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 inaccurate as the mapping catheter and the bioprobe 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-inflamatory 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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REFERENCES


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
platelet aggregation parameters with light transmission aggregometry (2,3) and point-of-care, VerifyNow P2Y12 assay (Accumetrics, San Diego, California) (4). In a previous publication (5), the authors demonstrated a good correlation between MEA and light transmission aggregometry results. Do the obtained values in that population fit a normal distribution? Can any distinctive methodological characteristics of the MEA system explain this finding?

Another intriguing observation, conflicting with the published evidence (6), is the significantly higher proportion of active smokers in the group of low (upper quintile) responders to clopidogrel. We should expect a higher rate of active smokers among patients presenting with acute myocardial infarction, which was also related to lower response in the current study. It would be very interesting to know the individual influence of these variables by performing a multivariate analysis considering lower response to clopidogrel as the dependent variable.

Stent thrombosis (ST) is probably the most feared complication after percutaneous coronary intervention, irrespective of the time of appearance. Early ST (acute and subacute) still occurs despite the aggressive use of antiplatelet agents. Apart from adherence to the antiplatelet treatment and platelet aggregation response, some factors have been correlated with ST (7): lower left ventricle ejection fraction, smaller diameter of the reference vessel, longer stent lengths, and lower final pressure to implant the stents. The authors of the present study (1) focus the statistical analysis on the angiographic variables may play an important role in the development of ST, especially in the case of early ST. A Cox proportional hazards model that includes the above-mentioned variables could be very helpful to detect all the independent predictors of ST.

We absolutely agree with the authors that low response to clopidogrel (or high post-treatment platelet reactivity) may identify patients at higher risk of stent thrombosis. But all the mechanisms and related factors should be clarified to better prevent ischemic cardiac events.

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REFERENCES


Reply

We appreciate the comments made by Dr. Perez de Prado and colleagues concerning our recent article (1).

The observation of normally distributed platelet aggregation (PA) values is only an in vitro phenomenon depending on the population studied and the method applied. Indeed, PA measurements were not normally distributed in our study population (1), and in a previous study (2) we undertook with multiple electrode platelet aggregometry (MEA) on the Multiplate analyzer (Dynabyte GmbH, Munich, Germany). This is in contrast to observations made with light transmission aggregometry (LTA) and the VerifyNow P2Y12 assay (Accumetrics, San Diego, California). In MEA, adhesion and PA leads to an increased impedance signal; the more platelets that adhere to the electrode, the higher the impedance. Hence, MEA measurements have no inherent upper limit, and this is likely to explain not normally distributed PA data with MEA.

In fact, the observation of a higher proportion of active smokers in the group of clopidogrel low responders (1) is in contrast to a recently published study using LTA and finding lower PA values in active smokers compared with nonsmokers (3). For LTA, it must be kept in mind that platelet-rich plasma is an artificial milieu lacking erythrocytes, leukocytes, and larger platelet subspecies, all of which influence the amount of PA (4). The link of smoking and leukocytosis is well known, and also the interaction of leukocytes and platelets in atherothrombotic processes has been established (5). Endothelial dysfunctions and platelet hyperreactivity have been well described in smokers, as well as a negative effect of smoking on the pharmacokinetics of clopidogrel (6). In light of this conflicting data, the issue of smoking and clopidogrel response warrants further investigations, which we are currently undertaking in separate studies.

Concerning predictors of stent thrombosis (ST), we are aware that other variables apart from the ones included in our primary analysis may play a role in this setting. ST is a very rare event, and a comprehensive analysis on its predictors requires thousands of patients. This was beyond the scope of our study, which was designed to assess the relationship of MEA measurements and ST. As requested, however, by Dr. Perez de Prado and colleagues, we expanded the multivariable analysis by adding the suggested variables (ejection fraction [already included], vessel diameter, total