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Editorial commentary: The challenge of sudden cardiac arrest in patients with structural heart disease: Still a long way to go☆,☆☆

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In this issue of the Journal, Krokhaleva and Vaseghi provide a concise but comprehensive update [1] on sudden cardiac arrest (SCA), still a major challenge confronting contemporary cardiologists in developed countries. The presentation ranges from epidemiology and pathophysiology to prevention and treatment, with a focus on ablation of ventricular tachycardia (VT) and on the emerging field of neuromodulation.

This brief editorial aims to provide a critical perspective on the current approach to ventricular arrhythmias (VAs) management in patients with structural heart diseases (SHD) discussing current role and future potential of these two therapeutic approaches.

Understanding the problem

SHDs include a heterogeneous group of cardiac disorders characterized by different degrees of ventricular dysfunction, myocardial structural abnormalities and cardiac autonomic nervous system (ANS) impairment. The final result is an increased arrhythmic risk due to a variable combination of focal and global pro-arrhythmic mechanisms that may lead to monomorphic ventricular tachycardia (VT), polymorphic VAs (including ventricular fibrillation, VF) or both in the same patient.

The most effective strategy to prevent VAs is likely to vary based on the type and mechanisms of arrhythmia, which in turn may vary in different stages of SHDs. Unfortunately, the characterization of the arrhythmic substrate and mechanisms in ischemic (ICM) and idiopathic cardiomyopathy (NICM), the two most common causes of SHDs, is very limited in clinical practice, with inevitable consequences on the subsequent management of these patients. Left ventricular ejection fraction (LVEF), NYHA functional class and QRS duration are still the main parameters driving the decision of implanting an internal cardioverter defibrillator (ICD), eventually associated with cardiac resynchronization therapy, to reduce mortality. Albeit this simplistic approach has merits, its capability to appropriately identify patients most likely to benefit from ICDs is poor, as underlined by the results of the DANISH trial. A polyparametric risk assessment combining non-invasive tests (such as cardiac MRI, T-wave alternans, autonomic markers and imaging) seems promising to add predictive value but should be assessed in dedicated prospective studies. A better risk stratification may benefit low-risk patients avoiding unnecessary ICD implantations. Theoretically, it may also identify very high-risk subjects in whom an aggressive preventive strategy may be considered aiming to reduce the risk of both isolated VT/VF and electrical storms (ES). In a French registry [2] enrolling >5500 ICM and NICM patients receiving an ICD for primary prevention followed for >3 years, VT/VF requiring therapy and ES occurred in 19.4% and 2.9% of patients, respectively. Both occurrences were associated with subsequent increased mortality (adjusted HRs 1.77 and 3.77, respectively). These data clearly underline the strong negative prognostic impact of the occurrence of VAs. Although the unfavorable prognosis may be due to a large extent to progression of heart failure [3], an approach aimed to reduce prophylactically shocks and ES appears reasonable. The International VT Ablation Center Collaborative Group [4] compared patients undergoing ablation after ES ($n=677$) with 1263 remaining patients. Patients with ES tended to be sicker and slightly older, had a higher 1-year rate of TV recurrence (32.1% vs 22.6%) and mortality (20.1% vs 8.5%). After adjustment, ES was a weak predictor of TV recurrence (HR 1.23) and a moderate predictor of mortality (HR 1.5). Inducible VT after ablation predicted VT recurrence and mortality. Overall, patients with ES had a 1-year survival of 61.3% if they experienced VT after ablation but 88.7% when no recurrence occurred.

The proper timing of VT ablation in patients with SHD and isolated VT/VF episodes is still debated. With the exception of CALYPSO, interrupted for insufficient enrollment, there are no randomized clinical trials (RCT) comparing antiarrhythmic drugs (AADs) with VT ablation after a first ICD shock in primary prevention. The VANISH trial [5] compared VT ablation with escalation of AAD in ICM patients who suffered VT recurrences despite first-line AAD therapy: VT ablation was superior in reducing the composite outcome of death, VT storm, or appropriate ICD shocks. The result was driven by VT since mortality was identical in the two groups. The arrhythmia enrollment criteria were extremely heterogeneous, ranging from a single sustained VT below ICD detection rate to ES with no details on the arrhythmic burden at baseline. Interestingly,

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VT ablation appeared equally effective to AADs in the subgroup of patients not on amiodarone, in whom ablation was compared with initiation of amiodarone, but more effective among patients already on amiodarone. This suggests that the modification of the arrhythmic substrate through VT ablation may be particularly beneficial when combined with an intervention increasing the global electrical stability of the heart, such as amiodarone.

No RCT exists on VT ablation in patients with NICM.

Which way should we go?

VT ablation still has important challenges to face. First of all, despite the deadly nature of the disease approached, there is no proven mortality benefit from RCTs [6]. The long-term recurrence rate after a first ablation attempt is still high and extremely heterogeneous between studies, ranging from 30 to over 80%. Several mechanisms such as non-inducibility of the arrhythmia, inadequate mapping or unrecognized VT circuits, deep target location not accessible with the current energy approaches and evolving substrates may be involved in VT ablation failures. The procedure absorbs large resources, is time-consuming and the rate of complications, including death, is not negligible, particularly in low-volume centers [7]. Research is ongoing aiming to improve these drawbacks. For instance, better transmurality could be achieved with half-normal saline irrigation or with needle or wide-tip electrodes. New energies such as normothermic irreversible electroporation hold promise for the future as well as non-invasive ablation with the use of radiation energy or more focused protons or carbon ions.

As indicated in the paper, neuromodulation may be an important additional and possibly complementary approach, particularly in NICM patients. The cardiac ANS undergoes a dramatic remodeling in patients with SHD affecting the entire neuraxis; pre-clinical studies demonstrated the profound impact of this remodeling on arrhythmogenesis, acting both on scar-related arrhythmias and on functional reentry-related complex arrhythmias. Therefore, directly targeting the ANS (with the gross objective to reduce the autonomic imbalance tilted toward a sympathetic dominance) has a strong pathophysiological rationale. The clinical experience of direct antiarrhythmic ANS modulation in this setting is still very limited. Not unexpectedly, the first reported series include only very severe patients. This is the indeed the case with cardiac sympathetic denervation (CSD). In the largest word-wide experience with CSD for the treatment of refractory VA in SHD [8], 75% of patients had a history of ES, 99% were being treated with amiodarone and 66% had undergone VT ablation. Despite these very high risk characteristics, 58% were still free from VT/ICD shock recurrences one year after CSD. Since ANS remodeling is a progressive process, it is conceivable that CSD would be more effective if applied earlier. However, more data on the efficacy of the procedure appear needed to support such an earlier strategy. Some preliminary confirmation could derive from a propensity score-matched analysis comparing patients undergoing CSD with patients treated with a traditional approach. Compelling evidence must come from a prospective RCT. Notably, VT Ablation trials have proven to be difficult to conduct with no more than a handful of patients enrolled in each center each year and such a CSD trial would possibly be even more complicated to perform. However, such an investigation would significantly advance our knowledge on the prevention of sudden cardiac arrest in SHD. It is thus in the interest of the scientific community to perform it and of Governmental Agencies, such as NIH, to support it.

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