Syncope: A Review

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Syncope is defined as sudden transient loss of consciousness and postural tone with spontaneous and complete recovery that occurs as a result of reduced cerebral perfusion. Presyncope is the condition described in human patients where cerebral hypoperfusion produces signs of episodic dizziness, weakness or light-headedness without loss of consciousness. In cats and dogs, this may be seen as transient weakness or appendicular instability without loss of consciousness.

Syncope is a distressing clinical event for most pet owners and their concern is not misplaced. While some syncopal etiologies, such as reflex syncope, are very benign, others such as ventricular tachycardia are malignant; failure of sustained ventricular tachycardia to spontaneously revert to sinus rhythm will precipitate sudden death.

Assessment of the syncopal patient presents a diagnostic challenge for the veterinarian since recovery is typically quick and complete prior to presentation and physical examination may reveal no abnormality.

SYNCOPAL PATHOPHYSIOLOGY & ETIOLOGY

Cessation of cerebral blood flow for 6-8 seconds producing a drop in cerebral arterial pressure to less than 25mmHg is necessary to provoke a complete loss of consciousness[1]. Reduced cerebral blood flow may be a result of reduced cardiac output or reduced peripheral vascular resistance or a variable combination of both.

In human patients, syncope is classified by pathophysiology into three categories: reflex (neutrally-mediated) syncope, orthostatic syncope, and cardiovascular syncope[1]. Reflex syncope is subdivided into the categories of vasovagal (ie. mediated by emotional distress or orthostatic stress), situational (ie. cough, micturition, defacation, exercise, others) and carotid sinus syncope. Orthostatic syncope describes the positional hypotension exacerbated by primary autonomic failure (eg. Parkinson's disease), secondary autonomic failure (eg. diabetes), drugs (eg. vasodilators, diuretics) or volume depletion (with hemorrhage, diarrhoea, vomiting). Cardiovascular syncope includes syncope elicited by cardiovascular

pathology including arrhythmias (ie. tachycardia, bradycardia), acquired structural cardiac disease (eg. cardiomyopathies, cardiac masses, pulmonary thromboembolus, pulmonary hypertension, pericardial disease, others) and congenital structural disease (eg. subaortic/ pulmonic stenosis, mitral stenosis, others).

Reflex Syncope

This form of syncope refers to a heterogenous group of conditions in which normal physiologic reflexes aimed at preservation of cardiac output and tissue perfusion are executed inappropriately in response to a specific trigger to precipitate vasodilation and bradycardia sufficient to compromise cerebral perfusion and result in loss of consciousness. The afferent limb of the reflex is poorly understood, but essentially, the nucleus tractus solitarii of the brainstem is either directly or indirectly stimulated by the inciting trigger. The efferent limb of the reflex is characterized by augmented parasympathetic tone (producing a cardioinhibitory response of negative chronotropy and inotropy) and withdrawal of sympathetic tone (producing a vasodepressor response of peripheral vasodilation). Either the cardioinhibitory or the vasodepressor response may predominate the efferent limb of the reflex, but often there a variable contribution of these two mechanisms. For veterinary patients, triggers for reflex syncope include exercise/ excitement,[2,3] cough, micturition, defacation and advanced myxomatous mitral valve degeneration.

Cardiovascular Syncope

Congenital (eg subaortic stenosis and pulmonic stenosis) and acquired (eg. pulmonary hypertension, pulmonary thromboembolism, cardiac neoplasia) cardiovascular diseases that increase the pressure against which ventricular contraction occurs are associated with risk for syncope. When sympathetically stimulated, augmented inotropy and chronotropy provoke an abrupt rise in intraventricular pressure stimulating ventricular mechanoreceptors to initiate vagal afferent pathways to the brainstem where the efferent response is increased vagal tone and withdrawal of sympathetic activity to effect a reduction in cardiac output coupled with peripheral vasodilation which can precipitously drop cerebral perfusion pressure to trigger syncope.

Primary cardiomyopathic diseases and cardiac diseases with secondary cardiac remodelling (eg. subaortic stenosis) histologically feature necrosis

with replacement fibrous or fibrous/ fibro-fatty infiltrates which provide a known substrate for ventricular arrhythmias. Rapid and sustained supraventricular tachycardia, sufficient to provoke syncope, can occur with congenital accessory pathways and may also arise secondary to atrial remodelling or primary myopathic processes involving the atria. The abrupt reduction in diastolic filling associated with sustained supraventricular or ventricular tachycardia in these patients can confer a sufficient reduction in cardiac output, particularly if coupled with systolic myocardial dysfunction, to provoke syncope.

Conduction system diseases (eg. high grade AV block and sick sinus syndrome) can precipitate syncope when a prolonged sinus pause/ arrest is not supported by cardiac output via subsidiary pacemakers in a diseased conduction system. For high grade AV block, syncope can result if the escape focus is unreliable resulting in period of complete ventricular quiescence of if a patient's activity level can not be matched by the rate-limited ventricular output.

DIAGNOSTIC TESTS

Minimum Screening Tests

A complete blood count, biochemistry and urinalysis is likely to be low-yield in most dogs and cats with syncope but is necessary to rule out metabolic causes of collapse (eg. seizures associated with hypoglycaemia, hepatic insufficiency) and concurrent or precipitating disease (eg. protein loosing nephropathy and low ATIII levels may theoretically increase risk of pulmonary thromboembolism).

Echocardiography

Echocardiography is indicated for any patient with syncope to identify structural or mechanical heart disease which is either primarily implicated (eg. outflow tract obstruction, pulmonary hypertension) or associated (eg. dilated cardiomyopathy) with syncopal etiology. It is also necessary to indirectly measure pulmonary arterial pressures via determination of tricuspid and/or pulmonic regurgitant velocity to identify pulmonary hypertension.

Electrocardiography

A resting ECG is incapable of definitively identifying a causative arrhythmia unless it is recorded at the time of the syncopal event. However, a resting

ECG may provide supportive evidence for arrhythmia-associated syncope in some dogs and cats. For example, the identification of pre-excitation (short PR interval and delta waves) on sinus complexes is indicative of a congenital accessory pathway with risk for orthodromic AV reciprocating tachycardia. Similarly, the identification of ventricular premature complexes of left bundle branch block morphology on a 2-minute resting ECG of a Boxer is poorly sensitive but highly specific for a diagnosis of arrhythmogenic right ventricular cardiomyopathy.[4]

Ambulatory 24hr Holter ECG

Ambulatory 24hr Holter ECG monitoring is indicated whenever an arrhythmogenic cause for syncope is suspected, to screen for occult dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy in at-risk dogs, and to confirm efficacy of antiarrhythmic medication following commencement. It has a far greater sensitivity at detection of arrhythmias than the resting ECG which records <0.1% of the patient's daily cardiac electrical activity and which may miss intermittent or transient arrhythmias. The presence of >50-100 VPCs during a 24 hr Holter ECG recording is diagnostic for occult dilated cardiomyopathy[5] or arrhythmogenic right ventricular cardiomyopathy[6]. Documentation of cardiac rhythm during a syncopal event is unnecessary and 24hr Holter ECG diagnosis of occult dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy is typically definitive for syncopal etiology.

Event recorders

Event recorders are portable ECG recording devices that record a 10-15 minute loop of ECG by continually over-writing previously acquired data. When the device is manually triggered (by the owner upon witnessing the collapse event), the ECG from a few minutes prior to the trigger, and a few minutes after the trigger, is transferred from the buffer into memory, and can be subsequently downloaded and analyzed.

Event recorders are used to assess the cardiac electrical activity at the time of a witnessed event to identify an arrhythmogenic syncopal etiology. They are not used for patients suspected of having potentially fatal collapse etiology, such as a Boxer with suspected arrhythmogenic right ventricular cardiomyopathy where syncopal events may precipitate sudden death. Instead an event recorder is valuable at excluding an arrhythmogenic etiology in patients with collapse or identifying an arrhythmogenic cause

in patients with disease unlikely to confer a risk of sudden death eg. sinus pauses/ profound bradycardias in patients with cardioinhibitory reflex syncope or sick sinus syndrome.[7]

Event monitors require a patient to experience an event while the monitor is worn. Typically, event monitors are attached for 7 days and require that collapse frequency to be sufficient to facilitate capture of an event during this period.

Implantable loop recorders
Implanted subcutaneously over the left hemithorax, these recording devices have a battery life of up to 36 months and have recently been validated for use in canine patients[8,9]. These devices have a solid state loop memory that stores retrospective ECG recordings, when activated by an owner witnessing a syncopal epidsode or automatically activated if predefined arrhythmias are recognized. Although cost may be prohibitive for some patients, this technology may facilitate accurate arrhythmia etiology for a subset of patients where more routine diagnostics have failed to identify an elusive arrhythmia or in patients with infrequent and unpredictably inducible reflex-syncope.

Tilt table testing
For human patients with presumed vasovagal syncope, tilt table testing may facilitate definitive diagnosis. Essentially, tilt table testing aims to provoke syncope during simultaneous documentation of heart rate and blood pressure to demonstrate a vasodepressor and/or cardioinhibitory response as the syncopal etiology. Patients are positioned supine on the table and tilted upright to 60-80 degrees for 20-45mins. Various pharmacological agents may be employed to increase test sensitivity but obviously do so at the expense of reduced specificity. Clearly, this diagnostic methodology is not applicable to veterinary patients, where reflex-syncope may remain a diagnosis of exclusion, particularly for patients with a predominant vasodepressor form where profound bradycardias need not contribute to syncope and definitive diagnosis is not possible even for patients with ambulatory ECG recording during an event.

TREATMENT

Ventricular tachycardia
Large multi-centre placebo-controlled, double-blinded trials in human

cardiology (notably the CAST trials) have shown that although antiarrhythmic drugs can suppress ventricular arrhythmias, this does not correspond to a reduction in risk for sudden cardiac death[10]. Several studies in canine have similarly documented the efficacy of antiarrhythmics to minimize frequency and severity of ventricular arrhythmias but clinical translation to reduced risk for syncope and sudden death is tenuous[11]. Several antiarrhythmics have been used in veterinary patients including: Mexiletine, flecainide, procainamide, atenolol, propanolol, tocainide, sotalol, amiodarone.

Combination therapy with sotalol and mexiletine (but not either agent alone) has demonstrated efficacy at suppression of arrhythmias in German shepherd dogs with inherited ventricular arrhythmias[12]. In Boxers with arrhythmogenic right ventricular cardiomyopathy, sotalol and combined mexiletine/atenolol (but not atenolol or procainamide) effectively reduced the frequency and severity of ventricular arrhythmias without altering the frequency of synopal events[13]. Similarly, sotalol and combination sotalol/mexiletine therapy has demonstrated efficacy at reduction of arrhythmia frequency and grade in Boxers with arrhythmogenic right ventricular cardiomyopathy, however, a commensurate reduction in syncopal frequency and reduction in risk for arrhythmogenic sudden death has not be documented[14].

Supraventricular tachycardia

Supraventricular tachycardia sufficient to result in syncope, is often associated with a congenital accessory pathway and rapid rate orthodromic AV reciprocating tachycardia (OAVRT). For these patients, Class IA, IC and Class III agents are typically indicated to retard the conduction properties of the accessory pathway and reduce the propensity for OAVRT. Radiofrequency ablation is a curative option for these patients[15,16].

Bradycardias

Positive chronotropes such as sympathomimetics (eg. terbutaline, phenylpropanolamine), anticholinergics, and PDEII-inhibitors (eg. theophylline) have been utilized in syncopal patients with bradycardic conduction system disease. However, response to medical therapy is typically partial and temporary at best and permanent pacemaker implantation is typically necessary. Permanent pacing is curative for these

patients and various pacing modalities are well-described in the veterinary literature.

Outflow tract obstructions

Beta-blockers are widely administered to patients with severe subaortic stenosis with aims to attenuate sympathetically-stimulated rise in left ventricular pressure against the fixed outflow obstruction and minimize risk for syncope/ sudden death. However, available data suggests that beta-blockade does not affect survival time of severely affected individuals[17]. Surgical excision of the obstructive lesion and balloon valvuloplasty have similarly failed to extend survival times when compared to long-term atenolol treatment, even when the obstruction is significantly attenuated[18,19]. Combined cutting balloon and high pressure balloon valvuloplasty has recently been described for dogs with subaortic stenosis but it's clinical merit is yet to be determined[20].

Conversely, the treatment of choice for syncopal patients with severe valvular pulmonic stenosis is balloon valvuloplasty which has been demonstrated to reduce minimize clinical signs and extend survival time when compared to untreated dogs[21,22].

Reflex syncope

Effective treatment of reflex syncope is predominantly dependant on the avoidance of known triggers for an individual. For affected dogs, this may mean avoiding abrupt onset or extremes of activity, particularly in high ambient temperatures where peripheral vasodilation may increase risk for an event. Medical cough suppression may also be sufficient to attenuate syncopal frequency in patients with cough-syncope.

For human patients when trigger-avoidance is not possible, there is no convincing data to support the use of one therapy over another as a first line therapy. Beta-blocker therapy was once the most commonly utilized medication but this has recently been demonstrated to be ineffective and according to the guidelines of the Euporopen Society of Cardiology, beta-blockers should no longer be used for this indication. Medications which may prove effective for affected people may include: fludrocortisone, midodrine (an alpha-agonist vasoconstrictor) or fluoxetine or paroxetine (serotonin reuptake inhibitors), but experience with these agents in veterinary patients is lacking. For people with the cardioinhibitory form of vasovagal syncope, pacemaker implantation may be effective.

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