Diagnostic evaluation of unexplained ventricular tachyarrhythmias in younger adults

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Abstract

Background: The diagnostic work-up for cardiac arrest from ventricular tachyarrhythmias occurring in younger adults and structurally normal hearts is variable and often incomplete. *Methods:* We reviewed records for all recipients of a secondary prevention implantable cardiac defibrillator (ICD) younger than 60 years at a single quaternary referral hospital from 2010-2021. Patients were included if they had unexplained ventricular arrhythmias (UVA) and absence of structural heart disease on echocardiogram, normal coronary assessment and no clear diagnostic features on ECG. We specifically evaluated the adoption rate of five modalities of 'second-line' cardiac investigations: cardiac magnetic resonance imaging (CMR), exercise ECG, flecainide challenge, electrophysiology study (EPS) and genetic testing. We also evaluated patterns of anti-arrhythmic drug therapy and device-detected arrhythmias and compared them with secondary prevention ICD recipients with a clear aetiology found on initial assessment. *Results:* 102 recipients of a secondary prevention ICD under the age of 60 were analysed. 39 patients (38.2%) were identified with UVA and were compared with the remaining 63 patients with VA of clear aetiology (61.8%). UVA patients were younger (35.6 ± 13.0 years vs 46.0 ± 8.6 years, p<0.001) and were more often female (48.7% vs 28.6%, p=0.04). CMR was performed in 32 patients with UVA (82.1%), whereas flecainide challenge, stress ECG, genetic testing and EPS were only performed in a minority of patients. Overall, the use of a second-line investigation suggested an aetiology in 17 patients with UVA (43.5%). Compared to patients with VA of clear aetiology, UVA patients had lower rates of antiarrhythmic drug prescription (64.1% vs 88.9%, p=0.003) and had a higher rate of device-delivered tachy-therapies (30.8% vs 14.3%, p=0.045). *Conclusion:* In this real-world analysis of patients with UVA, the diagnostic work-up is often incomplete. While CMR was increasingly utilized at our institution, investigations for channelopathies and genetic causes appear to be underutilized. Implementation of a systematic protocol for work-up of these patients requires further study.

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Abstract.

Background: The diagnostic work-up for cardiac arrest from ventricular tachyarrhythmias occurring in younger adults and structurally normal hearts is variable and often incomplete.

Methods: We reviewed records for all recipients of a secondary prevention implantable cardiac defibrillator (ICD) younger than 60 years at a single quaternary referral hospital from 2010-2021. Patients were included if they had unexplained ventricular arrhythmias (UVA) and absence of structural heart disease on echocardiogram, normal coronary assessment and no clear diagnostic features on ECG. We specifically evaluated the adoption rate of five modalities of 'second-line' cardiac investigations: cardiac magnetic resonance imaging (CMR), exercise ECG, flecainide challenge, electrophysiology study (EPS) and genetic testing. We also evaluated patterns of anti-arrhythmic drug therapy and device-detected arrhythmias and compared them with secondary prevention ICD recipients with a clear aetiology found on initial assessment.

Results: 102 recipients of a secondary prevention ICD under the age of 60 were analysed. 39 patients (38.2%) were identified with UVA and were compared with the remaining 63 patients with VA of clear aetiology (61.8%). UVA patients were younger (35.6 ± 13.0 years vs 46.0 ± 8.6 years, $p<0.001$) and were more often female (48.7% vs 28.6%, $p=0.04$). CMR was performed in 32 patients with UVA (82.1%), whereas flecainide challenge, stress ECG, genetic testing and EPS were only performed in a minority of patients. Overall, the use of a second-line investigation suggested an aetiology in 17 patients with UVA (43.5%). Compared to patients with VA of clear aetiology, UVA patients had lower rates of antiarrhythmic drug prescription (64.1% vs 88.9%, $p=0.003$) and had a higher rate of device-delivered tachy-therapies (30.8% vs 14.3%, $p=0.045$).

Conclusion: In this real-world analysis of patients with UVA, the diagnostic work-up is often incomplete. While CMR was increasingly utilized at our institution, investigations for channelopathies and genetic causes appear to be underutilized. Implementation of a systematic protocol for work-up of these patients requires further study.

Introduction.

Ventricular tachyarrhythmia is a term used to describe a spectrum of cardiac arrhythmias arising from the ventricular myocardium. It comprises monomorphic ventricular tachycardia (VT), polymorphic VT, ventricular fibrillation (VF) and ventricular flutter[1]. Sustained ventricular tachyarrhythmia is a highly lethal arrhythmia and is implicated in an estimated 95% of cases of arrhythmic sudden cardiac death[2].

In the majority of cases, ventricular tachyarrhythmias are secondary to either an identifiable structural heart abnormality (e.g., coronary artery disease, non-ischaemic cardiomyopathy) or a primary electrophysiological disease evident on baseline electrocardiography (e.g., long QT syndrome, Brugada syndrome). However, an estimated 6-10% of patients who present with ventricular tachyarrhythmias have no clear aetiology suggested by ECG, transthoracic echocardiography (TTE) or coronary assessment[3,4]. While data in these patients with unexplained ventricular arrhythmia (UVA) is sparse, small case series have shown that these patients are often younger[5] and have a higher risk of recurrent cardiac arrest in the future[6].

Management of patients with UVA represents a clinical challenge, with the diagnostic workup for these patients being poorly standardised and often incomplete. Consensus guidelines published by the American

College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) on the evaluation of patients with ventricular tachyarrhythmias provides a Class I recommendation for the use of a baseline ECG, resting TTE and coronary angiography in the workup of patients presenting with ventricular tachyarrhythmia[7]. Other investigations, such as cardiac magnetic resonance imaging (CMR), electrophysiology study (EPS) and genetic testing, carry a Class II recommendation. Exercise stress testing, provocative testing for Brugada Syndrome (flecainide/ajmaline challenges) are not referenced in this guideline. The relative yield of each of these modalities of testing in the evaluation of UVA is uncertain.

Aims.

The present study had three aims. First, we aimed to evaluate the clinical characteristics of younger adults presenting with unexplained ventricular arrhythmia (UVA), as compared with patients who have an identifiable aetiology of ventricular tachyarrhythmia. Second, we aim to examine the variability in diagnostic evaluation undertaken in this UVA cohort. In particular, we will evaluate the adoption rate of five 'second-line' investigations: CMR, exercise stress ECG, flecainide challenge, EP study and genetic testing. Third, we aimed to assess differences in management and subsequent outcomes in patients with unexplained ventricular arrhythmia compared to their counterparts with an identified aetiological mechanism.

We hypothesised that the diagnostic workup in patients with UVA will be heterogeneous and incomplete. We also hypothesised that these patients with UVA will have lower rates of prescribed anti-arrhythmic drugs and a higher rate of recurrent ventricular tachyarrhythmia, as failure to identify a specific underlying aetiology may preclude appropriate targeted therapy.

Methodology.

The study was approved by our institutional ethics committee (Alfred Health Ethics Research Administration) as a low-risk project. Records were reviewed for all patients under the age of 60 who underwent implantation of a secondary prevention implantable cardiac defibrillator (ICD) between January 2010 and July 2021 at a single quaternary cardiology centre in Melbourne, Australia. Secondary prevention ICD was defined in our study as a device implanted after a clinical presentation with either 1) ventricular tachyarrhythmias resulting in syncope and/or cardiac arrest, or 2) conscious sustained ventricular tachycardia. We included patients receiving both subcutaneous ICDs and transvenous devices, with the transvenous devices comprising single chamber ICDs, dual chamber ICDs and biventricular ICDs.

Records were reviewed for all cardiac investigations performed as part of the diagnostic evaluation in these device recipients, defined as investigations performed either within 3 months prior to device implant or within 6 months following device implant. Baseline ECGs were accessed to record rhythm, cardiac axis, QT interval and the presence or absence of the early repolarisation pattern. Transthoracic echocardiography (TTE) records were accessed to collect both qualitative parameters (overall left and right ventricular function, presence of segmental hypokinesis, degree of valvular dysfunction) and quantitative parameters (LV diastolic diameter and left ventricular ejection fraction). Investigations for coronary artery disease, including invasive coronary angiography and computerised tomographic coronary angiography (CTCA), were accessed to record the presence of obstructive coronary artery disease, defined as >70% luminal stenosis, and requirement for follow-on coronary revascularisation.

We then identified a cohort of patients with unexplained ventricular arrhythmias (UVA, Group 1) in whom the aetiology for ventricular arrhythmia remained unexplained after three 'first-line' cardiac investigations: TTE, ECG and coronary assessment (Table 1). More specifically, patients with UVA were defined as those structurally normal heart on TTE, absence of obstructive disease on coronary assessment and no clear diagnostic features on ECG. Examples of clear diagnostic features on ECG included long or short QT inter-

vals, features of arrhythmogenic right ventricular cardiomyopathy (ARVC), features of Brugada syndrome or manifest pre-excitation.

We compared this UVA cohort of patients with patients having a confirmed or strongly suspected aetiology of their ventricular arrhythmia on the basis of 12-lead ECG, TTE and coronary assessment. This group was labelled was labelled VA with clear aetiology (Group 2).

We then evaluated the adoption rate of five modalities of 'second-line' investigations for ventricular arrhythmia in both groups. These second-line investigations included cardiac magnetic resonance imaging (CMR), exercise stress ECG, flecainide challenge, electrophysiology studies (EP) and genetic testing. Where these investigations were available, we recorded whether the result elucidated the underlying aetiology of the presenting ventricular arrhythmia.

Clinical discharge summaries were reviewed to determine which antiarrhythmic drugs were prescribed to patients following presentation with a ventricular arrhythmia. We recorded rates of prescription of beta blockers, amiodarone, flecainide and sotalol.

Finally, we sought to evaluate outcome data for patients with respect to future burden of ventricular arrhythmia and all-cause mortality. We reviewed all available records from subsequent device interrogations for the first five years following device implantation. In order to be included for this phase of the analysis, patients were required to have documentation of at least two device interrogation reports over this five-year period. We assessed for the frequency of device-detected NSVT and requirement for tachycardia therapies, including anti-tachycardia pacing (ATP) and device-delivered shocks. Hospital records were reviewed to assess for patient mortality up to 10 years following device implant.

Statistical analysis.

Differences between the two groups were assessed by the Student's unpaired t-test for all parametric data, by the Mann-Whitney U test for non-parametric data. These quantitative data were expressed as the mean ± standard deviation (SD). Differences between the two groups for categorical data was performed using the Chi-Square test. These data are represented as the number of patients in the category followed by the percentage of the group total, as *n (%)*. Statistical analysis was performed using SPSS version 21 (IBM SPSS, Armonk, NY). A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

Records were reviewed for 287 recipients of a secondary prevention ICD between January 2010 and July 2021 (Figure 1). Of these, 185 patients were excluded on the basis of being >60 years of age. The remaining 102 patients were included for further investigation. These patients were dichotomised based on the criteria described in Table 1, such that 39 patients (38.2%) were identified with unexplained ventricular arrhythmia (UVA, Group 1) and the remaining 63 patients (61.8%) were labelled VA with clear aetiology (Group 2). Of these 63 patients, the identified aetiologies of ventricular arrhythmia fit into the following categories: 16 (25.3%) had ischaemic cardiomyopathy, 38 (60.3%) had non-ischaemic cardiomyopathy and 9 (14.3%) had a primary electrical aetiology which was evident on their resting baseline ECG.

The baseline characteristics for the patients in described in Table 2. Patients with UVA were clinically distinct from their counterparts with VA of clear aetiology. UVA patients were younger in age (35.6 ± 13.0 years vs 46.0 ± 8.6 years, $p<0.001$) and were more often female (48.7% vs 28.6%, $p=0.04$). A lower proportion of the patients with UVA had traditional cardiovascular risk factors, including hypertension (10.3% vs 30.2%,

p=0.02) and diabetes (2.6% vs 15.9%, p=0.04). A greater proportion of UVA patients gave a history of prior syncope compared to patients with VA of clear aetiology (20.5% vs 9.5%, p=0.03).

When reviewing the culprit rhythm disorder which formed the indication for ICD, a higher proportion of patients with UVA had ventricular fibrillation compared to their counterparts with VA of clear aetiology (87.2% vs 50.8%, p<0.001), while a lower proportion had monomorphic VT (7.7% vs 46.0%, p<0.001). There was consequently a trend towards a greater proportion of UVA patients presenting in the context of a cardiac arrest (82.1% vs 65.1%, p=0.06).

When reviewing the ICD subtype across the two groups, patients with UVA were more likely to receive subcutaneous ICDs than their counterparts with VA of clear aetiology (20.5% vs 4.8%, p=0.01). Both groups had similar rates of implantation with single chamber and dual chamber devices. No patients in the UVA group received a biventricular device compared with 5 patients with VA of clear aetiology (7.9%).

First-line cardiac investigations

The results of baseline ECGs, transthoracic echocardiograms and coronary assessments are shown in Table 3. All patients reviewed had a baseline ECG available for analysis. Baseline ECG characteristics were similar across the three groups, with the only significant difference being a higher rate of axis deviation in patients with VA of clear aetiology compared to those with UVA (28.6% vs 10.3%, p=0.02). Sinus rhythm was the prevalent baseline rhythm in the majority of patients in both groups (UVA: 97.4%, VA of clear aetiology: 87.3%, p=0.08). Of note, two patients (5.1%) in the UVA group exhibited the early repolarisation pattern on their ECG (without additional diagnostic features of early repolarisation syndrome), while no patients with VA of clear aetiology exhibited this finding.

All patients analysed had a baseline transthoracic echocardiogram available for review. In keeping with the criteria used to defined the two groups, patients with UVAs had significantly lower rates of structural heart disease compared with their counterparts with VA of clear aetiology. Specifically, UVA patients had a higher LV ejection fraction (59 ± 8.4% vs 42.1 ± 15.3%, p<0.001) and smaller LV cavity size (50.8 ± 6.4mm vs 56.1 ± 11.0mm). By definition, no patients in the UVA group exhibited impaired RV function, moderate-or-worse valve dysfunction or segmental hypokinesis. These features were respectively present in 30.2%, 14.3% and 30.2% of the patients with VA of clear aetiology.

Coronary assessments (either CTCA or invasive coronary angiography) were widely performed in patients with UVA (87.2%) and VA of clear aetiology (84.1%). By definition, no patients in the UVA group had obstructive coronary disease, which in turn was present in 27.0% of patients with VA of clear aetiology. 14.3% of patients with VA of clear aetiology required follow-on revascularisation.

Second-line cardiac investigations

Table 4 demonstrates the adoption rate of 'second-line' investigations for the workup of ventricular arrhythmia in patients with UVA and VA of clear aetiology. Cardiac MRI was the most commonly utilised modality in both groups, but was more commonly adopted in patients with UVA (82.1% vs 63.5%, p=0.046). The remainder of the second-line investigations, flecainide challenge, genetic testing, EP study and exercise stress ECG, were only utilised in a minority of patients in both groups. Combined workup with all five second-line investigations was only utilised in 3 patients, all of whom were patients with UVA.

The individual diagnoses that were identified as a result of second-line investigations in patients with UVA is shown in Figure 2. CMR facilitated diagnosis of an underlying aetiology of ventricular arrhythmia in 8 patients. The late gadolinium enhancement (LGE) pattern of ventricular scar was suggestive of a diagnosis in the majority of these cases, including 2 cases of sarcoidosis, 1 case of old (inactive) myocarditis and 1 case of transmural scar in a patient with non-obstructive CAD (suggestive of a coronary embolic event). Morphological analysis of the RV was suggestive of underlying arrhythmogenic cardiomyopathy in 2 patients.

Flecainide challenge was performed in 8 patients (20.5%) and revealed a provokable ECG pattern suggestive of Brugada syndrome in 2 cases. Genetic screening was performed in 10 patients; 8 of these patients reported a family history of sudden cardiac death. A likely genetic culprit was identified in 3 cases. One patient was found to have a ryanodine receptor-2 mutation suggestive of catecholaminergic polymorphic VT (CPVT), one patient was found to have a desmoglein-2 mutation suggestive of ARVC, and one patient was found to have a desmin mutation signalling the presence of an underlying early NICM. An EP study was performed in 6 patients (15.4%). Focal VT originating from the LV inferior septum and perimitral VT were found in one patient each. In one case, the EP study demonstrated evidence of a right posterior accessory pathway; suggesting that the malignant arrhythmia in question may have been a pre-excited tachycardia rather than a ventricular tachyarrhythmia. While exercise stress ECGs were performed in 8 patients (20.5%), no patients were identified to have catecholaminergic polymorphic VT or congenital long QT syndrome.

Taken together, 17 patients in the UVA cohort (43.5%) had a suggestive aetiology for ventricular arrhythmia identified on one or more of the five second-line investigations.

Prescribed anti-arrhythmic therapy

Table 5 reviews the rates of prescription of antiarrhythmic therapies at time of hospital discharge in each group. A lower proportion of patients with UVA were prescribed at least one antiarrhythmic drug at time of hospital discharge compared with their counterparts with VA of clear aetiology (64.1% vs 88.9%, p=0.003). This was predominantly driven by lower rates of prescription of beta blockers (51.3% vs 81.0%, p=0.002) and amiodarone (5.1% vs 34.9%, p=0.001).

Device-detected arrhythmia burden

Table 6 reviews the data collected from device interrogations in the first 5 years post-device implantation. At least two device interrogation reports were available for 34 patients with UVA (87.1%) and 51 patients with VA of clear aetiology (81.0%). Reviewing these records revealed a significantly greater requirement for device-delivered tachy-therapies in the UVA group compared with the VA of clear aetiology group (30.8% vs 14.3%, p=0.04). Rates of device-detected NSVT were similar across the UVA and VA of clear aetiology cohorts (43.6% vs 38.1%, p=0.58). 3 patients were found to have died during follow-up: all three were in the VA of clear aetiology cohort. 2 deaths resulted from end-stage systolic heart failure and one death resulted from VT storm.

Discussion.

Our data provide important insights into the prevalence, clinical features and diagnostic evaluation of patients with unexplained ventricular arrhythmia in a real-world analysis. The key finding of this study is that only a minority of patients with UVA underwent a comprehensive assessment with an extended panel of investigations. Furthermore, our data suggest that completing a more comprehensive assessment in patients with UVA may allow for a significant proportion of these patients to be assigned a more specific diagnosis with subsequent targeted treatment.

Prevalence and clinical features of patients with UVA

In the present study, 38% of secondary prevention ICD recipients who were evaluated met our criteria for UVA. This is a higher proportion of UVA than has been demonstrated in existing research. In a retrospective review of 717 survivors of sudden cardiac arrest by Waldmann et al[8], the proportion of cases which remained unexplained following assessment of baseline ECG, TTE and coronary arteries was 12.3%. We posit two reasons for this discrepancy. First, our analysis was restricted to ICD recipients under the age of 60. Younger patients are more likely to present at an earlier stage of their cardiac pathology and are thus more likely to

have subclinical cardiomyopathies or only subtle baseline ECG changes at their time of presentation. Second, our study only examined patients receiving secondary prevention ICDs, rather than evaluating all-comers with cardiac arrest or ventricular tachyarrhythmia. This excluded patients who presented with ventricular tachyarrhythmias secondary to acute ischaemia or other reversible causes, in whom an ICD would not be implanted. Both features of our analysis may have led to a higher representation of UVA.

Our data suggest that patients with UVA are clinically distinct from their counterparts with ventricular tachyarrhythmias with manifest structural or electrical heart disease. UVA patients in the present study were significantly younger, more often female had a lower burden of traditional cardiovascular risk factors. Our findings are largely in keeping with previous research in this field, which has consistently demonstrated that patients with unexplained or idiopathic ventricular arrhythmia are of younger age at time of presentation[8,9]. Existing data on sex differences in patients with UVA are more conflicted. While women account for a higher proportion of overall presentations of ventricular arrhythmia with structurally normal hearts[10], men account for a higher percentage of patients presenting with unexplained sudden cardiac arrest or death[5,6].

A history of a past episode of syncope preceding the acute presentation with ventricular tachyarrhythmia was reported in 23% of patients in the UVA cohort of the present study. This high proportion of prior syncope highlights the propensity for recurrent malignant arrhythmias in this cohort. This is further supported by the fact that patients in the UVA cohort more frequently required device delivered tachy-therapies during follow-up compared to patients with VA of clear aetiology. This higher risk for recurrent arrhythmia was also demonstrated in a previous review of medium-term outcomes in 66 patients with idiopathic ventricular fibrillation, in which recurrent ventricular arrhythmias were seen in 20% of patients[6].

Significant differences in the pattern of prescribed therapies were demonstrated between patients with UVA compared to those with VA of clear aetiology. This may be due to the higher proportion of structural heart disease in the VA of clear aetiology group, including coronary artery disease and heart failure with reduced ejection fraction. Both of these conditions represent an indication for beta blockade independent of presentation with ventricular arrhythmia. However, amiodarone was also prescribed at a lower rate to UVA patients. One reason for this may be a reluctance to overprescribe medications to patients with structurally normal heart and no clear diagnosis, particularly in medicines with long-term toxicity such as amiodarone.

Diagnostic evaluation of UVA in current practice

In this single-centre review, 12-lead ECG and transthoracic echocardiogram data was acquired in all patients requiring a secondary prevention ICD. Conversely, coronary evaluation was acquired in most, but not all secondary prevention ICD recipients, and 13% of patients in the UVA cohort did not undergo any form of coronary assessment. Current ACC/AHA provide a Class I recommendation for the use of either CT or invasive coronary angiography in patients with unexplained cardiac arrest[7]. Potential reasons for patients with UVA not being selected for coronary assessment in the present study include younger age and lack of traditional cardiovascular risk factors. However, non-atherosclerotic coronary disease remains an important cause of ventricular arrhythmia in younger patients, and may be due to anomalous coronary arteries[11], coronary embolic events[12] or coronary vasospasm[13].

In our analysed cohort of 39 patients with UVA, the utilisation of second-line investigations was highly heterogenous. As the statewide CMR quaternary referral centre for Victoria, CMR was the most commonly utilised modality of testing, adopted in 82% of participants. However, other investigations were comparatively underutilised, including genetic testing (26%), flecainide challenge (21%), exercise ECG (21%) and EP study (15.4%). Such inconsistency in the evaluation of UVA has been replicated in existing literature. Waldmann et al demonstrated that in a cohort of 81 cases of unexplained cardiac arrest, while CMR was utilised in 81% of patients, other investigations including ajmaline challenge, EP study and genetic testing were performed in only a minority of cases (43%, 25% and 18% respectively).

Reasons for this variability are uncertain, but several factors are probably involved. First, standardised protocols for the evaluation of UVA are not in place. Such a standardised assessment has been studied and

advocated for in the past[9], but has not gained traction in current practice. Second, most of these second-line investigations are usually completed in the outpatient setting, where it can be more challenging to organise further investigations and perhaps many patients with UVA may be lost to follow-up, particularly given their younger age. One reason why the uptake of CMR is higher than other modalities may be the impetus to complete this investigation as an inpatient prior to the insertion of an ICD to allow for maximal diagnostic yield.

Diagnostic yield of comprehensive assessment in UVA

In our study, 17 out of 39 patients (43%) of patients with UVA had a cause for ventricular arrhythmia suggested by one of the five second-line investigations which were evaluated. This is in spite of the highly variable nature of the work-up performed, and an even higher proportion of patients may have had a diagnosis confirmed if complete work-up was performed in all patients.

CMR had the highest diagnostic yield of all the investigations studied, suggesting an underlying diagnosis in 8 patients. All diagnoses related to structural heart disease initially not identified on transthoracic echocardiography. This included diagnoses related to enhanced evaluation of right ventricular function (ARVC diagnosed in 2 patients), better visualisation of subtle structural anomalies (mitral annular disjunction diagnosed in 1 patient), evaluation of tissue oedema (acute myocarditis diagnosed in 1 patient) and patterns of late gadolinium enhancement (cardiac sarcoidosis diagnosed in 2 patients, previous myocarditis diagnosed in 1 patient, transmural scar suggestive of prior infarct diagnosed in 1 patient). CMR is well understood to be more sensitive for the diagnosis of cardiac sarcoid[14], myocarditis[15] and ARVC[16] compared to echocardiography, all of which have a strong association with ventricular arrhythmia.

Conversely, exercise ECG had the lowest diagnostic yield in this study, with no additional information gained in 8 patients that underwent this test. Part of this may be explained by the small number of patients who underwent this investigation. While this study alone does not lend support to the utility of exercise ECG in providing diagnostic clarity in patients with UVA, previous research has shown that exercise testing can unmask primary electrical disorders such as catecholaminergic polymorphic VT[17] and long QT syndrome[18]. Furthermore, a negative stress ECG may provide value as a marker of improved prognosis and lower risk of recurrent arrhythmia in patients with previous cardiac arrest[19].

Ascertaining the underlying cause for unexplained ventricular arrhythmia is of substantial clinical importance. First, it allows for targeted therapies to be utilised, not only to prevent future arrhythmia but also prevent the development of future structural heart disease. An example of this is prescription of immunosuppressive therapy after diagnosis of active sarcoidosis or myocarditis. Second, it allows for better risk stratification and lifestyle modification advice. For instance, two patients in our cohort were diagnosed with concealed Brugada syndrome with the use of a flecainide challenge, and appropriate advice about avoidance sodium channel blocking drugs and awareness of hyperthermia was provided. Third, it has important implications for family screening, particularly in cases of subclinical non-ischaemic cardiomyopathy (e.g. ARVC) or channelopathies. Fourth, in certain cases, elucidation of the underlying diagnosis may preclude the need for ICD therapy. An example in our cohort was one patient who was found to have a right paraseptal accessory pathway on EP study with malignant anterograde conduction properties. Diagnosis and ablation of this pathway would effectively prevent future pre-excited tachycardia and may have obviated the need for a defibrillator.

Limitations and directions for future research

Our analysis has a number of important limitations. First, this study is limited by the small sample size. This is an inherent limitation of studying ventricular arrhythmia and cardiac arrest in younger patients, which remains a relatively infrequent, albeit important clinical entity.

Second, this was a single-centre retrospective review. The findings relating to the adoption of certain diagnostic tests therefore only reflects the practice at our own institution, and cannot be extrapolated to the

practice in the larger Australian or international cardiology community. One important distinction was the high rate of utilisation of CMR in this study, as access to CMR in varies significantly between cardiac centres in Australia. However, it is notable that the adoption rates for CMR, flecainide challenge and genetic testing in our study were similar to the rates described in a previous European retrospective review of patients with unexplained sudden cardiac arrest[8]. Both this limitation and the small sample size could be mitigated by a multi-centre extension of the current study.

Third, this study did not evaluate the role of early versus delayed diagnosis in patients with UVA. A proportion of the patients in the UVA cohort were diagnosed with an underlying aetiology for ventricular arrhythmia early in their clinical course; for instance, patients who underwent CMR prior to ICD implant while still an inpatient after presenting with cardiac arrest. Such patients would therefore not have had 'unexplained' ventricular arrhythmia from this point onwards and during their subsequent follow-up. In future research, this limitation could be mitigated by evaluating patients who had a label of 'unexplained ventricular arrhythmia' at their time of hospital discharge. In such an analysis, it would be interesting to measure the time delay between the initial presentation with ventricular arrhythmia and the eventual diagnosis being made.

Finally, our analysis was restricted to patients implanted with a secondary prevention ICD. This was chosen as a practical method to collect data on patients who had suffered from ventricular tachyarrhythmias presenting to our institution. However, this fails to capture patients presenting with ventricular arrhythmia in whom defibrillators are not implanted, and those patients who die from sudden cardiac arrest whose diagnoses may be made on post-mortem autopsy. Future research in this field could instead review registry data for patients with sudden cardiac arrest, to more widely explore the subject of unexplained ventricular arrhythmia.

Conclusion.

A substantial proportion of adults under the age of 60 who present with ventricular tachyarrhythmia requiring an ICD will not have an apparent diagnosis after baseline ECG, TTE and coronary assessment. Comprehensive assessment with second-line investigations such as CMR, flecainide challenge and genetic testing may provide an underlying diagnosis in many of these patients, however the diagnostic evaluation in these patients is highly variable and often incomplete. Implementation of a systematic protocol for work-up of these patients requires further study.

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