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Assessment of paediatric exertional or peri-exertional syncope: does the story matter?

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Abstract

Exertional syncope has been suggested to correlate with a cardiac aetiology, particularly when occurring in mid-stride. The aim of the study is to evaluate the incidence of cardiac disease among children presenting with exertional syncope, determine the influence of timing within activity, and determine the utility of genetic testing and implantable event monitors in the evaluation of cardiac syncope. The patients ≤18 years old with exertional syncope who underwent exercise stress testing between 2008 and 2019 were retrospectively included. Patients were assessed to be in one of three groups: mid-exertion (mid-stride syncope), peri-exertion (syncope during activity but not moving), and post-exertion (within minutes of the activity). A total of 334 patients were included; 46 % were mid-exertion, 18 % were peri-exertion, and 36 % were post-exertion. Thirteen patients (3.8 %) were diagnosed with cardiac syncope; n = 9 (69 %) mid-exertion. Only mid-exertional syncope was significantly associated with a cardiac diagnosis (OR: 2.6). Cardiac diagnoses included inherited arrhythmia syndromes (n = 9), abnormal coronary origins (n = 2), and supraventricular tachycardia (n = 2). Only catecholaminergic polymorphic ventricular tachycardia (n = 5) was associated with mid-exertional syncope (OR: 1.4). The definitive diagnostic test was exercise testing (n = 8), echocardiogram (n = 2), genetic testing (n = 1), ambulatory monitor (n = 1), and EKG (n = 1). Mid-stride syncope was more likely to result in a cardiac diagnosis, and exercise testing is the most common definitive test as catecholaminergic polymorphic ventricular tachycardia was the primary aetiology of exertional syncope in our cohort. Implantable event monitors and genetic testing could be helpful in ruling out cardiac disease.

Syncope is a sudden, brief loss of consciousness associated with loss of postural tone results from inadequate cerebral perfusion which recovery is spontaneous. Although most causes are benign and self-limited, exertional syncope always raises concern with cardiac aetiology and often warrants further evaluation.[1,2] The clinical characteristics capable of predicting cardiac causes are variable and often unreliable in children and require evaluation including a detailed and focused history and physical with addition of case-dependent diagnostic tests.[3]

Patients with exertional syncope often undergo multiple tests including EKG, echocardiogram, and heart rate monitoring. Exercise stress test is well-validated test and can be used for diagnostic or prognostic purposes. Genetic testing and implantable looping event monitors have become more prevalent in the evaluation of patients with exertional syncope but their utility in this group is unknown. There are limited studies for paediatric syncope particularly when occurring in mid-stride. To our knowledge, there are no studies evaluating the influence of timing within activity among children. The purpose of this study is to evaluate the incidence of cardiac disease among children presenting with exertional syncope, determine the influence of timing within activity, and define which tests were most helpful in the diagnosis of cardiac syncope.

Patients and methods

We performed a single-centre retrospective review of patients with exertional syncope who underwent exercise stress testing between 2008 and 2019. This study was conducted with the internal review board's approval. Inclusion criteria included the following: age ≤18 years, exertional syncope documented in the medical record, having completed an exercise stress test and evaluated by a paediatric cardiologist. Exclusion criteria included patients with prior known structural heart defects or arrhythmia disorders. Patients who received cardiopulmonary resuscitation at their syncopal event were also excluded.

Exertional syncope was defined as a transient loss of consciousness with loss of postural tone and was subdivided as mid-exertion, peri-exertion, and post-exertion. Mid-exertion syncope was defined as syncope which occurred mid-stride, as in passing out during the action of

running across a court or field. Peri-exertion syncope was defined as occurred during activity, game, or competition but not moving, such as standing on the field during a soccer game. *Post-exertion syncope* was defined as events which occurred immediately after completing an exercise, such as crossing the finish line of a running race.

On presentation of syncope, patients were evaluated in the emergency room, as an inpatient admission, or in the outpatient clinic. Follow-up was defined as the last identifiable encounter in the electronic medical record in which we could verify the patient's clinical status. Data collection included prior syncope, the preceding and recovery symptoms surrounding the presenting event, the exercise or activity in which the syncope occurred, any injury as a result of the syncope, and family history. Type of exertional activity during exertional syncope was classified as low, low-moderate, moderate, high-moderate to high, based on the Task force 8 classification of sports, 36th Bethesda Conference.[4] As this was a retrospective review, each patient was evaluated at the discretion of the paediatric cardiologist. Charts were reviewed for all diagnostic testing completed for each patient, which could include, EKG, echocardiogram, exercise stress test, intravenous drug challenge, invasive electrophysiologic study, ambulatory cardiac monitor, implantable loop event monitor, cardiac MRI, genetic testing. The final diagnosis for the testing, if one was documented in the medical record, was recorded. Non-cardiac diagnosis was defined as vasovagal, psychogenic, or unknown.

Statistical analysis

Statistical analysis was performed using IBM, SPSS Statistics Version 25.0. Categorical variables were reported as count and percentages. Pearson's chi-square tests were conducted to examine bivariate differences between categorical variables in cases where the expected number assumed less than 5 should not exceed 20 % for variables structure. The difference between the groups was tested with the Mann–Whitney U-test. Those not suitable for this situation were made using Fisher's exact chi-square test. A p-value below 0.05 was accepted as significant.

Results

Patient characteristics

A total of 334 patients (173 female, 51.7%) with exertional syncope were included the study. Age at presentation 13.7 ± 2.38. Only 13/334 patients (3.8%) were diagnosed with a primary cardiac cause. There was no difference between patients with cardiac versus non-cardiac diagnosis with respect to sex (female; 54% versus 52%, $p = 0.88$) or age at presentation (13.6 ± 3.11 versus 13.7 ± 2.30, $p = 0.80$).

Patients diagnosed with cardiac disease were most likely to have an inherited arrhythmia syndrome (n = 9), including catecholaminergic polymorphic ventricular tachycardia (n = 5), long QT syndrome (n = 3), and arrhythmogenic right ventricular cardiomyopathy (n = 1). Other cardiac diagnosis were anomalous origin of coronary arteries (n = 2), and non-Wolf Parkinson–White supraventricular tachycardia (n = 2) (Table 1). Vasovagal syncope as the aetiology of the exertional syncope was diagnosed in 211 of 334 patients in the cohort (63 %).

Timing within activity and level of exertion

Of the 334 patients, 46% were during mid-exertion, 18% during peri-exertion, and 36% post-exertion. Thirteen patients were diagnosed with cardiac syncope: n = 9 (69%) mid-exertion, n = 3 (23%) post-exertion, and n = 1 (7%) peri-exertion. There was no statistically significant difference in timing of activity between the cardiac and non-cardiac patients. In the patients diagnosed with cardiac aetiology, mid-exertional syncope was significantly associated with a cardiac diagnosis (OR 2.6).

In both cardiac and non-cardiac groups, there is significant difference in the level of exertional activity (Table 2). Cardiac exertional syncope mostly occurs during high-moderate exercise (75%). Exertional syncope occurred primarily during two sports activities: running (40.7%), basketball (9.2%).

Symptoms

Symptoms immediately preceding syncope did not differ between the cardiac and non-cardiac patients (Table 2). In both the groups, the most common reported symptoms were vasovagal symptoms. Dizziness was the most common vasovagal symptom and was seen in both cardiac and non-cardiac groups (60%, 63.2%, $p = 1$). The absence of immediately preceding symptoms did not differentiate cardiac group versus non-cardiac group (38%, 21.8%, $p = 1$). Likewise, there were no significant differences in post-syncopal symptoms between the cardiac and non-cardiac groups (Table 2). No symptoms prior to syncope were reported in 84.6% of cardiac and 70.4% of non-cardiac patients ($p = 0.36$). A previous history of syncope, whether single or multiple episodes, did not distinguish those with or without a cardiac diagnosis.

Emergency room visit and hospital admissions

There were no significant differences in emergency room visits and hospital admissions between the cardiac and non-cardiac groups (Table 2). Five patients presented to the Emergency Room demonstrated QTc prolongation (450–480 ms) on EKG. After evaluation by a paediatric cardiologist in clinic, none of them were diagnosed with long QT syndrome.

Follow-up

There was a significant difference in median total follow-up for cardiac patients at 2 years (range 1 day – 11 years), and median total follow-up for non-cardiac patients was 1 year (range 1 day – 4 years) ($Z = 5.607$, $p = 0.0001$). Of this cohort, there was one death. The patient presented with syncope during a 10K race. Of note, the history was not of mid-stride, but of the patient wondering off to the side and laying down on the grass. An initial evaluation of exam, EKG, echocardiogram, and exercise stress test were all normal and specifically without ventricular ectopy. A cardiac MRI was recommended. The patient's next event was sudden cardiac collapse during a 5K race and was not able to be resuscitated. Postmortem genetic testing diagnosed a pathogenic mutation consistent with arrhythmogenic right ventricular cardiomyopathy.

Diagnostic and definitive testing

All patients underwent exercise stress testing as it was the inclusion criteria of the study. Diagnostic testing varied by patient and included EKG, echocardiogram, electrophysiology study,

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Table 1. Characteristics of the cardiac patients.

Diagnosis	Level of exertion	FHx	Sport activity	Timing with exercise	ERa	Definitive diagnostic test	ICD
CPVT	No	N/A	N/A	Mid-exertion	Yes	Exercise test	Yes
CPVT	No	Moderate	Gymnastics	Mid-exertion	No	Exercise test	No
SVT	No	High-moderate	Cycling	Mid-exertion	No	Exercise test	No
AOCA	No	High-moderate	Swimming	Mid-exertion	No	Echocardiogram	No
AOCA	No	High-moderate	Basketball	Mid-exertion	No	Echocardiogram-CT	No
CPVT	No	High-moderate	Basketball	Mid-exertion	No	Exercise test	No
LQTS	No	High-moderate	Basketball	Peri-exertion	No	Exercise test	No
ARVC	No	High-moderate	Running	Mid-exertion	No	Genetic testing	No
CPVT	No	High-moderate	Basketball	Post-exertion	Yes	Exercise test	Yes
LQTS	No	High-moderate	Basketball	Post-exertion	No	Exercise test	No
CPVT	No	High-moderate	N/A	Mid-exertion	No	Exercise test	Yes
LQTS	No	High-low	Soccer	Mid-exertion	No	EKG	Yes

AOCA = Anomalous origin of coronary artery; ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy; CPVT = Catecholaminergic polymorphic ventricular tachycardia; Era = Emergency service application; FHx = Family history; ICD = Implantable cardioverter-defibrillator; LQTS = Long QT syndrome; SVT = Supraventricular tachycardia.

intravenous drug challenge using procainamide, epinephrine, or isoproterenol, cardiac MRI/CT, ambulatory cardiac monitor, implantable loop recorder, and cardiac genetic testing for inheritable arrhythmias and cardiomyopathies (Fig 1). The total number of diagnostic tests performed among patients with cardiac diagnosis – median five tests (range 4–6 tests), patients with non-cardiac diagnosis – median three tests (range 2–6 tests). There was a significant difference between the groups in the total number of diagnostic tests performed ($Z = 5.446$, $p = 0.0001$). The most performed tests were EKG (329/ 98.5%), echocardiogram (305/ 91.3%), and Holter monitor (142/ 42.5%).

Among the seven patients with borderline corrected QT intervals on baseline, EKG underwent exercise testing that three of them demonstrated markedly abnormal corrected QT prolongation in the recovery period diagnosed long QT syndrome syndrome, the corrected QT interval ranged between 500 and 580 ms. Among patients with a cardiac diagnosis, an abnormal electrocardiogram was observed in 38.4%. Abnormal EKGs seen 12.6 % in non-cardiac patients – single premature atrial and ventricular contractions, first-degree atrioventricular block and incomplete bundle branch block – were not diagnostic.

Echocardiogram was abnormal in three cardiac patients – two with the diagnosis with anomalous origin of coronary arteries confirmed with cardiac CT, one with mild dilated right ventricle in catecholaminergic polymorphic ventricular tachycardia patient which is not diagnostic. Among nine non-cardiac patients with abnormal echocardiogram, none of them were diagnostic (Fig 1).

Exercise stress testing was abnormal among nine (69%) cardiac patients – eight were diagnostic, five with bidirectional ventricular tachycardia (catecholaminergic polymorphic ventricular tachycardia), one with sustain supraventricular tachycardia, two with QT prolongation in recovery period. Abnormal exercise tests (premature ventricular beats, premature atrial ectopic beats, non-specific ST depression, and ectopic atrial rhythm) were present in 11% of the non-cardiac patients.

Genetic testing was performed on 13 patients, positive for cardiac *Ryanodine receptor* mutations in 2 patients with catecholaminergic polymorphic ventricular tachycardia, in 1 patient diagnosed with long QT type 1 (*KCNQ1* mutations) and 1 patient diagnosed with arrhythmogenic right ventricular cardiomyopathy (*DSC2* mutation). For the entire cohort, the definitive diagnostic test was exercise testing (n = 8), echocardiogram (n = 2), genetic testing (n = 1), ambulatory monitor (n = 1), and EKG (n = 1) (Table 1).

Discussion

In this retrospective single-centre study, we found that 3.8% of all patients referred for exertional syncope had a cardiac diagnosis. Timing of syncope during activity did not predict a cardiac versus non-cardiac aetiology. When diagnosed, cardiac syncope mostly occurred during mid-exertion and mostly with high-moderate exercise (running). Although the incidence of cardiac syncope was reported between 0.4 and 4.6% before,[5,6] there have been very limited data focusing on exertional syncope and influence of timing within activity in paediatric population. Different from our data, Miyake et al. reported nearly 50% cardiac aetiology in patients presented with mid-exertional syncope.[7]

Patients with cardiac diagnosis are most likely to have an arrhythmia syndrome compared with other cardiac aetiologies. Catecholaminergic polymorphic ventricular tachycardia was the common diagnosis in our cohort. As cardiomyopathies may present with exertional chest pain before syncopal episodes, this can explain lack of these patients. Like our findings, Miyake et al. also reported mostly inherited arrhythmia syndromes and rhythm disorders in the paediatric age.[7]

Similar to literature, most of our patients were diagnosed with potentially benign conditions. Vasovagal syncope was found to be most common non-cardiac diagnosis in our study; 71% of non-cardiac patients were preceded by vasovagal symptoms and dizziness was most common vasovagal symptom in both groups. Although some studies and published guidelines suggest that lack of prodromal symptoms is common in cardiac syncope, our findings showed that symptoms preceding syncope did not differentiate cardiac and non-cardiac aetiology.[8,9]

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Table 2. The clinical characteristics of the cohort.

Variables	Cardiac Patients	Non-Cardiac Patients	p
Time during exercise			
Mid-stride (Mid-exertion	9/13 (69%)	146/321 (45%)	
Standing during (peri-exertion)	1/13 (8%)	59/321 (18%)	
After ≤ 30 min (post-exertion)	3/13 (23%)	116/321 (36%)	
Immediate preceding symptoms			
Chest pain	2/10 (20%)	23/318 (7%)	0.17
Palpitations	2/10 (20%)	33/318 (10%)	0.29
Vasovagal symptoms	7/13 (54%)	229/321 (71%)	0.21
No symptoms	5/13 (38%)	70/321 (21.8%)	1.00
Immediate recovery symptoms			
Chest pain	0/10 (0%)	14/318 (4%)	1.00
Palpitations	0/10 (0%)	11/318 (3%)	1.00
Neurological symptoms	2/10 (20%)	27/317 (9%)	0.22
No symptoms	11/13 (84.6%)	226/321 (70.4%)	0.36
Previous history			
Syncope	6/10 (60%)	177/316 (56%)	1.00
Palpitations	2/10 (20%)	29/321 (9%)	0.24
Seizures	0/10 (0%)	12/316 (4%)	1.00
No previous symptoms	4/13 (31%)	92/321 (29%)	1.00
Level of exertion			0.018*
Low (IA)	0/8 (0%)	2/251 (1%)	
Low-moderate (IIA, IB)	0/8 (0%)	7/251 (3%)	
Moderate (IIIA, IIB, IC)	1/8 (13%)	166/251 (66%)	
High-moderate (IIIB, IIC)	6/8 (75%)	64/251 (25%)	
High (IIIC)	1/8 (13%)	12/251 (5%)	
Injury	1/10 (10%)	15/317 (5%)	0.40
Family history of sudden death	0/10 (0%)	12/312 (4%)	1.00
Presentation to ER	2/10 (20%)	94/316 (30%)	0.73
Hospital admit	0/10 (0%)	9/316 (3%)	1.00

*Adjusted p-values < 0.05 were considered statistically significant.
ECG = Electrocardiogram; ER = Emergency room.

Like our findings, Colman et al. showed that long QT syndrome patients also experience vasovagal symptoms typically associated with vasovagal syncope.[10]

There were no significant differences in post-syncopal symptoms between the cardiac and non-cardiac groups in our study. Likewise, there were no significant differences in family history of sudden death between the groups. Although symptoms and family history did not distinguish cardiac versus non-cardiac aetiology in our study, they are still important for cardiac diagnosis of syncope and should raise concern in evaluation of these patients.[11] Different from our data, Colman et al. reported positive family history of sudden death in 63% of the patients with LQTs.[10]

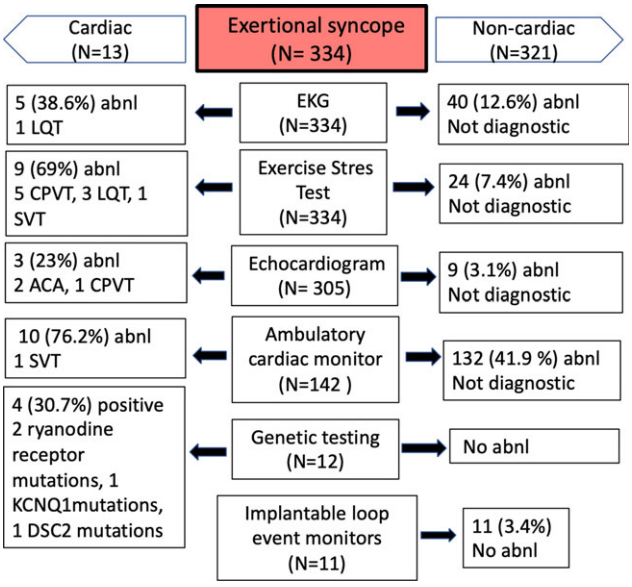

Fig. 1 Diagnostic testing results for syncope.

Patients being evaluated for syncope should undergo additional testing even though their symptoms are strongly correlated with vasovagal aetiology. Extensive use of diagnostic tests does not guarantee clinical success so carefully planned approach is preferred to avoid an involved and expensive diagnostic evaluation. But as all suggested guidelines (AHA and ESC) for management of syncope are for adults, limited information is available on the impact of similar protocols for paediatric syncope.[8,9] Zhang et al. developed a diagnostic two-step approach for management of syncope and achieved a overall diagnostic performance with 81.1% patients receiving a diagnosis.[12] Also, Phelps et al. reported a clinical practice guideline for managing syncopal events, but not enough for diagnostic approach.[13]

In our study, there was a significant difference between cardiac and non-cardiac groups in the total number of diagnostic tests performed. EKG is inexpensive test which can provide information and demonstrate an underlying arrhythmogenic substrate for syncope or sudden cardiac death.[14] Diagnostic work-up mostly started with EKG (98.5%), and all the patients underwent exercise stress testing as it was the inclusion criteria of the study. Among patients with cardiac diagnosis, an abnormal EKG was observed in 38.4%. All the patients with exertional syncope should undergo additional evaluation with echocardiogram and exercise stress test. Although there were no patients diagnosed hypertrophic cardiomyopathy in our study group, echocardiograms are necessary for diagnosis of cardiomyopathy, anomalous coronary arteries, pulmonary hypertension, and arrhythmogenic right ventricular cardiomyopathy.[15] Echocardiogram was abnormal in three cardiac patients – two with diagnosis with anomalous origin of coronary arteries confirmed with cardiac CT, one with mild dilated right ventricle in catecholaminergic polymorphic ventricular tachycardia patient which is not diagnostic. However, in patients with exertional syncope, additional testing is likely needed when EKG and echocardiograms are normal. Miyake et al. showed that 18 patients (56%) with cardiac diagnosis have a normal EKG and echocardiogram at presentation.[7] An exercise test is mostly necessary for diagnosis of catecholaminergic polymorphic ventricular tachycardia. In our study, we showed that exercise testing is the

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most common definitive test as catecholaminergic polymorphic ventricular tachycardia was the primary aetiology of exertional syncope in our cohort.

Additional testing may include a signal-averaged EKG, Holter monitor, MRI, cardiac catheterisation, genetic testing, and invasive electrophysiologic study. Genetic testing was positive in four patients; two patients with catecholaminergic polymorphic ventricular tachycardia have *Ryanodine receptor* mutation, one patient with long QT type 1 has *KCNQ1* mutation, and one patient with arrhythmogenic right ventricular cardiomyopathy has *DSC2* mutation which is diagnostic. Positive family history, no alternative clinical explanation for the phenotype, and younger age can be a signal of greater chance that underlying basis of the disease is genetic. Not only the appropriate patient selection with clear indication but also interpretation of genetic variants is very important. Cardiac genetic testing should be avoided in the patients whose pre-test possibility is low, due to the risk of misclassifying a mutation as causative which may give harm.[16]

For the entire cohort, ambulatory monitor was a definitive test in one patient with the diagnosis of supraventricular tachycardia. The published guidelines recommend that selection of monitor technology mostly should base on frequency of symptoms.[14] External loop recorders seem have higher yield than Holter monitoring with a longer monitoring period and may prefer after negative Holter results. Prospective, multicenter study showed that 392 patients (28% with syncope) reported a 4-week diagnostic yield of external loop recorders were 24.5% and history of supraventricular tachycardia being a strong predictor of diagnostic events.[17] Studies showed that benefit of implantable event monitors for a diagnosis of syncope is unclear aetiology. In a prospective study of 60 patients with an unknown aetiology of syncope, 55% of patients were diagnosed with implantable event monitors compared to other diagnostic tests.[18]

Of the 96 patients presented to emergency room, 9 were admitted, all of them were with non-cardiac diagnosis. Further diagnostic testing was required that could not be obtained while in the emergency room. No cardiac diagnoses was missed in emergency room. Emergency room evaluation sometimes can be difficult to exclude cardiac aetiology; postexercise atrioventricular nodal re-entrant tachycardia can easily be diagnosed when referred to cardiology outpatient clinic but some exercise-related syncope like catecholaminergic polymorphic ventricular tachycardia can be considered like epileptic and miss in emergency room. To our knowledge none of the children's non-cardiac diagnosis subsequently received a cardiac diagnosis, there has been one death with the diagnosis with arrhythmogenic right ventricular cardiomyopathy.

The main limitation of the present study is its retrospective nature and the referral bias for exertional syncope. Some patients had given a limited information about the syncopal event in the chart review. Moreover, the reported preceding and recovery symptoms may be incomplete, not reported in detail dependent of the physician. As we have limited available protocols for paediatric syncope, diagnostic work-up may vary from physician to physician. The technology of cardiac rhythm monitoring and genetic testing is advancing in years, so some patients may receive less cardiac diagnostic testing than others and may have resulted in missing some cardiac diagnosis.

Conclusion

In this study, we found that exertional syncope, even occurring during mid-exertion, has a lower incidence of cardiac disease than previously reported. Timing of activity did not predict a cardiac versus non-cardiac aetiology. Diagnostic work-up typically begins with EKG and echocardiogram. An exercise stress test is a highly considered next step, especially for the diagnosis of catecholaminergic polymorphic ventricular tachycardia. Implantable looping event monitors and genetic testing were most helpful in ruling out cardiac disease.

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Conflict of interest. None.

Ethical standards. The study was approved by the University of Colorado Institutional Review Board (IRB) (24-Feb-2020 / Initial submission ID: APP001-3).

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