Reply: Debating the Definition and Incidence of Isolated Cardiac Sarcoidosis

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this group with 42 patients with "true" ARVC. They showed that atrioventricular block (first, second, or third degree) had a sensitivity of 67% and specificity of 100% for the diagnosis of CS (2).

The third comment relates to the Hoogendoorn et al. (1) statement, "it is likely that isolated CS is underdiagnosed." We would argue that the accumulating data suggest quite the opposite. There are many patients, with manifest CS, who have no clinically apparent disease in other organs, but sarcoidosis is, by definition and biology, a systemic disease. The reported prevalence of isolated CS varies widely, from 3.2% to 54%, and there are likely 2 main reasons for this: 1) the lack of an agreed definition of isolated CS; and 2) the diagnostic method(s) for assessing extracardiac involvement. Hence, a key starting point to understand isolated CS is to agree on a standardized definition. The 2017 version of the Japanese CS guidelines tackled, for the first time, the definition of and criteria for the diagnosis for isolated CS (3). They included the following 3 criteria: 1) no clinical findings characteristics of sarcoidosis are observed in any organs other than the heart; 2) ^{67}Ga scintigraphy or ^{18}F-fluorodeoxyglucose positron emission tomography reveals no abnormal tracer accumulation in any organs other than the heart; and 3) a chest computed tomography scan reveals no shadowing along the lymphatic tracts in the lungs or no hilar and mediastinal lymphadenopathy (minor axis >10 mm).

Using a similar definition, we found isolated CS in only 1 in 31 cases presenting with clinically manifest CS (4). Also, other data suggest that even these apparent isolated cases may not be truly isolated. Petek et al. (5) investigated 10 patients with presentations and cardiac imaging consistent with the Japanese definition of isolated CS. Four of these 10 patients had granulomas on bronchial biopsy. Hence, these data suggest that there is a small subset of patients who at the moment of fluorodeoxyglucose positron emission tomography imaging have "PET detectable inflammation" *only* in their heart. However, it also follows that additional or interval investigation will likely reveal extracardiac disease. This debate is more than just semantics, as the overdiagnosis of "isolated CS" can lead to unnecessary immunosuppression or "missed" alternative diagnoses.

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REPLY: Debating the Definition and Incidence of Isolated Cardiac Sarcoidosis

We thank Drs. Birnie and Nery for their interest in our study concerning the value of electroanatomical voltage mapping (EAVM) to distinguish cardiac sarcoidosis (CS) from arrhythmogenic right ventricular cardiomyopathy (ARVC) (1).

Diagnostic criteria for isolated CS have been suggested only since 2017, and despite these criteria, this entity is imperfectly characterized because of imprecise imaging tools, the potential of inactive CS, and the imprecision of biopsy sampling. Prior to the introduction of these criteria, isolated CS relied solely on endomyocardial biopsies. The diagnosis of isolated CS requires active inflammation on ^{18}F-fluorodeoxyglucose positron emission tomography or ^{67}Ga scintigraphy and ≥3 additional criteria, mainly reflecting septal or left ventricular involvement.

However, in patients with dominant right ventricular involvement, these criteria might not be present, as left ventricular function and atrioventricular (AV) conduction may be normal (43% and 50% of patients in our cohort, respectively). Although AV block has been reported to be specific in distinguishing right-

sided CS from ARVC, the sensitivity is low. High-grade AV block was observed in only 14%, and any AV conduction delay in 50%, in our study. Therefore, additional criteria are needed to suspect CS.

Notably, without extracardiac symptoms, physicians may not consider additional evaluation to detect extracardiac involvement. In this context, we stated that if we exclude extracardiac findings (which may not be present at the time of presentation with ventricular tachycardia), the diagnosis of CS would have been suspected in only 6 (43%) of our CS patients based on clinical criteria. In particular, in patients with dominant right ventricular involvement, once Task Force criteria for ARVC are fulfilled, additional diagnostic testing may not be carried out.

Birnie and Nery suspect that only a small subset of patients may have isolated CS. We agree that the concept of isolated CS conflicts with the biology of the disease, and that thorough and repeated diagnostic evaluation is likely to detect extracardiac involvement more frequently. Small cohorts including selected patients (like ours) cannot provide meaningful data on the true incidence of isolated CS; this was not our intention. Rather, we aimed to provide an additional diagnostic tool for patients presenting with scar-related ventricular tachycardia without symptoms or signs of extracardiac sarcoidosis (2,3). Our EAVM algorithm may prompt additional testing required to support the diagnosis of CS (2), including endosonography-guided transbronchial or transesophageal needle aspiration in the absence of extracardiac complaints or fluorodeoxyglucose uptake.

We are convinced that more awareness among electrophysiologists for the diagnosis of CS is important. With our study, we provide a diagnostic tool which is based on EAVM, a well-known procedure among electrophysiologists, which hopefully will contribute to earlier diagnosis and treatment of this challenging disease.

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