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 complex “menage a trois” remains an open task, but some findings in our study could shed some light. In the last years, some have hypothesized that fibrofatty replacement represents the consequence of myocyte apoptosis induced by right ventricular (RV) myocarditis or that myocardial inflammation whenever observed is a reaction to myocyte apoptosis caused by genetic abnormalities, or rather that myocarditis may superimpose on a genetically abnormal myocardium, possibly accelerating the fibrofatty replacement or even triggering ventricular arrhythmias. In our study, we never observed fibrofatty replacement in endomyocardial biopsies (EMB) of patients with a histological diagnosis of myocarditis, as well as no evidence of inflammatory infiltrates or viral genome was documented in myocardial samples from ARVC patients. Of note, EMB were drawn from electrically abnormal areas, thus it appears unlikely that fibrofatty replacement, not observed in these biopsies, could have been present elsewhere. As observed in the abstract quoted by Drs. Thomas and Tavares, the association of focal inflammatory infiltrates and fibrofatty replacement is frequently observed in autopsy studies when the whole RV is analyzed but is uncommon in EMBs. In a recent elegant study by the Padua group (2), patchy focal myocarditis was observed only in 3 of 20 ARVC explanted hearts submitted to extensive biopsy sampling in multiple RV sites, including outflow tract and free wall. Our findings suggest that with the novel biopsy approach described, we were able to identify 2 distinct subgroups of patients with different myocardial disorders.

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 morphological, 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, electrophysiological, histological, ultrastructural (i.e., electron microscopy to evaluate the presence of preclinical desmosomal abnormalities), and virological 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 histological 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...
by frozen end-diastolic angiographic frames) otherwise frequently neglected in a conventionally executed map. We adopted this technique as we previously observed that, in many cases, electroanatomic maps failed to reflect RV angiographic shape and dimensions, in particular not depicting the true anatomical RV apex. In this regard, the criticism of the fluoroscopic images in our study appears completely inappropriate as the mapping catheter and the biopsy introducer clearly point to the free wall, well above the apex. In fact, Figure 1 illustrates the same patient as in Figure 2, in which the site of biopsy is clearly indicated in panel 2D. In addition, in our study, the biopsy site was always visualized through contrast medium flashes so that the execution of biopsies with both electroanatomic and angiographic guide further increased the accuracy and the safety of the procedure. On the contrary, it remains unclear how Drs. Avella and d’Amati, in the absence of both cardiac MRI and angiography, presume to identify “the border zone” and “the thinner core” of the RV wall solely on the basis of electroanatomic map. The identification of a low-voltage area, conventionally defined as “scar,” cannot provide any information on the thickness, and mostly on the histological substrate of the wall segment. Moreover, like delayed enhancement at cardiac MRI reflects an interstitial expansion whatever the cause (fibrosis, necrosis, edema, or amyloid deposition), different histological substrates (fibrofatty replacement, fibrosis, necrosis, edema, and inflammatory infiltrates) can determine the presence of low-voltage areas in different myocardial disorders.

As far as it concerns the absence of myocarditis in EMB from low-voltage areas in their study, this finding may “seem logical” when starting from the wrong assumption that “myocarditis is unlikely to produce solid transmural scars detectable as low-voltage areas with endocardial electroanatomic mapping.” In fact, it is well established by experimental and clinical studies that myocarditis may produce transmural lesions at cardiac MRI and even inflammatory or post-inflammatory ventricular aneurysms (3,4), so that it seems obvious that these alterations of ventricular structure and function may represent the substrate of electroanatomical abnormalities and mostly of repetitive ventricular arrhythmias. Accordingly, abnormal electroanatomic maps in patients with myocarditis as well as some cases of sarcoidosis mimicking ARVC electroanatomic features have already been reported (5,6). It is thus intriguing that Avella and coworkers failed to find patients with myocarditis, either with normal or pathological electroanatomic map, as this figure was reported in 50% of cases in both our and the Corrado et al. (7) series, probably denoting a bias in their patients’ selection or EMB interpretation. In this regard, it should be emphasized that the Dallas criteria cited by Drs. Avella and d’Amati are no longer considered sufficient, even in recent EMB guidelines (8,9), to establish the diagnosis of inflammatory cardiomyopathy, as immunohistochemistry is considered essential and polymerase chain reaction for cardiotropic viruses relevant to define the inflammatory and viral etiology, respectively, of cardiac lesions. Accordingly, in their hands, the analysis of EMB from low-voltage areas, exclusively confirming the diagnosis of ARVC and being nondiagnostic in 20% of cases, failed to add any diagnostic contribution to the sole execution of electroanatomic map. These findings may be misleading and, as previously suggested, may result from potential methodological biases.

Therefore, we can correctly state, as we did, that our study is the first to demonstrate that electroanatomic mapping-guided EMB may allow to modify the initial diagnosis and mostly the treatment and prognosis of patients with noninvasive diagnosis of ARVC.

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**Platelet Reactivity and Stent Thrombosis: Still Some Issues to Solve**

We read with great interest the recent article by Sibbing et al. (1). They concluded that low response to clopidogrel assessed with multiple electrode platelet aggregometry (MEA) is significantly associated with an increased risk of stent thrombosis. Considering the potential clinical implications of this attractive study, addressing some methodological issues would be appreciated.

The authors remark that the platelet aggregation measurements were not normally distributed, suggesting a right-skewed curve of the observed values. Different studies with smaller populations than the current one have shown a normal distribution of the