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EDITORIAL COMMENT

Idiopathic ventricular fibrillation: A never ending ''clinical'' history

Fibrilhação ventricular idiopática: uma história ''clínica'' sem fim

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Sudden cardiac arrest (SCA) and sudden cardiac death (SCD) are terrible outcomes of various prevalent cardiac diseases and are the two sides of the same coin[1]. Several well-known diseases are linked to the occurrence of SCD, however the pathophysiology is often obscured.

The term idiopathic has had the same definition for many years: it relates to or denotes any disease or condition which arises spontaneously or for which the cause is unknown. Late in the 1990s we referred to idiopathic ventricular fibrillation (IVF) as a condition that best defined our inability to identify a causal relationship between the clinical circumstance—SCD or SCA—and arrhythmia in a structurally normal heart.

The game changed when Brugada Syndrome (BrS) was recognized in 1992 as an arrhythmogenic syndrome able to cause SCD in mainly young patients.[2] This discovery was followed by the recognition of other primary syndromes such as CPVT, LQTS, short-QT syndrome, and the Early Repolarization Syndrome.[3] The diagnosis of IVF implies the absence of a substrate for ventricular fibrillation and the exclusion of specific diseases, including structural cardiac disease (i.e. myocarditis, cardiac sarcoidosis, arrhythmogenic right ventricular, hypertrophic, dilated cardiomyopathy and coronary artery disease) or metabolic and toxicological etiologies [4,5]

The correct diagnosis of IVF is one of exclusion and requires extensive diagnostic testing. Routine testing excludes the most common causes of VF. Routine testing usually comprises an ECG, echocardiogram, exercise testing, Holter or telemetry monitoring, coronary angiography and magnetic resonance imaging.

In young patients (<45 years) with a low risk for coronary artery disease, a coronary CT scan or cardiac magnetic resonance (CMR) are alternatives for coronary angiography because their sensitivity, specificity, and especially the negative predictive value in such patients are high.[6,7] Additional diagnostic tests may include ergonovine or acetylcholine provocation to exclude coronary artery spasm (although less commonly performed today for safety reasons) and the administration of a sodium channel blocker (ajmaline or flecainide) to exclude BrS. It is essential to follow a systematic protocol that includes all the available diagnostic tools and also an assessment of the patient's family with genetic testing if necessary[8].

The work done by Cátia Oliveira and collaborators is remarkable. In the study published in the journal, entitled ''Long-term prognosis of IVF: an eighteen-year experience from a tertiary center'',[9] the authors retrospectively assessed patients labeled as IVF who underwent ICD implantation between January 2005 and May 2023. During this period, the study workflow changed gradually due to increasing knowledge of arrhythmogenic syndromes and cardiomyopathies and SCA underlying mechanisms, increasing usage of CMR and genetic testing, enhancing the detection of

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small structural abnormalities and facilitating the diagnosis of early-stage cardiomyopathies. Thus, it is understandable that some patients may undergo an evaluation more than once in light of better knowledge of SCD mechanisms, with IVF sometimes relabeled with major implications for the management of the index case and the family.

The article underlines three main aspects: i) the increasing importance of genetic testing, ii) the role of vasospasm and short-coupling ventricular or ventricular tachycardia causing SCA and iii) the potential reclassification of IVF as non-idiopathic. First, genetic testing: ''patients in whom genetic testing was carried out had an underlying diagnosis identified in 57.1% of cases, compared to only 26.3% of patients who did not have genetic testing''. The authors justified such a high percentage in comparison with previous studies (ranging from 3% to 48%) due to the heterogeneity of the population, testing based on clinical suspicion vs. indiscriminate testing, as well as differences in genetic panel selection. The genetic testing panel was chosen according to the initial clinical suspicion (channelopathies and/or cardiomyopathies), or single gene testing was performed if there was a family member with an identified genetic cardiac condition associated with ventricular arrhythmias.[9] The identification of one causal gene mutation is also a way to possibly anticipate the disorder in relatives. In other words, specific genetic testing of relatives after identification of the disease-causing mutation in the index case has the power to distinguish between mutation-positive, potentially at-risk relatives and mutation-negative relatives who did not inherit the disorder and subsequently are not at increased risk of SCA. However, it is common to have variants of uncertain significance in these tests, in which case no conclusions can be made. At times, such variants are eventually shown to be deleterious. In a well-known editorial published in Heart Rhythm in 2015, Michael J. Ackerman called it ''genetic purgatory'', referring to an uncomfortable setting where the cardiologist and geneticist are unable to provide useful counseling.[10]

The second subject highlighted in the study was that one of the most frequent diagnoses at follow-up was SCPVT (23% of all diagnosis). SCPVT is a polymorphic ventricular tachycardia variant initiated by an extremely premature ventricular contraction (<300 ms) arising frequently from the peripheral His-Purkinje system. Previously considered to be rare, this variant was observed in up to 30% of cases of IVF[11,12]. In this condition, VF is initiated by premature ventricular complexes (PVCs) or degeneration of ventricular tachycardia (VT). In patients with VF, PVCs that trigger the arrhythmia originate from the Purkinje system in up to 93% of the cases.[11,12] More rarely, they may originate from the ventricular myocardium, including the right ventricular outflow tract or the papillary muscles. These PVCs may result from abnormal automaticity, triggered activity, or more rarely from reentry (either phase 2 reentry or re-entry using the Purkinje system). Arrhythmogenic mechanisms become more prevalent in the presence of electrolyte imbalance, exposure to drugs, and in the presence of myocardial ischemia.[13] Animal studies suggest re-entry and multiple wavelets as the main mechanisms supporting early VF, and the Purkinje system as a principal mechanism that maintains long-duration VF. Structural heterogeneity is critical for the occurrence of re-entry by decreasing the conduction velocity and thereby anchoring re-entry, but also important is the fact that the complex myocardial cell arrangement at the papillary muscle insertions and at the Purkinje tissue can maintain fibrillatory activity even in the absence of additional pathology.[13,14]

Ablation of the trigger and/or substrate for VF is at times possible. Ablation should be performed during or as soon as possible after an electrical storm when ectopy is more frequent. A pioneer in the field, Michel Hassaguerre, also proposed an ajmaline challenge test to awake and help locate ectopy that is in the origin of CSPVT and VF, increasing the possibility of ablation. Electroanatomic mapping should be made both endocardially and epicardially with multipolar catheters and guided by imaging. The specificities of the ablation and mapping procedure must be carefully planned because these procedures may be very different between patients.

Third, in this study vasospasm was encountered in 23% of patients, and the authors referred to the potential role of ergonovine or acetylcholine challenge aimed at provoking coronary spasm during the initial evaluation of an episode of unexplained SCA. Future studies should focus on establishing a uniform diagnostic definition, standardization of protocol of evaluation and addressing nuances during testing (pharmacological agent, administration route and time, dosage regimen, vessels tested, and support of temporary pacing, safety). In addition, incorporating negative control populations in such studies would provide objective evidence for the sensitivity and specificity of different regimens to incorporate this procedure for the evaluation of vasospasm in SCA survivals [15].

Major progress has been made in the 21st century in the study and management of SCA/SCD in general, and IVF specifically, but there is still much to research and a long way to go, as perfectly highlighted in the recent *The Lancet Commission on Sudden Cardiac Death*.[16] SCA labeled as IVF is decreasing thanks to those involved in the management of these patients: cardiologists, electrophysiologists, geneticists, and emergency doctors. Reclassifying IVF into more specific causes can dramatically change the outcome of SCA survivors and their relatives. I believe that this matter will soon have a happy end.

Conflicts of interest

The author have no conflicts of interest to declare.

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