803 (100)	161 (6)	321 (11)	2,321 (83)	
Total RV biopsy samples	14,258 (100)	1,305 (9)	2,472 (17)	10,481 (74)	
Number of RV biopsy samples/patient	5 (4–8)	6 (4–12)	7 (4–10)	4 (3–5)	<0.001
Nonseptal sites for EMB sampling	0 (0–2)	2 (1–3)	1 (0–2)	0 (0–0)	<0.001
Complications/procedure					
Death	0	0	0	0	
Sustained ventricular tachyarrhythmias	0	0	0	0	
Complete AV block	3 (0.1)	0*	1 (0.3)*	2 (0.1)	0.53
Total PE	36 (1.3)	6 (3.7)*	17 (5.2)*	13 (0.6)	<0.001; 0.51*
Major PE†	8 (0.3)	1 (0.6)*	7 (2.2)*	0	<0.001; 0.21*
Minor PE‡	28 (1.0)	5 (3.1)*	10 (3.1)*	13 (0.6)	<0.001; 1.0*
Complications/RV biopsy samples					
Death	0	0	0	0	
Sustained ventricular tachyarrhythmias	0	0	0	0	
Complete AV block	3 (0.02)	0	1 (0.04)	2 (0.02)	NS
Total PE	36 (0.2)	6 (0.5)*	17 (0.7)*	13 (0.1)	<0.001; NS*
Major PE†	8 (0.06)	1 (0.08)*	7 (0.3)*	0	<0.001; NS*
Minor PE‡	28 (0.2)	5 (0.4)*	10 (0.4)*	13 (0.1)	<0.01; NS*

Values are n (%), mean ± SD, or median (interquartile range). *Subgroup comparison: arrhythmogenic right ventricular cardiomyopathy (ARVC) versus right ventricular (RV) diseases/cardiomyopathy (CMP) (Control-1). †Requiring pericardiocentesis/drainage due to hemodynamic instability. ‡Requiring no further intervention/treatment.

AV = atrioventricular; EMB = endomyocardial biopsy sampling; HTx = heart transplantation; PE = pericardial effusion.

histological diagnosis of ARVC were present—and "indicative" in case histological findings were specific for ARVC according to current criteria (4).

Statistical analysis. Differences of metric target variables between groups were assessed by parametric methods (analysis of variance, Student *t* test) or nonparametric methods (Kruskal–Wallis test, Mann–Whitney *U* test) as appropriate. In case of binary target variables, the chi-square-test was used, and p values <0.05 were regarded as significant. Data are expressed as mean ± SD or median (interquartile range) where applicable (SPSS; version 16.0 for Windows, SPSS, Inc., Chicago, Illinois).

Results

Patient characteristics. To assess the procedure-related complications of multisite target-directed EMB in patients with ARVC in relation to the 2 control groups (Table 2), major and minor adverse events were analyzed for the entire study population as well as for different groups according to the final clinical diagnosis of the patients (Table 1). Among these were 161 patients with ARVC (21%) and 271 patients (36%) after HTx (control-2). Control Group-1 comprised 321 patients (43%), including 108 patients with dilative cardiomyopathy (34%), 11 patients with hypertrophic cardiomyopathy (3%), 59 patients with acute suspected or confirmed myocarditis (18%), 48 patients with Brugada syndrome (15%), 6 patients with long QT syndrome (2%), 19 patients with idiopathic ventricular fibrillation (6%), and 70 patients with RV outflow tract (22%).

In the overall cohort of 2,803 procedures, 51% of procedures (n = 2,119) were performed by 7 interventionalists with experience of more than 100 RV EMB procedures (range n = 111 to 442). Interventionalists with experience of more than 25 RV biopsy procedures (range: 25 to 66) performed 19% of procedures (n = 529 procedures), and the low number of remaining procedures (n = 155; 5%) was performed by interventionalists with less training in EMB sampling who were supervised by an experienced proctor in this field.

Accordingly, in the 161 RV EMB procedures in ARVC patients, 66% were performed by 3 interventionalists with experience in 10 or more biopsy procedures in ARVC (range 10 to 86). The remaining ARVC biopsy procedures were performed by interventionalists with less experience in ARVC but extended expertise in biopsy sampling in other cohorts. Given that biopsy procedures were performed only by experienced interventionalists, the event rates of compli-

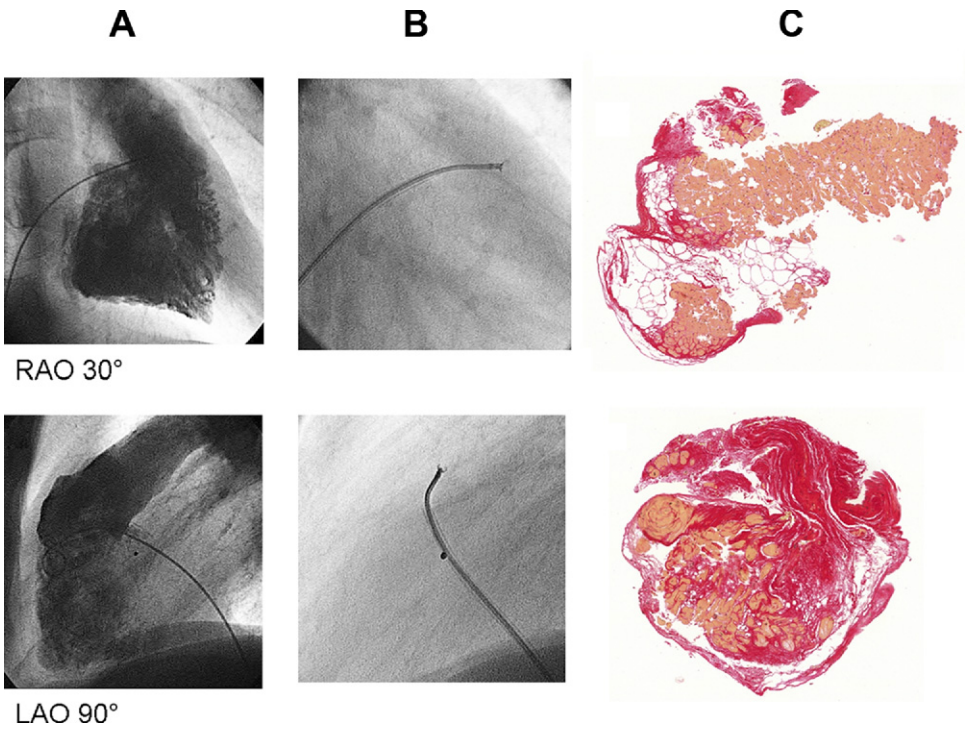

Figure 1. Example of RV Endomyocardial Biopsy Sampling With Corresponding Histopathology

Right ventricular (RV) angiogram of a patient with arrhythmogenic RV cardiomyopathy depicting regional RV dyskinesia (in a right anterior oblique [RAO] 30° and left anterior oblique [LAO] 90° projection) **(A)**, and the corresponding positioning of the bioptome in the same fluoroscopic projection **(B)**. Sampling in this area resulted in histological findings with fibrofatty replacement of RV myocardium diagnostic for arrhythmogenic RV cardiomyopathy. **(C)** Sirius red staining, 10-fold magnification.

cations were low in both the overall cohort and the ARVC subgroup and did not allow a useful correlation with individual extent of investigator experience.

Semi-quantitative histological analyses of RV biopsy specimen demonstrated indicative results in 82 of 161 patients (51%) with ARVC according to the current histological criteria (4) (Fig. 1). In 53 of 161 patients (33%), abnormal histological findings—such as isolated fatty replacement, mild interstitial fibrosis, or lymphocytic cell infiltration, which are considered compatible but nonspecific for the histological diagnosis of ARVC—were present. Only in 26 of 161 patients (16%) were no

Table 2. Localization of EMB Sampling in Study Patients

	All Patients	ARVC	RV Diseases/CMP (Control-1)	HTx (Control-2)	p Value
Patients	753	161	321	271	
Total EMB procedures	2,803 (100)	161 (6)	321 (11)	2,321 (83)	
Location of RV biopsy sampling					
Number of different RV EMB sampling locations	1 (1–1)	3 (2–4)	2 (1–3)	1 (1–1)	
Septum	2,784 (99)	154 (94)	309 (96)	2,321 (100)	0.805
Inferior	52 (2)	26 (16)	26 (8)	0	0.008
Supra-apical	229 (8)	111 (69)	118 (37)	0	<0.01
Free wall	16 (1)	7 (4)	9 (3)	0	0.422
Outflow-tract	245 (9)	106 (66)	139 (43)	0	<0.01
Anterior	97 (4)	46 (29)	51 (16)	0	<0.01

Values are n, n (%), or median (interquartile range). The reported p values refer to the comparison of the ARVC group versus RV diseases/CMP (Control-1).

Abbreviations as in Table 1.

histological abnormalities detectable, indicating a sampling error due to several potential reasons (i.e., missed area, minor disease expression, non-subendocardial disease manifestation not accessible for RV EMB). These data demonstrate a high diagnostic yield and efficacy of target-directed RV biopsy sampling (including RV free wall and predilection areas) in comparison with conventional RV septal sampling in patients with ARVC.

Major procedure-related complications of EMB. There were no procedure-related deaths or sustained ventricular tachyarrhythmias requiring intervention. A transient complete AV block occurred in 3 patients (Table 1): in 2 HTx patients it resolved spontaneously; 1 control-1 patient with the final diagnosis of hypertrophic cardiomyopathy required temporary cardiac pacing due to hemodynamic relevant bradycardia. After recovery of conduction, the transient pacemaker lead was removed at the end of the invasive procedure before the patient was referred to the intermediate care unit. No further episodes of conduction abnormalities or AV block occurred during the in-hospital monitoring phase or during a 3-month follow-up.

Cardiac perforation with hemodynamic relevant tamponade necessitating immediate pericardiocentesis occurred in 8 patients (Table 1). Among these were 1 patient with ARVC and 7 control-1 patients. No control-2 patient experienced cardiac tamponade. Pericardiocentesis was performed with a standard technique with subxiphoidal percutaneous access and insertion of a 5-F pigtail catheter into the pericardial space for drainage. In all patients, the pigtail catheter inserted in the pericardial space could be removed within 48 h after there was no additional drainage. No patient required surgical intervention. However, as a complication of the pericardiocentesis, 1 patient (control-1) developed a small seropneumothorax, which resolved spontaneously.

Minor procedure-related complications of EMB. The incidence of minor PE was identical between patients with ARVC and control-1 (3.1%/EMB procedure; 0.4%/EMB samples) (Table 1). In patients after HTx, septal EMB sampling resulted in a lower rate (0.6%/total control-2 EMB procedures; 0.1%/total control-2 EMB samples) (Table 1).

Discussion

Target-directed multisite sampling of EMB in patients with ARVC is perceived to carry a higher risk of major adverse events, such as myocardial perforation. In our analysis of 161 EMB procedures, sampling of RV biopsies from predilection areas in ARVC patients was not associated with an increased rate of major complications in comparison with other diseases when performed by experienced interventionalists following a precise and dedicated protocol (Online Appendix).

Even though EMB in patients with ARVC were obtained from multiple RV sites, including the RV free wall (Table 2), only 1 hemodynamic relevant tamponade requiring immediate pericardiocentesis occurred (0.6%/total ARVC EMB procedures; 0.08%/total ARVC EMB samples) (Table 1). A search of the Medline database (National Library of Medicine, Bethesda, Maryland) for comparable studies reporting on endovascular EMB in ARVC (query terms: "ARVC endomyocardial biopsy" and "ARVD endomyocardial biopsy"; prerequisites: English language, >15 patients, published within the last 15 years, and EMB obtained in vivo) identified 8 studies comprising a total of 233 patients (12–19) (Table 3). Information on the number of RV biopsies (13,14,18,19) and the EMB sampling site were available in 4 studies (50%) (14,15,18,19) (Table 3). In these, the number of EMB/patient was lower, and EMB were sampled only from the RV septum when compared with our study (Table 3). Severe adverse events were not mentioned.

The overall incidence of major complications (i.e., death, sustained ventricular tachyarrhythmias, complete AV block, cardiac tamponade) in the present study is low (n = 11 patients; 0.4%/total EMB procedures; 0.08%/

Table 3. Synopsis of Studies, Including EMB in ARVC Patients Obtained Via an Endovascular Access

First Author (Ref. #)	Yr of Publication	Patients With EMB, n	Different EMB Sites, n	RV Site	Number of EMB	Complications*
Menghetti et al. (12)	1996	9	NA	NA	NA	NA
Valente et al. (13)	1998	20	1	Sept	NA	NA
Turrini et al. (14)	1999	38	1	Sept	98	NA
Calabrese et al. (15)	2000	20	NA	NA	120	NA
Nava et al. (16)	2000	47	NA	NA	NA	NA
Folino et al. (17)	2002	46	NA	NA	NA	NA
Basso et al. (18)	2006	21	1	Sept	2 ± 1/patient	NA
Cho et al. (19)	2007	32	1	Sept	5–7/patient	NA
Present study	2011	161	6	Sept, Inf, A, FW, OT, Ant	9 ± 5/patient	1 (0.6%)†
		Σ = 394				

*Defined as death, sustained ventricular tachyarrhythmias, complete AV block, or cardiac tamponade requiring pericardiocentesis/drainage. †Calculated for total ARVC EMB procedures.
A = supra-apical; Ant = anterior; FW = free wall; Inf = inferior; NA = not available; OT = outflow-tract; Sept = septum; other abbreviations as in Table 1.

total EMB samples) (Table 1). However, when comparing these results with available data from the published reports (5), one might be aware that these studies are based on observations recorded from exclusively septal EMB procedures.

Deckers et al. (20) reported a higher percentage of "definite perforations" (n = 3 patients; 0.5% of all procedures) in their survey of 546 diagnostic septal procedures resulting in the death of 2 of these patients in comparison with our findings with no sequelae (0.3%) (Table 1). In a recent larger single center study on septal EMB procedural complications in patients with suspected or confirmed myocarditis, the number of complete AV block (n = 13; 0.5%/EMB procedures) was higher and the number of pericardial tamponade (n = 2; 0.1%/all EMB procedures) was slightly lower when compared with ours (Table 1) (21). Although Yilmaz et al. (22) very recently reported a higher rate of cardiac tamponade (n = 4 of 490 [0.82%]) after RV-EMB.

The occurrence of a hemodynamically insignificant PE as a minor complication was comparable between patients with ARVC and control-1 patients (p = NS) (Table 1) as well that reported by others (0.7% [21]).

The reason for the low complication rates in the present study might be based in both the dedicated biopsy protocol (Online Appendix), which was meticulously followed, and the experience of the interventionalists who performed the procedure.

Study limitations. Because this topic is a major issue of concern, our analysis specifically assesses the feasibility and safety of RV EMB sampling. Data on the semiquantitative analyses of the RV specimen in our ARVC patients underscore that, with a target-directed EMB, the diagnostic yield of EMB in patients with suspected ARVC can significantly be improved (23–25). Yet this is beyond the primary scope of this manuscript, and results of quantitative analyses will be reported in detail elsewhere.

In the present study, 43 different experienced interventionalists performed the EMB sampling. In ARVC patients this was predominantly done (86 of 161 EMB procedures [53%]) by 1 investigator (T.W.), which might contribute to the overall low complication rate; however, 47% of the procedures in patients with ARVC were done by different cardiologists over a period of time.

Conclusions

Multisite and target-directed EMB sampling, including the predilection areas of the RV free wall in patients with ARVC, is a safe procedure when performed by experienced interventionalists. The procedure-related complications were low and comparable to those in other RV diseases. These findings might alter the policy of EMB procedures in ARVC, thereby potentially improving its diagnostic utility.

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Key Words: arrhythmogenic right ventricular cardiomyopathy ■ cardiac tamponade ■ complications ■ endomyocardial biopsy ■ pericardial effusion.

APPENDIX

For supplementary material, please see the online version of this article.