Right from the heart: when should myocardial biopsy be performed for suspected arrhythmogenic right ventricular cardiomyopathy/dysplasia?

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This editorial refers to ‘Quantitative assessment of endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy/dysplasia: an in vitro validation of diagnostic criteria’† by C. Basso et al., on page 2760

A host of uncommon but clinically important myocardial diseases including arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) have unique prognoses and treatments and should be strongly suspected in their characteristic clinical scenarios. ARVC/D is an inherited or sporadic form of predominantly right ventricular cardiomyopathy characterized by a progressive loss of myocytes that are replaced by fibrofatty tissue. The typical patient is in their third to fifth decade, and presents with ventricular arrhythmias, palpitations, syncope, or sudden death.1 The ECG may reveal epsilon waves, T-wave inversions, and/or localized QRS complex duration >110 ms in V1–V3. Imaging of the right ventricle by echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) may reveal focal or global dilatation or aneurysm formation.2 Because cardiac sarcoidosis or focal non-compaction syndrome, which have distinct aetiologies and treatments, can share ARVC/D's clinical features, and non-invasive testing can be inconclusive, histological confirmation of ARVC/D is sometimes necessary.

Basso et al. have presented a case series of 300 simulated biopsies, one each from five sites in 60 hearts obtained at transplantation or autopsy.3 They performed endomyocardial biopsy (EMB) on hearts with diffuse or segmental ARVC/D and compared the histological features of hearts from aged, obese, and normal people, and hearts with idiopathic dilated cardiomyopathy. The author’s primary finding is that the degree of residual myocardium from the right ventricular outflow tract, free wall, and apex can reliably distinguish focal and diffuse ARVC/D from these other conditions. In contrast, histology from the right ventricular septum, where myocardial tissue is typically sampled, and the left ventricle cannot distinguish ARVC/D from the comparator conditions. This study adds substantially to the knowledge of ARVC/D by informing us where to biopsy for suspected ARVC/D and what the precise histological criteria should be for diagnosis.

The Basso study used hearts obtained at autopsy or transplantation, presumably from patients with advanced histological disease. Patients in a typical clinical population may present earlier with palpitations or mild heart failure, and have less severe histological disease, which could result in a lower sensitivity of EMB. Because the authors did not include a control group with cardiac sarcoidosis, a typically focal disorder for which EMB has only a 20–30% sensitivity, the ability of EMB to distinguish ARVC/D from cardiac sarcoidosis remains unknown. Although the investigators used a single piece of myocardium from each site to derive their diagnostic criteria, we do not know the amount of myocardium needed to establish the diagnosis of ARVC/D in the clinical setting where several regional inflammatory and non-inflammatory disorders are possible.

Despite its limitations, the Basso study has clearly established that there is no role for right ventricular septal biopsy to establish a diagnosis solely for suspected ARVC/D. The clinician’s choice is either to rely on non-invasive tests to infer the diagnosis or to recommend EMB in the ‘triangle of dysplasia’, that includes the free wall, apex and right ventricular outflow tract. Unfortunately, we do not yet know whether cardiac MRI can ‘guide’ EMB to regions with characteristic histological findings, as has been demonstrated with lymphocytic myocarditis.4

When should EMB be performed in the clinical scenario of suspected ARVC/D? The consensus recommendation in the 2007 AHA/ACCF/ESC scientific statement on the role of EMB in
cardiovascular disease was that the usefulness of EMB in suspected ARVC/D was not well established (class of recommendation IIb, level of evidence C). This recommendation reflected the lack of published data and expert consensus on the safety of EMB in this disorder, and potential benefits of a histological diagnosis of ARVC/D beyond a clinical evaluation and non-invasive imaging. Almost all the reported safety data on EMB at the time of the scientific statement writing came from case series of right ventricular septal biopsies using the relatively stiff Stanford–Caves or similar disposable biotomes. In these series, infrequent but serious procedural risks of EMB included heart perforation, tamponade, and rarely death (~1/1000). The ability of EMB results to improve on a non-invasive risk stratification model that includes presentation with sudden death or syncope, age, and severity or right ventricular involvement amongst other variables was also not established.

The current procedural risks of EMB in suspected ARVC/D are difficult to estimate from the published data for several reasons. The regions of the right ventricle that are most commonly affected by ARVC/D are relatively thin, and most operators avoid removing tissue from these regions based on the untested assumption that the risk of ventricular perforation from biopsy in these regions is high. One serious risk, probable cardiac perforation, may be estimated from the 231 patients in the five published reports and 64 NIH registry probands who underwent EMB (unpublished, but cited in the article of Basso et al.). Out of these 295 patients there were no deaths and only three post-procedural pericardial effusions, yielding a probable perforation rate of ~1 in 100 procedures. This rate is somewhat higher than the rate of 1 in 200–250 procedures for right ventricular septal biopsy, but perhaps not outside the range of acceptable risk. Furthermore, some of the suspected ARVC/D patients in these series had EMB of more than one heart region. The three pericardial effusions may have resulted from perforation at sites sampled outside the triangle of dysplasia. Importantly, the risks of perforation and death may be significantly lower with newer, flexible biotomes with smaller ‘jaws’.

The risks to the patient with suspected ARVC/D include the possibility of an incorrect diagnosis. Correct pathological interpretation requires that a sufficient amount of myocardium be obtained without crush artefact and processed for the necessary histological, immunohistological, and/or molecular diagnostic tests. A pathologist with expertise in the features of primary cardiomypathies is needed to interpret these findings in the overall clinical context. Because of the need for specialized procedural skills and pathological expertise, the 2007 joint scientific statement recommended that the use of EMB for the evaluation of uncommon or rare cardiomyopathies should be limited to medical centres with the necessary expertise.

Because AVRD/C accounts for up to 10% of sudden death in persons younger than age 35, a correct diagnosis can lead to life-saving implantable defibrillator therapy and family screening. Although cardiac magnetic resonance has been reported to have up to a 75% sensitivity and a 97% specificity for ARVC/D, imaging is not always conclusive, and a histological diagnosis sometimes can provide unique and valuable prognostic and therapeutic information. For example, in the author’s experience, histology is sometimes required to distinguish idiopathic granulomatous myocarditis (cardiac sarcoidosis) and sometimes localized ventricular non-compaction from ARVC/D. Immunosuppression, which is commonly used for acute cardiac sarcoidosis, is not indicated for ARVC/D. Twelve genes that primarily encode desmosomal proteins have been associated with ARVC/D. A diagnosis of ARVC/D allows for family screening, genetic testing, and counselling. In the setting of mild right ventricular dysfunction and inconclusive clinical evaluation, normal histology supports a diagnosis of idiopathic ventricular tachycardia, a disorder that can also have left bundle branch morphology but a low risk of sudden death.

The study by Basso et al. serves to highlight several of the gaps in our knowledge of the use of EMB for rare and uncommon cardiomyopathies. We need correlative studies with state of the art imaging and EMB to determine whether histologically proven ARVC/D can be accurately diagnosed by less invasive means. A separate question is whether non-invasive imaging can be used to ‘guide’ biopsy to increase sensitivity and lower risk. Without prospective clinical data, we rely on expert opinion as to whether the additional information gained from histology is worth the cost and risks of EMB.

Histological confirmation of ARVC/D is needed in that group of suspected ARVC/D patients in whom non-invasive evaluation is inconclusive. It is not clear whether all patients with suspected ARVC/D will benefit from EMB. The treating clinician must estimate whether the incremental benefits of a histological diagnosis outweigh the procedural risks of EMB. This decision will always need to factor in variables that are not well represented in the published literature, including patient-specific co-morbidities, the local availability of adequate non-invasive imaging, necessary procedural skills and treatments, or interventions that would be based on the pathological diagnosis. Because the procedural risks, ability to distinguish ARVC/D from clinically similar disorders, and thereby the potential net benefit will vary by patient and by centre, it is not possible to give a single comprehensive practice recommendation for all patients with suspected ARVC/D. To fill some of the key gaps in our knowledge of the role of EMB in suspected ARVC/D will require a multicentre, prospective biopsy-based registry designed to compare a strategy of early EMB with delayed EMB in those cases with indeterminate non-invasive imaging. Such a study could answer the key questions of whether a strategy of early EMB improves clinical outcomes and determine the risks of free wall biopsy using the latest, lowest risk biopsy techniques. For now the level of evidence in support of EMB for suspected ARVC/D remains expert opinion or ‘C’, and the class of recommendation still reflects the overall uncertainty in the net clinical benefit, or ‘IIb’.

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References