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EDITORIAL

The Contemporary Era of Sudden Cardiac Death and Ventricular Arrhythmias: Basic Concepts, Recent Developments and Future Directions

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''Despite advances in prevention and treatment, sudden cardiac death (SCD) remains a leading cause of mortality and is responsible for approximately half of all deaths from cardiovascular disease'', state Wong et al. [1]. Their epidemiological review opens this Special Issue, in which we learn that SCD is responsible for 15–20% of all deaths in Western societies [1,2]. Sudden cardiac death is strongly associated with, and may be preceded by, various forms of ventricular arrhythmias (VA) which are themselves a common and widespread cause of the overall morbidity and mortality related to heart rhythm disturbances [3]. Given the significant, rapid evolution in our current state of knowledge in these fields, this entire Special Issue of *Heart, Lung and Circulation* is dedicated to SCD and VA.

In this introductory editorial, we highlight some of the basic concepts, many recent developments and controversies, and future directions in SCD and VA to be found within the State-of-the-Art reviews in this Special Issue; considered together, they elucidate the breadth and depth of contemporary diagnostic and management considerations in SCD and VA. Also, as background information to assist our general readers, we provide here a brief, broad overview of VA, and the scope of the problems they present in clinical practice.

Basic Concepts

Outcomes following out-of-hospital cardiac arrest remain poor, with most individuals *not* surviving to discharge, according to Wong et al., as evidenced by international data, such as from the AusROC Epistry in Australian and New Zealand, PAROS (the Pan-Asian Resuscitation Outcomes Study) and the European EuReCa ONE Study. However, they also say that, over time, progress *has* been made with better coronary heart disease management (the main, but not only, underlying condition of SCD), and more community-based CPR. Survival rates are also higher if the rhythm on first assessment is shockable [1].

As acknowledged in several of the reviews in this Special Issue, an implantable cardioverter-defibrillator (ICD) is considered the ''cornerstone'' therapy in primary prevention of SCD in high risk patients with ischaemic and non-ischaemic cardiomyopathy [4]; it also improves survival in patients who have survived previous sudden cardiac arrest due to ventricular tachycardia/ventricular fibrillation (VT/VF) [5–7]. ICDs do not prevent recurrent VT and VF, however, they do not affect the underlying arrhythmogenic substrate.

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Accordingly, up to 70% of recipients will need adjunctive anti-arrhythmic drug therapy [8].

Furthermore, catheter ablation has an established therapeutic role on the management of VT, with RCTs showing that catheter ablation is superior to medical therapy in the treatment of post-infarction-related VA [9–11].

Ventricular arrhythmias include not only polymorphic VT (PVT) and VF carrying a high risk of sudden cardiac death, but also isolated premature ventricular complexes (PVC), non-sustained ventricular tachycardia (NSVT), and sustained monomorphic ventricular tachycardia (SMVT). Accordingly, they can present clinically along a spectrum, ranging from asymptomatic ventricular ectopy to palpitations, chest pain, dyspnoea, syncope, ICD shocks, and heart failure, through to sudden cardiac arrest and sudden cardiac death (SCD). Similarly, ventricular arrhythmias can carry a prognostic significance from entirely benign to highly lethal. The wide variations in the clinical presentation and prognosis of VA, mean that their classification and underlying mechanisms must be appreciated (see Text Box and Figures), so that an accurate diagnosis and optimal management, as outlined in the reviews in the Special Issue, can be decided upon for each individual patient.

Haqqani and Marchlinski remind us that the 12-lead electrocardiograph (ECG) remains unsurpassed as a single tool for the diagnosis of wide complex ventricular tachycardia and for the fundamental characterisation and analysis of VA, possibly because so much of our current understanding of VA is related to ECG findings [12]. Further, they also point out that the surface ECG forms the basis of, and reference for, all mapping methods during catheter ablation of VT.

Text Box

Ventricular Arrhythmias: Definition and Classification Scheme

DEFINITION

A ventricular arrhythmia (VA) is any arrhythmia that originates in the ventricle and that does not require any cardiac tissue above the level of the His bundle for its perpetuation. In contrast to some forms of supraventricular tachycardia that require the participation of the ventricle for their maintenance, atrial or AV nodal tissue does not form part of the arrhythmogenic tissue sustaining any VA.

CLASSIFICATION SCHEMES

Ventricular arrhythmias are classified by several parameters: duration, electrocardiograph (ECG) appearance and electrophysiological mechanism.

Duration

Duration is the most fundamental classification and, obviously, the shortest this can be is one beat of arrhythmia i.e. an isolated **ventricular ectopic**, also known as a **premature ventricular complex (PVC)**. Ventricular ectopy can be arranged in varying ratios to normally conducted beats: if a PVC occurs after every normal beat then it is called **ventricular bigeminy**, or **ventricular trigeminy** if there is one PVC following every two consecutive sinus beats. Two PVCs in a row define a **ventricular couplet**; and, three ventricular ectopics in a row are sometimes called **ventricular triplets**. Technically, however, the latter constitute the shortest duration of **nonsustained ventricular tachycardia (NSVT)**. Any VA with rate >100 bpm and terminating spontaneously between 3 beats and 30 seconds is considered to be NSVT: obviously, this encompasses a huge range of possible ECG appearances and clinical consequences. **Sustained VT** is any VA with definable QRS complexes lasting greater than 30 seconds or requiring immediate cardioversion due to haemodynamic non-tolerance.

ECG Appearance

The second broad classification of VA is by ECG appearance. This is ideally based on a 12-lead ECG recording obtained during tachycardia, as the appearances on one or at most a few channels of telemetry data may mask the true nature of a VA. When all QRS complexes present during the VA have near-identical morphology, the term **monomorphic VT** is used. Widespread beat-to-beat variation in QRS morphology defines a **polymorphic VT** (Figure 1). A particular type of polymorphic VT known as ***torsades de pointes*** (**TdP**) is seen in the setting of congenital or acquired QT interval prolongation and exhibits pause-dependent initiation. However, the 'twisting of the points' appearance implied by its name may not be seen in the majority of the recorded ECG leads during this potentially lethal VA. When multiple distinct monomorphic QRS morphologies are seen during the one period of VT, the term **pleomorphic VT** is sometimes used. The absence of any recognisable QRS complexes during a sustained VA defines **ventricular fibrillation (VF)**.

Electrophysiologic mechanism

Finally, VA may be classified by their electrophysiologic mechanism. This is useful as it often has defined prognostic and therapeutic implications. By far the most frequent sustained VA in patients presenting emergently to hospital is sustained monomorphic VT (SMVT) due to re-entrant wavefront propagation through ventricular scar (Figure 2). These scar-related re-entrant VTs are generally seen in patients with significant structural heart disease, most commonly ischaemic or non-ischaemic cardiomyopathy and, in this context, they carry grave prognostic implications. By contrast, in the absence of structural heart disease and ventricular scarring, SMVT is generally not due to a re-entrant mechanism and instead usually arises from a focal point source of activation. These so called 'idiopathic' VTs in structurally normal hearts generally have an excellent prognosis (Figure 2).

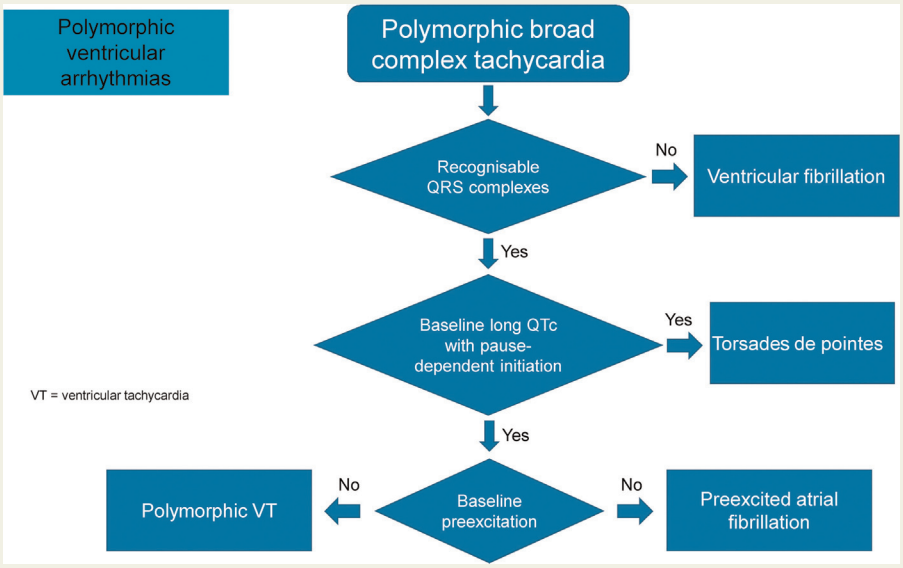

Figure 1

In one of several reviews focussing on specific circumstances associated with SCD and/or VA, Skinner et al. report that 40% of sudden, unexpected natural deaths in people younger than 35 years of age are associated with a negative autopsy [13]. In such cases, the cardiac ion channelopathies are the prime suspects—causing sudden death via rapid, usually polymorphic, VT or VF. They include long QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). Each condition has its own ECG signature, typical mode of presentation, and underlying genetic diatheses. If presenting other than with sudden death or cardiac arrest, cardiac ion channelopathies can be misdiagnosed as seizure disorders, but, if correctly detected before sudden cardiac death, condition-specific management can be recommended [13]. Flannery and La Gerche explain that it is thought a slightly greater risk in SCD in young athletes likely reflects the fact that intense exercise can serve as trigger for events in those with an underlying inherited or acquired cardiovascular disorder [14].

Recent Developments

Several reviews in this issue put forward the position that in patient selection for ICD, we need to move beyond the current international guidelines' LV ejection fraction cut-off [4,15,16]. Peters et al. report that the DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial, in particular, has highlighted the need to identify patients who would derive the *greatest* benefit from an ICD [15,17]. They emphasise that prophylactic implantable cardioverter-defibrillators (ICD) and early referral for heart transplantation may be indicated in particular individuals with nonischaemic dilated cardiomyopathy (DCM) who are high-risk *genotype-positive*. Meanwhile, Moore et al. point out that the extreme genetic heterogeneity in hypertrophic cardiomyopathy precludes routine genome-guided risk stratification for the present time [18].

Zaman et al. also call for the development of risk stratification tests to assist with optimal selection of patients for a prophylactic ICD [4]. In general, such tests would focus on detecting the presence of underlying substrate for arrhythmia, in which they see cardiac magnetic resonance (cMRI) imaging as promising. Chieng and Paul concur with this position, with the presence of late gadolinium enhancement on cMRI an important SCD risk predictor [16]. They also discuss recent developments in defibrillator technology, including subcutaneous and wearable devices.

Although ICDs effectively reduce sudden death, shocks are associated with significant adverse effects; indeed, recurrent ICD shocks can not only be distressing but also be associated with an increase in mortality. Consequently, given the limited efficacy and risks of antiarrhythmic drug therapy, catheter ablation is coming into its own as an effective management strategy in various structural heart disease contexts including not only post-infarct VT [19] but also nonischaemic cardiomyopathies [20,21]. Catheter ablation remains the favoured and only potentially curative treatment for idiopathic VT [22] and for recurrent PVC-triggeredVF [5]. Radiofrequency catheter ablation is also emerging as the life-saving standard of care in patients with structural heart disease presenting with electrical storm—multiple recurrences of VA over a short period of time [23]. Although ablative strategies will vary according to clinical setting, detailed pre-ablation mapping of substrate or trigger targets is key in all. In their review of catheter ablation of VF, Anderson et al. inform us that at the forefront of a potential mapping revolution is the ECG-I panoramic non-contact mapping system, which consists of a 252-electrode non-invasive mapping vest able to reconstruct panoramic three dimensional (3D) epicardial phase and

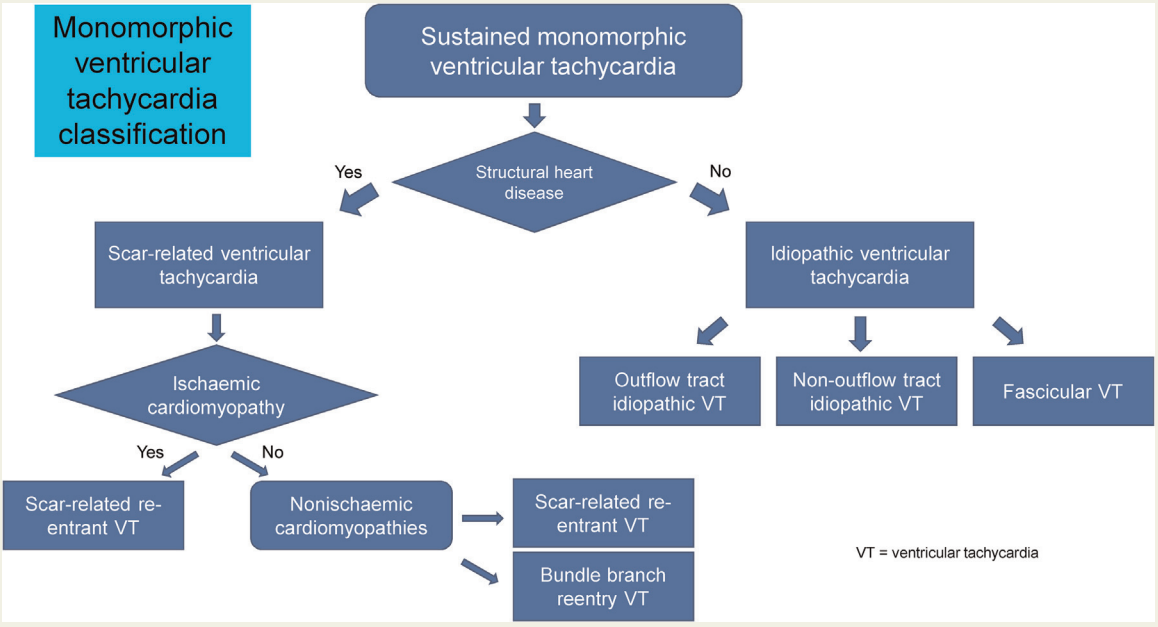

Figure 2

activation maps from surface ECG recordings [5,24]. In the meantime, in selected patients, mechanical circulatory support may permit mapping for longer periods by facilitating haemodynamic stability and preserving end-organ perfusion during sustained VT [24].

When, unfortunately, SCD has occurred, generally a full post-mortem examination is required. Femia et al. say that when this invasive ''gold standard'' is not possible, for example, because of advanced body decomposition or certain religious or cultural beliefs, alternative non-invasive approaches—such as post-mortem imaging with computed tomography (CT) in adults, or magnetic resonance imaging in fetal and paediatric cases—may provide a valid alternative approach to elucidate cause of death and are being explored [25]. Post-mortem CT angiography is also being developed, but currently remains a research tool [25].

In the final review of this Special Issue, Lee et al. confirm that frequent premature ventricular complexes (PVCs) are no longer always to be considered innocuous in the absence of structural heart disease. In a proportion of people, frequent PVCs may result in the development of an ectopy-mediated cardiomyopathy that may be reversed by PVC catheter ablation. Epidemiological studies also suggest that heart failure and mortality at a population level are associated with increasing PVC burden [26,27].

Future Directions

Sudden cardiac death is, simply put, a major public health issue [4]. However, Wong et al. remind us that our understanding of SCD epidemiology remains limited, particularly in low and middle-income countries and must be addressed with relevant studies and registries, such as the AusROC Epistry in Australia and New Zealand, if we are to further improve our knowledge of clinical risk factors [1,28].

Furthermore, Skinner et al. say that clinicians have a responsibility to not only screen the families of individuals with a cardiac ion channelopathy or unexplained sudden death, but also to encourage families to participate in clinical registries, to help us to reach a future goal of individualised therapy [13]. Given that cardiac ion channelopathies are largely Mendelian conditions, there is the possibility of gene therapy, and a mouse model of CPVT has already been created and cured by wild-type gene replacement using a viral vector [13,29].

Throughout this Special Issue, various of these highly detailed reviews point out the studies which need to be undertaken or completed to progress our understanding of SCD and VA and improve our management options. Chief amongst these will be the development of improved markers of SCD risk beyond the current crude use of left ventricular ejection fraction.

We hope this Special Issue will facilitate an understanding of the intricacies of what is already well known, an appreciation of emerging knowledge, and a sense of what we are yet to learn in the years to come.

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