Readers' Comments: Was the Interatrial Block in Patients With Takotsubo Syndrome in the Spanish National RETAKO Registry Partially or Totally Reversible?

I very much enjoyed reading the contribution by Martín-Demiguel et al[1] in the American Journal of Cardiology, reporting for first time on the prevalence of interatrial block (IAB) in patients with takotsubo syndrome (TTS) from the Spanish National RETAKO Registry. The authors found in their 246 patients that 61% had a normal P wave, 24% (58 patients) had a partial IAB, defined as P-wave duration of ≥120 ms and positive morphology in inferior leads, 5% (13 patients) had advanced IAB, defined as P-wave duration of ≥120 ms and biphasic (+/−) P-wave morphology in inferior leads, 7% had atrial fibrillation (AF), and 2% were pacemaker dependent in the admission electrocardiogram (ECG).[1] IAB is known to increase the risk of AF and stroke. At a mean 12 months follow-up, the authors observed a higher composite all-cause mortality/hospital readmission in patients with advanced IAB and AF than in the rest of the cohort, and advanced IAB was an independent predictor of the composite outcome.[1]

Patients with TTS suffer both ventricular (monomorphic and Torsades de pointes ventricular tachycardia), and atrial arrhythmias (e.g., AF), atrioventricular (second and third degree AV blocks), and intraventricular blocks (e.g. left bundle branch block), and sinoatrial block, some of which are transient or persistent, occasionally requiring the implantation of temporary, or even permanent electronic devices. Atrial arrhythmias and IAB may be related solely to the underlying aging process and associated atrial fibrosis, or hemodymnamic decompensation due to TTS, or myocardial and even atrial edema consequent to TTS,[2] or a combination of the previously mentioned.

I know that the authors do not have data on left atrial size or function, or cardiac magnetic resonance imaging, or ECGs beyond the ECG recorded on admission[1]; however the RETAKO Registry Investigators will provide an additional service to both clinicians and researchers if they obtain and analyze ECGs, corresponding to the mean 12-months follow-up, of their 13 patients with advanced IAB, to ascertain whether the IAB was transient (due to TTS), or permanent. Were the ECGs of these 13 patients with TTS show advanced IAB, partial IAB, or normal interatrial conduction?

John E. Madias, MD
Icahn School of Medicine, Elmhurst Hospital Center Cardiology, Elmhurst, New York
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1. Martín-Demiguel I, Núñez-Gil IJ, Pérez-Castellanos A, Vedia O, Uribarri A, Durán-Cambra A, Martín-García A, Corbí-Pascual M, Guillén Marzo M, Martínez-Sellés M. Prevalence and significance of interatrial block in takotsubo syndrome (from the RETAKO Registry). *Am J Cardiol* 2019. https://doi.org/10.1016/j.amjcard.2019.03.028. pii: S0002-9149(19)30328-5. [Epub ahead of print].
2. Madias JE. To the editor- implantation of permanent devices in patients with Takotsubo syndrome. *Heart Rhythm* 2016;13:e328.

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Type 2 Myocardial Infarction: Trying to Fit a Square Peg Into a Round Hole?

The Humors...will be compacted into...most obstinate Infarctions
G. Harvey 1689

Any cardiologist who performs consultative services acknowledges the numerous requests to clarify the significance of an elevated troponin, frequently involving patients who did not present with chest pain. Typical symptoms and ECG changes are often lacking, arguing against an acute coronary syndrome. We are then pressed to provide a diagnosis, and more importantly, to recommend therapy. Is an elevated troponin in a dialysis patient a "Type 2 myocardial infarction" or the newly coined "myocardial injury?"[1] Are aspirin, B-blockers, statins, and stress testing or cardiac catheterization the appropriate diagnostic and therapeutic approaches? We believe the current classification schema categorizing this heterogenous group of patients is misleading mechanistically, may cause epidemiologic confusion, and implies a set of therapies which may not be useful or may even be harmful.

There are numerous settings where troponin elevations are commonly found without associated chest pain and ECG changes: arrhythmias, myocarditis, sepsis, heart failure, pulmonary emboli, intracranial bleeding and stroke, surgical disorders (trauma, massive gastrointestinal bleeding, bowel obstruction), renal failure, ablation, cardioversion, cardiotoxicity due to chemotherapy, inflammatory (myocarditis pericarditis) or infiltrative processes of myocardium (amyloidosis), infective endocarditis, significant left ventricular hypertrophy in aortic stenosis or hypertrophic obstructive cardiomyopathy, severe hypertension, hypertensive crisis, aortic dissection, or even strenuous exercise.[2] Multiple mechanisms have been proposed to explain the presence of an elevated troponin in these settings, including localized ischemia due to insufficient oxygen delivery or microvascular dysfunction, direct myocyte injury from endogenous or exogenous toxins, cellular apoptosis, direct injury from stretch or local inflammation, leakage of cytosolic troponin[2] . . . the list of proposed mechanisms is daunting, but what they all have in common is that none of them involve occlusion of a coronary artery. And despite the assortment of proposed mechanisms involved, we would expect that the standard approach for managing ischemic myocardial injury (antiplatelet agents, β-blockers, statins) may not be useful in these settings, and that diagnostic studies and therapies aimed at identifying and opening coronary obstructive lesions will be very low yield and likely offer little benefit.

We commend the World Health Organization for their efforts to construct a classification system which would unify the various causes of myocardial damage,[3] and we also acknowledge the efforts of the writing group for the recent Fourth Universal Definition of Myocardial Infarction where they further attempt to define the subset of patients with troponin release without actual vascular occlusion, and introduce the useful concept of "myocardial injury."[1] Still, we fear there remains confusion as we try to include these nonvascular causes of cardiac damage in a classification scheme

where the other categories all relate to myocyte necrosis due to vascular obstruction, whether spontaneous or iatrogenic. Indeed, we are trying to pound a square peg into a round hole.

The Oxford English Dictionary defines "infarction" as "the action of stuffing up" (from the Latin root meaning "to stuff up or obstruct"), with the word now defined as "morbid conditions of the tissues resulting from obstruction of the circulation." We feel by keeping with the original sense of the word and limiting the use of the term "myocardial infarction" to situations where there is clearly an obstructed coronary artery, we would harmonize the term with unequivocal physiology, guide our choice of diagnostic and therapeutic pathways, and avoid inappropriate clinical diagnoses which create epidemiologic as well as coding and billing confusion. We propose the collection of conditions and situations which result in troponin release without an obstructed coronary artery be labeled Troponin Release Without Vascular Obstruction. Type 1, 4a, 4b, 4c, and 5 myocardial infarctions would be managed with the usual panoply of diagnostic imaging, evidence-based therapies, and interventions, while given the multitude of possible causes of Troponin Release Without Vascular Obstruction ranging from renal insufficiency to Takotsubo syndrome, interventions (if any) which may improve the worsened outcome in these settings will likely vary greatly and usually have little to do with lipids or platelet-fibrin thrombi. By not classifying these causes of troponin release as myocardial infarctions, patients may not be mislabeled as having coronary disease, and we will improve coding, avoid inappropriate therapies, and redirect investigation into improved outcomes.

Ellis W. Lader, MD

WMC Health Heart and Vascular Institute, Kingston
Division of Cardiology, Kingston, NY

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Reply to "Comparison of Accuracy of Left Atrial Area and Volume by Two-Dimensional Transthoracic Echocardiography Versus Computed Tomography"

In their interesting study, Arsanjani et al[1] reported that left atrial (LA) volume, estimated by 2-dimensional echocardiography (2D-E) using the biplane area-length method, showed larger discrepancies than 4-chamber LA area when compared to the corresponding multi-detector computed tomography (MDCT) measurements. They conclude that LA volume determination is less reliable than direct LA area tracing for the estimation of LA size by 2D-E, suggesting a revisitation of current ASE guidelines.[2]

We believe that these conclusions should be considered with caution. Firstly, the agreement between 2D-E and other imaging techniques for the assessment of LA size has been extensively studied, with evidence showing that the magnitude of the discrepancies increases passing from comparisons of linear measurements (e.g., anteroposterior LA diameter)[3,4] to those of areas and volumes.[5–7] Interpreting this expected increase as poor reliability of volumetric measurements is questionable, as it simply reflects the effect of error propagation, a rule by which linear measurement errors are amplified when areas and particularly volumes are estimated.[8] This effect is evident when the area-length formula is used, as this method directly combines LA areas and length to estimate LA volume.[2] In this view, performing comparisons among discrepancies in cm^2 and ml, even if expressed as per cent differences, may be misleading.

Secondly, it must be pointed out that a different agreement between 2D-E and MDCT for the estimation of LA volume and LA area does not necessarily translate into differences in the clinical utility between the 2 LA measures. The concordance with a gold standard technique bears little relation with feasibility, reproducibility, diagnostic value, and prognostic performance, which mostly determine the clinical value of echocardiographic indexes. Accordingly, LA volume measurement by 2D-E was shown to be highly feasible and reproducible in many different populations,[9–11] and even in the study by Arsanjani et al[1] showed a good interobserver variability (7.1%). From a diagnostic point of view, the simple observation of good agreement between the values of 4-chamber LA area measured by 2D-E and MDCT has doubtful clinical utility, since 4-chamber LA area − irrespective of the technique used − has intrinsic limitations as a measure of LA size, resulting from the difficulty to account for the asymmetric LA shape using a single-plane measure.[12] Consistently with these limitations, 2D-E LA volume is superior to LA area as a predictor of LV diastolic dysfunction[13] and for the estimation of LA enlargement as identified by three-dimensional echocardiography.[14] In this context, the use of LA area for the categorical assessment of LA size yields a high risk of underestimation, with misclassification rates up to 70%.[15]

Thirdly, similar considerations can be made for the use of LA size as a prognostic marker. The clinical utility of LA volume for the prediction of cardiovascular outcome was established by a number of studies, both in general and referral populations,[16–19] with robust evidence of more accurate stratification of thromboembolic risk and better prognostic value when compared to LA area.[20–22] Among these studies, the authors cite an important Mayo Clinic paper where LA volume index outperformed LA area for the prediction of outcome in a group of 317 patients in sinus rhythm followed for a median of 3.5 years.[20] They argue that the difference in prognostic performance between LA area and LA volume in that analysis was modest (area under the curve 0.64 vs 0.71). Even assuming that such difference can be arbitrarily considered small, these values only refer to a single component of prognostic performance, i.e., discrimination. In that study, LA volume showed the strongest independent prognostic value for the prediction of the clinical endpoint, with a 6.6-fold