

## Mechanism and Prognosis of Syncope in Acquired and Inherited Cardiac Disorders

Martin H Ruwald

Martin H Ruwald, Department of Cardiology, Gentofte Hospital, Hellerup, Denmark

Martin H Ruwald, Division of Cardiology, Heart Research Follow-up Program, University of Rochester, Rochester, NY, the United States

Correspondence to: Martin H Ruwald, MD, PhD, Heart Research Follow-up Program, 265 Crittenden Boulevard, Rochester, 14642, NY, the United States

Email: [mruwald@hotmail.com](mailto:mruwald@hotmail.com)

Telephone: +585-775-7682

Fax: +585-273-5283

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### INTRODUCTION

Syncope is a condition defined as a sudden and transient loss of consciousness, loss of postural tone and complete and spontaneous recovery<sup>[1]</sup>. Syncope is a common condition both in the general population<sup>[2]</sup> and as a cause of hospital contact<sup>[3]</sup> and the proportion of patients presenting with syncope in emergency departments (ED) in Europe and the US is approximately 1%<sup>[3-5]</sup>. Admission rates vary significantly depending on health care systems and organization and ranges from 13-83%<sup>[6,7]</sup> resulting in up to 1-6% of all medical hospital admissions<sup>[3,4,8]</sup>. The lifetime cumulative incidence of syncope is higher than 35%<sup>[9]</sup> with bimodal incidence peaks at 20 and 80 years of age<sup>[3,10]</sup> while incidence rates increase dramatically after the age of 70<sup>[2,3]</sup>.

Broadly categorized syncope can be classified by etiology in three groups. Reflex (vasovagal/neurocardiogenic/neurally mediated), orthostatic hypotension syncope and cardiac syncope. The mechanisms of these etiological causes of syncope differ widely but all result in reduced cerebral perfusion and blood flow resulting in syncope<sup>1</sup>. Reflex is the most common form irrespective of age, sex and comorbid status, while orthostatic hypotension syncope is rare in younger persons and common among the elderly. Finally the proportion of cardiac syncope increases with age and underlying comorbid heart diseases. Important to remember is that the proportion of these syncope etiologies differ widely depending on the clinical setting, in the general population, at the general practitioner, ED or in specialized syncope clinics<sup>[2,11-23]</sup>.

The prognosis also differs widely depending on the etiological cause and underlying comorbidities. Reflex syncope is generally thought of as benign<sup>[2,24]</sup> but may result in trauma, hip fractures, cerebral hemorrhage and vehicle accidents particularly among those with many recurrences. The influence of syncope induced trauma and accidents on mortality has however not yet been evaluated. The prognosis of reflex syncope in patients with concomitant heart disease is furthermore probably mostly determined by the prognosis of the underlying heart disease itself<sup>[25]</sup>. On the other

### ABSTRACT

The overall prognosis of patients with syncope depends on the severity and type of underlying heart disease. Major differences in syncope study populations reflect this relationship and underline the difficulty of risk stratification of syncope in unselected mixed syncope populations. For most heart diseases, syncope is an independent marker of adverse prognosis and sudden death compared to patients without syncope often representing a malignant brady- or tachyarrhythmia. Underlying heart disease or not, specifically cardiac syncope is associated with adverse prognosis. The mechanism of syncope reflects the underlying heart disease with increasing likelihood of arrhythmic syncope in more severe heart diseases and increasing likelihood of reflex syncope in less severe heart disease. In selected acquired or inherited heart diseases syncope may be associated with increased mortality independently of the proposed causal mechanism. This review focuses primarily on the mechanism and prognosis of patients with various heart diseases and syncope compared to those without syncope. Further the review discusses risk factors and establishes the overall prognosis of syncope in mixed syncope populations.

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**Key words:** Syncope; Prognosis; Mechanism; Heart disease

hand, specifically a cardiac syncope in a patient with heart disease is most likely a marker of adverse prognosis compared to a patient with the same heart disease without cardiac syncope. The prognosis among patients with heart disease further differs widely depending on severity of the underlying heart disease. Finally orthostatic hypotension has been associated with increased mortality independent of traditional risk factors<sup>[26]</sup>. A syncopal event in a patient with known heart disease may be a cause for concern and for many physicians this knowledge results in a decision to admit the patient. This decision may be driven by fear of missing a potential adverse outcome and is often taken irrespective of a presentation with typical vasovagal syncope symptomatology. This leads to expensive and excessive testing without a just cause. Other reviews focus on diagnosis, treatment and pathophysiology. This review will focus on the epidemiology and mechanisms of the cardiac etiologies and associated prognosis.

## ETIOLOGY AND MECHANISM OF SYNCOPES IN HEART DISEASES

Syncope in patients with heart diseases can be caused by all three major etiology groups; either by vasovagal syncope, orthostatic hypotension, or by the acquired or inherited heart disease itself by various mechanisms. Table 1a and b gives an overview of the significance of syncope in various common and rare heart diseases. It is important to behold that there is quite a significant overlap of etiological causes and mechanisms<sup>[27]</sup> even in patients with severe heart disease and that presence of heart disease do not imply that the syncope was caused by the condition itself.

## ARRHYTHMIAS

Among patients with any (unspecific) underlying heart disease, usually the most frequent cause of cardiac syncope is arrhythmic based on the review by Kapoor in 2000<sup>[28]</sup>. However, among patients with ischemic and non-ischemic cardiomyopathy and moderate to severely reduced left ventricular ejection fraction (LVEF) recent evidence points to arrhythmias being common but not the most prevalent cause. In a sub-analysis from the SCD-HeFT study<sup>[29]</sup> 70 (15%) syncopal events of 458 events were arrhythmic in origin while 302 (66%) were non-arrhythmic and 86 were unknown. In the MADIT-RIT study<sup>[30]</sup> 39% (25/64) of the patients had arrhythmic syncope while 61% (39/64) had non-arrhythmic syncope. Along this line but including a broader range of heart diseases, a study by Alboni *et al*<sup>[18]</sup> evaluated 191 syncope patients with suspected or confirmed heart diseases. Of these patients 39% had a presumptive cardiac cause of syncope and most of these were arrhythmic while 49% had vasovagal syncope and 12% were unexplained. In a study by Mitro *et al*<sup>[31]</sup> 139 syncope patients had various heart diseases and among those 83 (60%) patients had cardiac syncope and here arrhythmic syncope was dominant cause of cardiac syncope. The results from three of these four populations involving various common underlying heart diseases reveal that in the majority of these cases syncope is often caused by non-arrhythmic causes, typically vasovagal or orthostatic hypotension. For rare cardiac disorders such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome, ventricular tachycardias (VT) may however dominate the cause of syncope. See details below in this review.

For arrhythmias both tachycardias and bradyarrhythmias may result in syncope. Supraventricular tachyarrhythmias are generally better tolerated than VT and the faster the heart rate the less well it is

tolerated. Patients with reduced LVEF are typically less able to tolerate fast heart rhythms. The MADIT-RIT investigated, by randomization, the influence of novel ICD programming on risk of inappropriate ICD therapies and a sub-analysis revealed that slow VTA (170 bpm-199 bpm) rarely result in syncope. Here 1% (1/118) of all VTA in that heart rate range resulted in syncope, while 8% (11/133) of fast VTA ( $\geq 200$  bpm) resulted in syncope. In the ADVANCE III trial<sup>[32]</sup> there was no significant increase in syncopal events between an ICD population with ICD programming set to long detection compared with traditional shorter detection with 24 events in 20 patients and 16 events in 14 patients in the two randomized groups, respectively. The individual breakdown of causes of syncope is not yet reported from the ADVANCE III trial, but so far it seems supportive of the results from the MADIT-RIT indicating that slow VTA rarely result in syncope and that ICD programming set to longer detections do not result in a significant increase in syncopal events. Lüsebrink *et al*<sup>[33]</sup> found in a recent study of 200 ICD patients that 12 patients (6%) experienced slow VTA ( $< 187$  bpm) without any syncope related symptoms. Finally, Sivagangabalan *et al*<sup>[34]</sup> found a syncope event rate of 0.7% for slow VTA (cycle length  $> 320$  ms) compared to 2.3% for fast VTA (cycle length 251-320) in an ICD programming study of 602 patients. The posture of a patient during the onset further affects the tolerability tallying a vasodepressor component with pooling of blood in the splanchnic veins and legs. Sinus node syndrome or high degree atrioventricular (AV) block causing bradycardia and asystolic episodes is another frequent cause of syncope in patients with cardiac conditions<sup>[35,36]</sup>. In the study by Alboni *et al*<sup>[18]</sup> most of the arrhythmic causes of syncope among patients with heart disease were bradyarrhythmic but the individual breakdown was not reported. For the total study population including patients without known heart disease the breakdown was reported: Of 51 patients with bradyarrhythmias, AV block was present in 40 (78%), sinus node dysfunction in 6 (12%) and atrial fibrillation with a slow ventricular response in 5 (10%). Of 17 patients with tachyarrhythmia, supraventricular tachycardia was present in 4 (24%) and ventricular tachycardia in 13 (76%). In comparison, in the MADIT-RIT study, all patients had ICD devices with backup pacing capability; here bradyarrhythmic causes of syncope were not seen but ventricular tachycardia accounted for 60% (15/25) of the arrhythmic syncopal events.

Other possible causes of cardiac syncope include mechanical outflow obstruction from the left ventricle affecting the cardiac output, particularly during exertion in conditions such as aortic stenosis<sup>[37]</sup> and severe hypertrophic cardiomyopathy<sup>[38]</sup>. A Pulmonary embolism in the setting of massive embolism with acute right ventricular failure also lead to impaired left ventricular filling and reduced cardiac output. Finally another mechanism specifically in the settings of acute myocardial infarction, aortic stenosis and acute pulmonary embolism is induction of a vasovagal specific mechanism.

## PROGNOSIS

What determines prognosis in syncope patients? Is it the underlying prognosis of a given heart disease or is syncope per se associated with increased mortality even without the presence of heart disease? Two major points can be made: The first is that syncope in a patient with underlying heart disease is a marker of a more severe presentation of the heart disease and secondly, that syncope in patients with no heart disease may be the first symptom of unrecognized heart disease<sup>[39]</sup>. To specifically claim that vasovagal syncope or orthostatic hypotension syncope in patients with heart disease is associated with increased mortality is however much more difficult and data from larger studies are needed.

**Table 1a** Cardiac conditions that frequently cause syncope by typical age groups and frequency at time of presentation. For every assesment the frequency of associated syncope may be related to the severity of the condition.

	Patients (15-50 years)	Patients (>50 years)
<b>Frequent cardiac condition</b>		
Valvular heart disease		Aortic stenosis <sup>[37,38,72]</sup>
Coronary artery disease and thrombosis		Acute ischemia or myocardial infarction <sup>[35,105-107]</sup> Pulmonary embolism <sup>[108-110]</sup>
Dilated cardiomyopathy		Ischemic <sup>29, 30, 36</sup> Non ischemic <sup>29, 30</sup>
Cardiac conduction disease		Sinus node dysfunction <sup>[111-113]</sup>
<b>Rare cardiac condition</b>		
Channelopathies	Long QT syndrome <sup>[92]</sup> Short QT syndrome <sup>[114]</sup> Brugada syndrome <sup>[99,115]</sup> CPVT <sup>[116]</sup>	
Myocardial disease	ARVD <sup>[81]</sup> Hypertrophic cardiomyopathy <sup>[77,117]</sup> Non-compaction <sup>[118]</sup>	
Infiltrative cardiomyopathies		Cardiac amyloidosis <sup>[119]</sup> Cardiac sarcoidosis <sup>[120,121]</sup>
Cardiac conduction diseases	Kearns-Sayre <sup>[122]</sup> Myotonic dystrophy <sup>[123]</sup>	Idiopathic atrioventricular block Lev-Lenegre <sup>[124]</sup>
Great vessel disease		Aortic dissection <sup>[125]</sup>

**Table 1b** Cardiac conditions that are less likely to cause syncope by typical age groups and frequency at time of presentation. For every assesment the frequency of associated syncope may be related to the severity of the condition.

	Patients (15-50 years)	Patients (>50 years)
<b>Frequent cardiac condition</b>		
Pericardial disease	Pericarditis <sup>[126]</sup>	
Valvular heart disease		Aortic regurgitation <sup>[127,128]</sup> Mitral regurgitation Tricuspid regurgitation
<b>Rare cardiac condition</b>		
Cardiac conduction disease	Wolf-Parkinson-White syndrome <sup>[129]</sup>	
Valvular heart disease		Mitral stenosis Tricuspid stenosis Pulmonic stenosis
Myocardial disease	Myocarditis <sup>[130,131]</sup>	
Other	Congenital heart diseases	
Pulmonary system		Severe pulmonary hypertension
Tumor		Atrial myxoma

Studies simply comparing mortality after syncope according to likely mechanism have consistently shown that patients with a cardiac cause have a higher mortality than those with a non-cardiac cause. In an older study from 1990 by Kapoor<sup>[24]</sup> of 433 syncope patients the 5-year mortality rate was 51% in patients with a cardiac cause compared with rates of 30% and 24%, respectively, in those with a non-cardiac or unknown cause. This study confirmed older smaller studies with 1-year mortality rate from 18-33% for cardiac causes and 0-12% for non-cardiac causes<sup>[40,41]</sup>. These mortality rates are however no longer applicable to unselected mixed syncope populations. Mixed syncope populations from more recent studies involved syncope patients from emergency departments and were prospectively collected for risk stratification purposes. In the first EGSYS study<sup>[12]</sup> the 1-year mortality rate was approximately 5%, while in the second EGSYS study<sup>[42]</sup> the 2-year mortality rate was 9%. In the OESIL study<sup>[43]</sup> the 1-year mortality was 12%, in the STePS Study<sup>[44]</sup> 6%, in the ROSE Study<sup>[45]</sup> 7%, in a study by Martin *et al*<sup>[46]</sup> 15% and 7% in a recent retrospective registry study from emergency departments<sup>[47]</sup>. For all these studies and others not involving long-term mortality<sup>[31,48,49]</sup>, the clinical characteristics, clinical definitions and the proportion of cardiac cause differed widely. Recently a meta-analysis was published summarizing some of the developed risk scores from emergency departments and associated risk factors and found that palpitations preceding syncope, syncope during effort, history of heart failure or ischemic heart disease and clinical and laboratory evidence or bleeding are the most powerful predictors of adverse outcome, while the most frequent to

appear in the included studies were a history of heart disease and an abnormal electrocardiogram (ECG)<sup>[7]</sup>. Table 2 shows condensed short-term risk factors to be recognized by physicians evaluating unselected syncope patients. All the risk stratification studies reported that with increasing number of risk factors the risk of mortality rose proportionately but several external validations have reported disappointing specificity<sup>[7,48,50,51]</sup>. None of the risk stratification scores have been implemented in routine care of syncope patients<sup>[1,51]</sup>.

## SYNCOPE IN CORONARY ARTERY DISEASE

The presence of ischemic heart disease increases the risk of syncope due to VTA. If syncope is unexplained and sustained VT or ventricular fibrillation (VF) can be induced in an electrophysiological study (EPS) an ICD is indicated or appropriate<sup>[52]</sup>. The EVSEM trial<sup>[53]</sup> demonstrated that both unexplained syncope ( $n=25$ ) and syncope associated with induced VTA in EPS ( $n=24$ ) indicated as high risk for death as patients who had documented spontaneous VTAs ( $n=332$ ). The 1-year all-cause death rates were 24%, 29% and 19%, respectively and 17% received an ICD during follow-up. In the AVID trial<sup>[54]</sup> including patients with structural heart disease, syncope and inducible VTA at an EPS an ICD implantation was associated with a reduction in mortality. Survival of the syncope patients (predominantly treated by ICD) was similar to the VTA patients treated by ICD and superior to the VTA patients treated by an antiarrhythmic drug ( $P=0.05$ ). In this trial the 1-year mortality rate for the syncope patients was 7%. Mittal *et al*<sup>[55]</sup> evaluated 67 patients

with coronary artery disease and unexplained syncope, 48% of these had inducible VTA on EPS and 1-year mortality was 23% despite ICD treatment versus 6% in the non-inducible group. Several groups have documented that inducible VTA predict later arrhythmias and appropriate ICD therapy in patients with unexplained syncope<sup>[56-59]</sup>. The ISSUE trial<sup>[60]</sup> documented that among patients (n=35) with unexplained syncope, structural heart disease and negative EPS the prognosis is good with no deaths during follow-up of 16±11 months.

## SYNCOPE IN NON-ISCHEMIC AND ISCHEMIC CARDIOMYOPATHY

The risk of death in patients with syncope and cardiomyopathy with moderate to severely depressed LVEF ≤35% is dramatically increased. Most likely causes of sudden death include VTA and bradyarrhythmias. Middlekauf *et al*<sup>[61]</sup> demonstrated in a pre-ICD era study (n=491, mean LVEF 20%) that syncope was associated with adverse outcome and a very high 1-year sudden death rate of 45% compared to 12% in those without syncope. The risk of death was independent of the cause of syncope indicating that syncope in this population was a significant and independent prognostic sign of adverse outcome. Several smaller studies have found that among patients with heart failure and unexplained syncope the risk of arrhythmic death is comparable to those patients with sustained VT. After the introduction of an ICD device, Knight *et al*<sup>[62]</sup> compared patients with unexplained syncope, non-ischemic cardiomyopathy (n=14) and negative EPS to patients who had survived a cardiac arrest. Among those with syncope all recurrent episodes of syncope were associated with VTA and the risk of appropriate ICD therapy was equally high for both groups (50%). In a study by Fonarow *et al*<sup>[63]</sup> of 147 patients with non-ischemic cardiomyopathy and unexplained syncope, 25 patients received an ICD and 122 did not in a non-randomized fashion. The 2-year mortality was significantly different with 15% in those with ICD compared to 33% without. Similarly, in a study by Sanchez *et al*<sup>[64]</sup> 19 patients with non-ischemic cardiomyopathy and negative EPS received an ICD and were matched with 32 patients who did not receive ICD. Implantation with an ICD was associated with significantly decreased risk of death or cardiac arrest with only 2 events (11%) versus 12 events (38%) during 44±20 months of follow-up. These studies led to Class IIA, level C recommendation of ICD implantation for reduction of sudden

cardiac death to patients with depressed LVEF and unexplained syncope among patients with non-ischemic cardiomyopathy, despite negative EPS<sup>[65]</sup>. This underlines the importance of stratifying by cardiomyopathy in patients with unexplained syncope when selecting diagnostic approach with EPS.

In ischemic cardiomyopathy, an ICD is well documented and indicated for reduction of mortality and sudden death for those who have an LVEF ≤35%<sup>[66,67]</sup>. The MADIT-II trial<sup>[67]</sup> enrolled patients with ischemic and non-ischemic cardiomyopathy and showed 1-year mortality rates of 9% in ICD group versus 10% in control group (conventional heart failure medications). On long-term follow-up the mortality was significantly reduced in the ICD group. In the SCD-HeFT trial<sup>[66]</sup> the 5-year mortality rates were 29%, 34% and 36% in ICD group, amiodarone and placebo group, respectively. The DEFINITE trial<sup>[68]</sup> enrolled only patients with non-ischemic heart failure and showed an overall borderline reduction in overall mortality with 1-year mortality rates of 3% in ICD group and 6% in conventional group<sup>[68]</sup>. Neither the DEFINITE nor the MADIT-II trials have specifically investigated syncope in their populations. Sub-analyses from the SCD-HeFT<sup>[29]</sup> and MADIT-RIT<sup>[30]</sup> evaluated the outcome of heart failure patients with and without syncope and both found that syncope in these populations is associated with increased mortality. In the SCD-HeFT trial 14% of the patients experienced syncope during the trial and those patients had 41% increased risk of all-cause mortality compared to those without syncope, independent of whether or not the patient was treated with amiodarone, placebo or received an ICD. In the MADIT-RIT study, syncope occurred in 4% of the patients and was associated with more than 3.5-fold increased mortality, independent of ICD programming and independent of etiology of syncope. These results supported the hypothesis in the original findings by Middlekauf *et al*<sup>[61]</sup> that syncope in heart failure patients is a marker of adverse prognosis independent of etiology. This is most likely due to a combination of identifying sicker patients, induced traumas, more heavily medicated patients and orthostatic intolerance rather than establishing causality with mortality for vasovagal syncope.

## SYNCOPE IN AORTIC STENOSIS

Aortic stenosis is the most common valvular heart disease in Western populations<sup>[69]</sup>. The prevalence of aortic stenosis in mixed syncope

**Table 2** Short-term risk factors adapted from<sup>[1]</sup> and<sup>[32]</sup>.

Significant heart disease	Prior myocardial infarction or other severe coronary artery disease Heart failure, particularly with low LVEF Other structural heart disease, ie. aortic stenosis
History	Syncope during exertion or in supine position A family history of sudden cardiac death or premature death Palpitations at time of syncope Shortness of breath
ECG features	Ventricular tachycardia (sustained or non-sustained) Left bundle branch block, intraventricular block or right bundle branch block with hemiblock Bradycardia without obvious explanation Sinoatrial block without obvious explanation Brugada type ECG pattern ARVC type ECG pattern Long or short QTc Early repolarization Q-waves Pre-exited QRS complex
Comorbidities associated with syncope and adverse outcome	Renal failure Severe anemia Electrolyte disturbances
Other suggested features	Age > 65 High BNP levels Low blood pressure at presentation

populations reflects the prevalence in the background population found in the Cardiovascular Health Study<sup>[37,69,70]</sup> accounting for approximately 1%, 2%, and 4% in age groups <65 years, 65-85 years and >85 years. Aortic stenosis was further found to be the influential comorbid risk factor for recurrent syncope<sup>[37]</sup>. Syncope in aortic stenosis is usually a sign of advanced aortic stenosis and the cause is likely to be multifactorial. In general syncope with aortic stenosis however often occurs with exercise. One theory is that the augmented stroke volume that follows exercise is limited in aortic stenosis by the narrowed obstructed orifice combined with an exercise-related decrease in arterial resistance resulting in a blood pressure decrease and syncope<sup>[71]</sup>. Other proposed mechanisms include a vasodepressor response triggered by increased left ventricular pressure during exercise in patients with aortic stenosis<sup>[38]</sup>. Although severe aortic stenosis is relatively rare amongst individuals who present with syncope the prognosis is highly dependent on available treatment which is, in most cases, valve replacement. The prognosis specifically for syncope patients (symptomatic) is difficult to determine and further depends (besides valve replacement) on degree of left ventricular dysfunction and/or development of ventricular arrhythmias<sup>[72-74]</sup>. Symptomatic (including syncope) patients not treated with valve replacement have a 25% 1-year mortality rate compared to 5-10% in those treated based on the reports from Schwarz *et al* from 1982<sup>[75]</sup> and Monin *et al* from 2003<sup>[72]</sup>. Comparatively, asymptomatic patients with aortic stenosis seem to have the same short-term risk as the age and gender matched background population (1-2% per year) and most patients seem to develop symptoms within 5 years<sup>[76]</sup>. ICD could be considered in patients with aortic stenosis and affected LVEF.

## SYNCOPE IN HYPERTROPHIC CARDIOMYOPATHY

Unexplained recent (within <6 months) syncope in hypertrophic cardiomyopathy increased the risk of sudden cardiac death almost five-fold in a large study of 1511 patients (mean age 46±20)<sup>[77]</sup>. Syncope was frequent (14%) in this population and dominated by unexplained syncope (>75%) and yearly mortality rate was ~3%. Conversely, for older patients (>40 years) and for those with remote syncope episodes (>6 months) there was no significant association with mortality demonstrated in this cohort. In hypertrophic cardiomyopathy, syncope or not, VTAs are very frequent as reported in results by Maron *et al*<sup>[78]</sup> with appropriate ICD therapy given in 39% for secondary prevention indication and in 17% in primary prevention indication. Despite this high risk of VTAs, syncope in this disorder is not solely caused by this mechanism. Patients with obstruction of the left ventricular outflow tract may experience syncope during exercise. In a study by Spirito *et al*<sup>[77]</sup> syncope during intense effort occurred more frequently in patients with outflow obstruction than in patients without. Conversely, both vasovagal and unexplained syncope at rest or during ordinary activity occurred with similar frequency in patients with and without outflow obstruction.

The main treatment for patients at high risk of sudden death is an ICD and is recommended for patients resuscitated from sudden cardiac death or sustained VT and is considered indicated if there is a family history of sudden cardiac death, maximum wall thickness of  $\geq 30$  mm or recent unexplained syncope<sup>[1,65,79,80]</sup>.

## SYNCOPE IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Syncope in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) is the presenting symptom in up to 30% of the patients<sup>[81,82]</sup> and may be the first manifestation of the disease. Syncope continues to be a predominant symptom in this population<sup>[83,84]</sup>. The fatty/fibrous tissue in the right ventricle is the substrate for VTAs causing syncope or even sudden cardiac death and high risk features for VTA include induction of VT during EPS, male gender, unexplained syncope, prior cardiac arrest and severe right ventricle dilation and involvement<sup>[65]</sup>. Multiple studies report a high proportion (range 50-78%) of appropriate ICD firing with or without syncope in high-risk patients implanted with ICD<sup>[81,85-87]</sup>. The 1-year mortality rates reported by Corrado *et al* in 132 patients (mean age 40 years) with high-risk ICD patients was 1% in patients without any occurrence of VF and 12% in patients with occurrence of VF. Further this study found that patients with unexplained syncope had similar rates of appropriate ICD firing (yearly rates of 15%) to patients with prior cardiac arrest or VT.

In a small sample of 37 syncope patients<sup>[83]</sup> without inducible VTA, electrical conduction disease with various degrees of AV block was the most predominant cause of syncope but nearly one third remained unexplained. Positive EPS or not, implantation with ICD is appropriate in patients with unexplained syncope and ARVC<sup>[52]</sup>.

## SYNCOPE IN CHANNELOPATHIES

These cardiac conditions include short and long QT syndrome (LQTS), Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). They are typically caused, but not limited to inherited defects in sodium, calcium or potassium channels or in the ryanodine receptor in the cardiac myocytes. Syncope is a very common symptom in these rare conditions and in all cases a marker of adverse prognosis compared to those without syncope. For LQTS, the risk of aborted cardiac arrest, appropriate ICD therapy and sudden cardiac death increases with increasing number of syncopal events. Syncope is present at time of ICD implantation in LQTS patients in 40-50%<sup>[88]</sup> and during follow-up occurs frequently in up to 50% depending on genotype, QTc, gender and use of beta-blocker therapy<sup>[89-91]</sup>. The 5-year cumulative probability of aborted cardiac arrest or sudden cardiac death was 5% in otherwise high risk (QTc>500 ms) patients without syncope, compared to 13%, 14%, 20% and 21% in patients with 1, 2, 3, and 4 number of syncopal events<sup>[92,93]</sup>. It is evident that the frequency of vasovagal syncope may be substantial in LQTS<sup>[94,95]</sup>, implied by a discrepancy between appropriate ICD shocks and number of syncopal episodes during follow-up. Syncope (most likely vasovagal) further occurred in 11% of genotype-negative family members of LQTS patients and has been shown to be associated with an almost zero rate of fatal events<sup>[96]</sup>. Vasovagal syncope may however still pose a threat to these patients by introducing bradycardia induced torsade de pointes further highlighting the difficulty of risk stratifying these patients based on an event of syncope<sup>[97]</sup>. So far, all events of syncope in LQTS patients should be considered a high risk feature. No data exists that compare mortality rates of adjudicated syncope events in LQTS patients. An ICD is appropriate in LQTS patients with unexplained syncope while on beta-blocker treatment<sup>[52]</sup>.

Syncope in Brugada Syndrome is often a presenting symptom and a frequent event occurring in up to 30% of the patients<sup>[98]</sup>. Appropriate ICD therapy among syncope patients occurs at approximately 2% per year compared to 5% in those with prior cardiac arrest and 1% in asymptomatic ICD recipients<sup>[99]</sup>. The prognosis of those with unexplained syncope or suspected non-arrhythmic syncope seems benign according to a recent report by Sacher *et al*<sup>[98]</sup> with no cardiac

deaths during a 5-year follow-up. The 1-year cardiac event rates from the FINGER Brugada Syndrome Registry<sup>[100]</sup> ( $n=1029$ ) was 8% for those with aborted cardiac arrest compared to 2% for syncope and 0.5% for asymptomatic. Positive EPS did not predict cardiac events in the PRELUDE study<sup>[101]</sup> of 308 patients (excluding those with prior cardiac arrest) while a history of syncope did. Sustained VTA or not in an EPS, an ICD is appropriate in patients with Brugada ECG pattern and unexplained syncope<sup>[52]</sup>. Implantable loop recorder may be an appropriate solution to clarify the cause of syncope in many cases, particular in non-type 1 ECG patterns since complication rates of ICDs in Brugada patients are high<sup>[1]</sup>.

Syncope in catecholaminergic polymorphic ventricular tachycardia is presenting symptom in 50% of the patients<sup>[102]</sup>. The largest study by Hayashi *et al*<sup>[102]</sup> of 101 patients (mean age  $12\pm 8$  years) demonstrated that prior syncope was not a significant predictive factor of cardiac events in CPVT patients. The study provided 8-year event rates of 32% for any cardiac event and 13% for fatal or near fatal event and a total of 37% of the patients experienced more than one cardiac event. If the study or subsequent studies were to investigate the influence of syncope on risk of sudden death or aborted cardiac arrest/appropriate ICD therapy it is highly likely that syncope (after diagnosis) would predict fatal outcome in this population. Beta-blockers protect to some degree with 82% relative risk reduction for fatal or near fatal events but patients remain at high risk with 8-year event rates of 27% and 11% for any cardiac event and fatal or near fatal events, respectively. This begets ICD treatment, independently of beta-blocker efficacy in patients with unexplained syncope but the therapeutic approach is less determined<sup>[52,65,103,104]</sup> as studies and patient populations are scarce.

High risk features for all channelopathies besides unexplained syncope and recurrent syncope include sustained VTA and aborted cardiac arrest. An ICD is commonly indicated to treat all patients at high risk of sudden cardiac death with a primary electrophysiological disorder/channelopathy<sup>[65]</sup>.

## CONCLUSION

The overall prognosis and mechanism of patients with syncope depends on the severity and type of underlying heart disease. Major differences in syncope study populations reflect this relationship and underline the difficulty of risk stratification of syncope in unselected mixed syncope populations. For most heart diseases, syncope is an independent marker of adverse prognosis and sudden death compared to patients without syncope often representing a malignant brady- or tachyarrhythmia. Underlying heart disease or not, cardiac syncope is associated with adverse prognosis. The mechanism of syncope reflects the underlying heart disease with increasing likelihood of arrhythmic syncope in more severe heart diseases and increasing likelihood of reflex syncope in less severe heart disease. In selected heart diseases syncope is further associated with increased mortality independently of the causal mechanism.

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### Abbreviations

ED: Emergency department

US: United States

LVEF: Left ventricular ejection fraction

SCD-HeFT: Sudden Cardiac Death in Heart Failure  
 MADIT-RIT: Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy  
 MADIT-II: Multicenter Automatic Defibrillator Implantation Trial-II  
 CPVT: Catecholaminergic polymorphic ventricular tachycardia  
 EPS: Electrophysiological study  
 ICD: Implantable cardioverter defibrillator  
 VTA: Ventricular tachyarrhythmia  
 VT: Ventricular tachycardia  
 VF: Ventricular fibrillation  
 LQTS: Long QT Syndrome  
 ARVC: Arrhythmogenic right ventricular cardiomyopathy  
 AVID: Antiarrhythmics versus Implantable Defibrillators  
 ROSE: Risk stratification of Syncope in the Emergency Department  
 ISSUE: International Study on Syncope of Uncertain Etiology  
 ADVANCE III: Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III  
 EGSYS: Evaluation of Guidelines in Syncope Study  
 OESIL: Osservatorio Epidemiologico sulla Sincope nel Lazio Study  
 AV: Atrioventricular  
 EVSEM: Electrophysiologic Study Versus Electrocardiographic Monitoring  
 DEFINITE: Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation  
 QTc: Corrected QT interval  
 FINGER: France Italy Netherlands Germany

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- Peer reviewers:** Petix Nunzia Rosa, MD, Department of Cardiology, San Giuseppe Hospital, Viale Boccaccio 2, Empoli, 50053, Florence, Italy; Paolo Alboni, Department of Medicine, Ospedale Privato Quisisana, Viale Cavour 128, 44121 Ferrara, Italy.