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Life threatening causes of syncope: Channelopathies and cardiomyopathies

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ABSTRACT

Syncope is common, has a high recurrence rate and carries a risk of morbidity and, dependent on the cause, mortality. Although the majority of patients with syncope have a benign prognosis, syncope as a result of cardiomyopathy or channelopathy carries a poor prognosis. In addition, the identification of these disorders allows for the institution of treatments, which are effective at reducing the risk of both syncope and mortality. It is for these reasons that the identification of a cardiomyopathy or channelopathy in patients with syncope is crucial. This review article will describe the characteristics of common cardiomyopathies and channelopathies and their investigation.

1. Introduction

Syncope is defined as a sudden transient loss of consciousness with postural failure due to inadequate cerebral perfusion with spontaneous recovery (Angaran et al., 2011; Bassetti, 2014). Syncope is both common, affecting 6.2 people per 1000 person-years, and associated with a high rate of recurrence (Soteriades et al., 2002). Furthermore, syncope carries a risk of morbidity from trauma associated with losing consciousness, and the fear of recurrence, death or that syncope will recur while driving or swimming (Rose et al., 2000; Van Dijk et al., 2006; Rose et al., 2009; Sheldon et al., 2009; Rosanio et al., 2013). The majority of cases of syncope have a benign prognosis, and often do not report their event to formal medical attention. Despite the common occurrence of syncope and its associated risks, 40% of patients presenting to the emergency room or primary care setting with an episode of syncope go home without a diagnosis (Kapoor, 1990). This article will focus on the exception to the generally benign prognosis, the patients with a manifest or latent cause of syncope that is life threatening.

2. Etiology

Syncope is classified based on the underlying cause of the episode (Fig. 1), and tools have been developed to aid in the distinction between the types of syncope. We refer the reader to the other articles in this Special Syncope Issue that outline the investigation of syncope-type symptoms and describe other causes of syncope (Van Dijk and Lim).

Syncope associated with structural cardiac disease or a channelopathy is associated with an increased risk of death (Ungar et al., 2010) and its treatment is often effective in reducing mortality (Khoo et al., 2013). Although this accounts for a minority of all syncope presentations, a comprehensive understanding of these conditions is essential. We will describe the features and mechanisms of the life threatening causes of syncope associated with cardiomyopathy and channelopathies.

2.1. Cardiomyopathy

The majority of patients with syncope in whom there is concern regarding underlying structural heart disease will have evidence of coronary artery disease or non-ischemic dilated cardiomyopathy. This is typically evident in the clinical history, and is a clear sign of risk of sudden death attributed to the risk of ventricular arrhythmia. Valvular heart disease is particularly common in the elderly, and is typically of concern if there is obstruction to forward flow leading to syncope (i.e. aortic stenosis with exertional syncope), or when associated with reduced left ventricular function. As outlined below, all patients presenting with syncope should undergo inquiry as to the presence of underlying structural heart disease, including a resting ECG in all patients, and an echocardiogram in the vast majority.

Less common causes of cardiomyopathy include infiltrative processes such as amyloidosis or hemochromatosis, and inherited causes such as hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC), familial dilated cardiomyopathy and myotonic dystrophy (Khoo et al., 2013). In most cases, the risk of sudden cardiac death (SCD) due to ventricular arrhythmia is proportional to the severity of left ventricular dysfunction (Buxton et al., 2000; Connolly et al., 2000; Katritsis et al., 2013). Detailed discussion of all of the causes of cardiomyopathy is beyond the scope of this review, but

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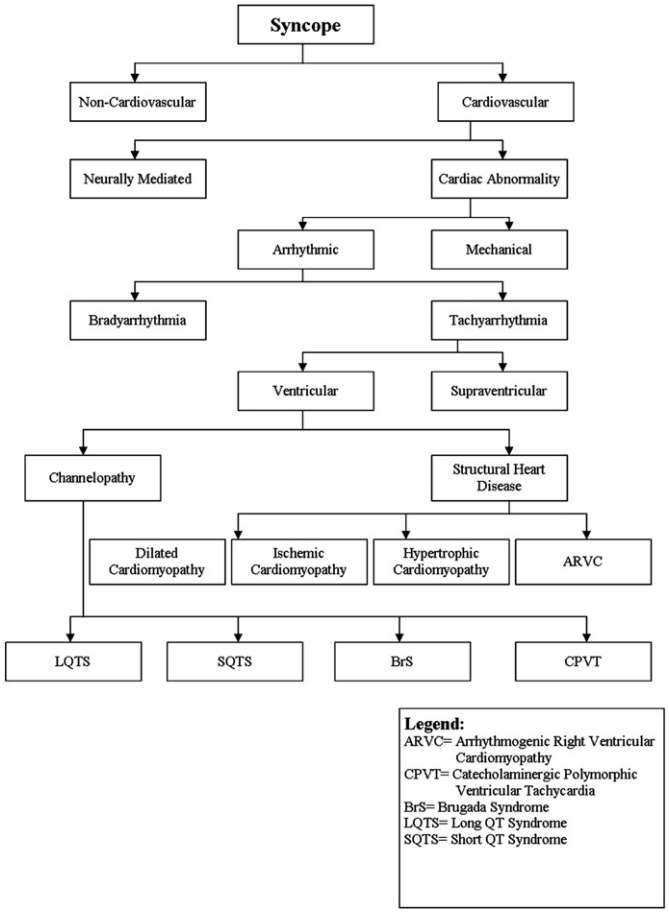

Fig. 1. Etiology of syncope.

awareness of the need to exclude underlying cardiomyopathy in evaluating the patient with syncope is crucial to understanding prognosis and preventing sudden death.

2.2. Familial cardiomyopathies

The cardiomyopathies that may have a familial component account for a small proportion of all causes of cardiomyopathy, though the precise proportion is not well described. These include HCM, ARVC, and cardiomyopathies associated with muscular or neuromuscular disorders such as Duchenne's, Becker's and myotonic dystrophies or Friedreich ataxia, Noonan syndrome and lentiginosis (Grunig et al., 1998; Judge and Johnson, 2008). HCM is the most common inherited cardiac disease with a prevalence of 1:500 (Maron et al., 1995) and an autosomal dominant inheritance pattern. It is characterized by the left ventricular wall thickness ≥15 mm with non-dilated ventricular chambers and microscopic myofibrillar disarray (Gersh et al., 2011). Left ventricular outflow tract obstruction can occur in patients who have septal hypertrophy, leading to mechanical obstruction to flow during exercise, or ventricular arrhythmias that lead to syncope or sudden cardiac death (Khoo et al., 2013). Syncope is a major risk factor for sudden death in HCM, and should lead to consideration of implantation of an implantable cardioverter defibrillator (ICD).

ARVC is a leading cause of ventricular arrhythmia and sudden death in young individuals, and can be challenging to diagnose (Marcus et al., 2010). There is an autosomal dominant inheritance with variable penetrance and expressivity, and involvement may extend to the left ventricle. Exercise may be a precipitant of ventricular arrhythmias leading to exertional syncope, and may also contribute to the progression of disease (Maron et al., 2004; Tan et al., 2005; Basso et al., 2009).

3. Channelopathies

Channelopathies refer to the group of inherited arrhythmia syndromes that result from mutations in genes encoding proteins that form or regulate ion channels (Cerrone and Priori, 2011). The currently identified channelopathies known to cause syncope and sudden death include Long QT Syndrome (LQTS), Short QT Syndrome (SQTS), Brugada Syndrome (BrS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). As the risk of cardiac arrest is high for patients with channelopathies presenting with syncope (Rosanio et al., 2013), identification of these causes of syncope is crucial (Krahn et al., 2013c).

3.1. Long QT Syndrome

LQTS is an inherited channelopathy characterized by QT interval prolongation and an increased risk of syncope and sudden death. This often under diagnosed condition has a prevalence of approximately 1:2500 and a ten-year mortality rate as high as 50% in untreated, symptomatic patients (Sauer et al., 2007; Schwartz et al., 2009; Ackerman et al., 2011). Typically, syncope usually occurs due to the polymorphic ventricular tachycardia called torsades de pointes or "twisting of points" (Roden, 2008) (Fig. 2). The diagnosis of LQTS is often difficult as the QT interval is dynamic and may not be prolonged at the time of the electrocardiogram. The diagnosis of LQTS is made through a combination of historical features (syncope, congenital deafness, torsade de pointes and family history of sudden death), and analysis of the QT interval at rest and during exercise (Schwartz and Crotti, 2011; Sy et al., 2011b; Priori et al., 2013b).

Following a clinical diagnosis of LQTS, patients undergo genetic testing to detect mutations in one of the 13 genes known to cause LQTS. These mutations can result in dysfunction of potassium, sodium, and calcium channels and membrane adaptor proteins (Priori et al., 2013a). LQTS subtypes 1–3 account for 92% of patients with gene-positive LQTS (Table 1) (Ackerman et al., 2011). The primary purpose of genetic testing is both risk stratification and family screening. The combination of history of syncope or cardiac arrest, gender, QT interval duration and LQTS subtype can be used to estimate the subsequent risk of cardiac events (Schwartz et al., 1993; Zareba et al., 1995, 1998; Priori et al., 2003; Zareba et al., 2003; Ackerman et al., 2011; Schwartz and Crotti, 2011; Priori et al., 2013a). In particular, recent syncope increases the risk of cardiac arrest and sudden death across all age categories by 5 to 27 times in patients (Zareba and Cygankiewicz, 2008). For this reason, the identification of LQTS is crucial in patients presenting with syncope. Treatment is usually with beta-blockers and infrequent recommendation of an ICD.

SQTS is a distinct syndrome that is analogous to LQTS that differs due to a gain of function mutations in LQTS related genes, presenting with familial syncope, atrial arrhythmias and sudden death. SQTS is characterized by the presence of a QTc interval of ≤300 ms or a QTc < 360 ms with one of the following: a pathogenic mutation, a relative with SQTS, resuscitated idiopathic VF arrest, or a family member with unexplained sudden death prior to 40 years old (Gollob et al., 2011b; Priori et al., 2013a).

3.2. Brugada Syndrome

BrS is a channelopathy characterized by the presence of ST elevation in the right precordial ECG leads in patients with a structurally normal heart, associated with risk of syncope and sudden death (Fig. 3) (Brugada and Brugada, 1992). The prevalence varies with ethnicity with an incidence as high as 1:1000 in Southeast Asians (Antzelevitch et al., 2005a).

Although BrS is considered an inherited disease, much of the genetics and pathophysiology is poorly understood. The yield of genetic testing is very low in Brugada patients with only 5% of sporadic cases and 20–25% of familial cases having an identifiable mutation. Recent series