1. Myocardial inflammation. Numerous previous reports document myocardial inflammation as a frequent finding (up to 80% of patients) in ARVC (3,4). The authors report, surprisingly, that none of their ARVC patients had accompanying inflammation. Furthermore, the results are not consistent with a recent report from another Italian group investigating autopsy material and explanted hearts in geno-positive ARVC patients (5). That study showed accompanying inflammatory infiltrations in 10 of 10 patients and no evidence of an infective etiopathogenesis (5). Have the authors considered the possibility that the inflammatory infiltrations seen in the "myocarditis" group are part of the ARVC phenotype and that fibrofatty replacements may occur later in the course of the disease? This possible difference in disease development may also explain the benign course seen in the group in the relatively short follow-up period.

2. Viral genome in the myocardium. Five of the 15 patients classified as having myocarditis had the presence of viral genome (parvo B19 virus in 3 cases, influenza virus in 2 cases) in the myocardium documented by PCR. Different viruses may persist in asymptomatic individuals without being pathogenic. A recent report from Italy showed 12 of 19 asymptomatic individuals had detectable parvo B19 deoxyribonucleic acid in their myocardium (6). In addition, ARVC patients may have increased susceptibility of having myocarditis as a secondary phenomenon.

3. Molecular genetics. No mutation screening of desmosomal genes was performed. Given the lack of reference diagnostic modality for ARVC, the frequency of desmosomal mutations in both groups is highly relevant. A positive molecular genetics finding in the "myocarditis" group would reclassify the patient into the "ARVC" group.

Based on the abovementioned observations, the results presented by Pieroni et al. (1) should be confirmed in larger ARVC cohorts with supplementary desmosomal mutation screening.

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Diagnosis of Myocarditis Mimicking Arrhythmogenic Right Ventricular Cardiomyopathy

The Role of Endomyocardial Biopsy Guided by Electroanatomic Voltage Map

Pieroni et al. (1) recently reported a 50% prevalence of right ventricular (RV) myocarditis in a cohort of 30 patients fulfilling standardized diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC). The differential diagnosis between myocarditis and ARVC was obtained by performing electroanatomic mapping of the RV and then focusing, "for the first time," an endomyocardial biopsy (EMB) on selected pathological areas characterized by low-voltage potentials (electroanatomic mapping-guided EMB). Adopting this "novel diagnostic technique," Pieroni et al. (1) significantly modified the initial ARVC diagnosis.

We would like to make some comments regarding this study and its results. First, to the best of our knowledge, this is not the first report describing the electroanatomic mapping-guided EMB since this "novel diagnostic technique" has already been exhaustively described by our group (2,3). In particular, in 2008, we published the first report (3) documenting the feasibility of RV voltage mapping-guided EMB in a series of 16 consecutive patients with clinical evidence or suspicion for ARVC.

Second, contrary to the findings reported by Pieroni et al. (1), in our study (3), we did not observe histological evidence of myocarditis in any of the 16 patients with clinical evidence or suspicion for ARVC, in whom a pathological RV voltage map was documented. Up to now, we have been performing EMB targeting RV low-voltage areas in more than 40 patients with clinical evidence or suspicion for ARVC, and we have never observed evidence of active or borderline myocarditis according to the Dallas criteria. Our findings, in agreement with the observations of Corrado et al. (4), seem logical: since myocarditis usually has a patchy distribution in the heart chambers, it is unlikely to produce solid transmural scars detectable as low-voltage areas with endocardial electroanatomic mapping.

Third, in the study of Pieroni et al. (1), the most frequently involved RV regions (Table 2 of their study), in descending order, were the outflow tract (77%), the anterior free wall (50%), and the postero-inferior wall (43%), whereas the RV apex and the septal wall were less frequently involved (13% and 3%, respectively). Coherently, the authors included in the article 2 RV voltage maps, obtained from representative patients with ARVC (Fig. 2D of their study) and myocarditis (Fig. 3D of their study), both showing...
pathological areas in RV free wall and outflow tract, but normal potentials in the apex. Nevertheless, the authors provided in the article only a fluoroscopic demonstration of biopsy sampling in the RV apex (Fig. 1 of their study) but not a demonstration of biopsy sampling in the RV free wall or outflow tract, as we did in our study (3).

Finally, in the Discussion section, Pieroni et al. (1) stated: “With regard to the safety of the invasive procedure, we must acknowledge that the high experience level of the cardiologist performing the biopsies could have minimized the risks related to this new approach. . . .” In our opinion, this statement is methodologically misleading since, in order to reduce the risk profile of the voltage-guided biopsy procedure, the crucial point is to perform the sampling on the border zone and not on the thinner core of low-voltage areas, as we suggested in our study (3).

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Reply

We thank the 3 different groups for their interest in our recent paper (1). In the first 2 letters, Drs. Thomas and Tavares and Drs. Christensen and Svendsen focus on the potential relationship between myocarditis and arrhythmogenic right ventricular cardiomyopathy (ARVC) and on the role of genetics in clarifying this issue. We agree that this complex “menage a trois” remains an open task, but some findings in our study could shed some light. In the last years, some findings in our study could have minimized the risks related to this new approach. . . .” In our opinion, this statement is methodologically misleading since, in order to reduce the risk profile of the voltage-guided biopsy procedure, the crucial point is to perform the sampling on the border zone and not on the thinner core of low-voltage areas, as we suggested in our study (3).

Finally, in the Discussion section, Pieroni et al. (1) stated: “With regard to the safety of the invasive procedure, we must acknowledge that the high experience level of the cardiologist performing the biopsies could have minimized the risks related to this new approach. . . .” In our opinion, this statement is methodologically misleading since, in order to reduce the risk profile of the voltage-guided biopsy procedure, the crucial point is to perform the sampling on the border zone and not on the thinner core of low-voltage areas, as we suggested in our study (3).

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We agree that genetic analysis could add further information, but this could not be conclusive as we would not be able to exclude the presence of mutations in genes currently not associated with ARVC. Moreover, this approach should be ideally completed by genetic and histologic studies in asymptomatic relatives carrying the same mutation of the probands, but not presenting morphologic, functional, and electrical abnormalities of the RV. In fact, similar to other disorders such as hypertrophic cardiomyopathy, the ideal setting to study the pathophysiology of ARVC and the role of genetic and environmental factors, we think would be represented by large families with more individuals harboring the same genetic defect but showing strikingly different clinical features, ranging from severe arrhythmic manifestations and RV abnormalities, to asymptomatic state in the presence of normal RV. In this context, a complete genetic, electrophysiologic, histologic, ultrastructural (i.e., electron microscopy to evaluate the presence of preclinical desmosomal abnormalities), and virologic evaluation of all carriers of a gene defect could provide crucial data on the pathophysiology of the disease. This kind of study, obviously, raises important ethical concerns regarding the execution of invasive studies in asymptomatic young subjects harboring a gene defect.

In patients with histologic evidence of myocarditis, the significance of viral genome persistence in myocardium is still debated with regard to the pathogenic role of some viruses, in particular parvovirus B19. Nevertheless, in the presence of myocardial inflammation, the persistence of viral genome strongly suggests the association between inflammation and viral infection. On the other hand, the detection of viral genome in myocardium of currently “asymptomatic” patients reported in some studies does not exclude that these subjects experienced some cardiovascular symptoms related to cardiac infection by parvovirus in previous years or rather that genome persistence is the hallmark of a previous self-limiting asymptomatic myocarditis.

In the third letter, Drs. Avella and d’Amati raise some methodological issues, allowing us to further discuss some important aspects of our innovative study.

With regard to the site of execution of EMB, it is important to highlight some relevant issues that distinguish our study from the more-limited imaging characterization adopted by Drs. Avella and d’Amati. At variance with their approach, in our series, all patients underwent cardiac magnetic resonance imaging (MRI) to define RV anatomy and function, and all were submitted to RV angiography before electroanatomic mapping. In particular, this sequence in invasive study allows to obtain maps more accurate than usual, by reaching apical and free wall intertrabecular recesses (visualized