Sudden Unexpected Death Due to Myocarditis in Young People, Including Athletes

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Sudden deaths in young active people and athletes are distinctly uncommon and frequently related to highly visible cardiovascular conditions including hypertrophic cardiomyopathy and congenital coronary anomalies. Myocarditis is also a cause of sudden death in the young, but frequently under-recognized clinically, and therefore deserving of the present analysis. Two large registries were interrogated for cases of myocarditis, and clinical, demographic, and pathologic findings were assessed. Of 97 cases of myocarditis identified, ages were 19.3 ± 6.2 years, 76% male, and 58 were physically active at or near the time of death. Almost one-half of the 97 cases (47%) had a viral prodrome or symptoms (i.e., syncope, malaise, chest pain or palpitations). Nine were evaluated by cardiologists, but in none was a diagnosis of myocarditis established before death. The inflammatory cellular infiltrate was predominantly lymphocytic (67%), was most frequently multifocal (59%) and involved the conduction system (including atrioventricular node), 38%. In conclusion, myocarditis is an important but under-recognized cause of sudden death in young people including competitive athletes. Clinical diagnosis is difficult because symptoms are nonspecific and often ignored, requiring high index of suspicion for diagnosis. Our data support the ACC/AHA consensus guidelines recommending removal of individuals with myocarditis from competitive sports during recovery. Selective examination of conduction systems showed a number of cases with involvement of myocarditis, suggesting a novel mechanism for sudden death. **(Am J Cardiol 2021;143:131−134)**

There is continuing interest in understanding the etiologies of sudden death in young people and athletes, and prevention by screening for inherited conditions including hypertrophic cardiomyopathy (HC). However, acquired diseases such as myocarditis account for as many as 7% of cases in large sudden death registries, although often, unrecognized clinically.[1,2] Myocarditis is an acute or chronic inflammatory condition caused by viral or other infectious etiologies often presenting with nonspecific symptoms (e.g., chest pain, dyspnea, or palpitations). Although patients may demonstrate a syndrome of acute chest pain, such as with myopericarditis, or acute or chronic heart failure, presentation with sudden death, caused by a bradyarrhythmia or potentially ventricular tachyarrhythmia is less common. Also there are limited clinical data specifically regarding competitive athletes dying of myocarditis and thus the AHA/ACC Task Force for Eligibility and Disqualification recommendations rely on an older literature in military recruits and experimental myocarditis models.[3,4] Therefore, we believe it is timely to report the clinical and pathologic findings in a youthful population for whom myocarditis was incriminated as the cause of sudden death.

Methods

A total of 97 cases of myocarditis were assembled from 2 large cardiovascular registries: 1) Sudden Death in Athletes Registry (n = 54) that has collected detailed autopsy and relevant clinical and demographic data on young people (age < 40 years), engaged in organized competitive sports.[1,2] Cases were gathered utilizing news media reports, internet searches, LexisNexis archival database, news clipping service, and personal reports from interested parties. Of 2,406 cases accessed between 1980 and 2011, myocarditis represented 7% of those assigned a cardiovascular cause of death; and 2) Jesse E. Edwards Registry of Cardiovascular Disease, (n = 43), a national referral center and depository of cardiovascular autopsy specimens since 1956 with >30,000 cases. Cases are referred from regional hospitals, as well as nationally for specific cardiovascular expertise, and are permanently retained. Cases were not included that were surgical specimens (age 10−39).

Causes of death and cardiac diagnoses were adjudicated in each case by the responsible medical examiner and validated by experienced investigators and pathologists from autopsy reports and/or examination of tissue. Myocarditis was classified as definite (n = 70) when foci of inflammatory cells were evident in close proximity to areas of myocyte damage/injury (necrosis) with loss of myocytes and associated replacement fibrosis, or when inflammatory cells were present in the conduction system; *probable* (n = 15)

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when inflammatory cells were evident in multiple foci associated with possible (although not definitive) areas of injury; and *possible* (n = 12) when inflammatory cells were present, but not in clear proximity to myocyte injury).[5–7] Data are expressed as mean ± SD.

Results

Myocarditis cases were primarily male (n = 74, 76%), 19.3 +6.2 (range 9 to 40) years of age. Many of these (n = 58) were known to have died during or just after physical activity including 48 involved in competitive sports programs. Athletes most commonly participated in football (n = 16) and basketball (n = 15), largely at the junior high or high school level (39). Symptoms were known to be present before death in 46 (47%), most frequently viral illness/malaise (n = 16), syncope (n = 9), nausea/abdominal pain (n = 7), chest pain, and palpitations (n-7). In the 25 cases for which the duration of symptoms were known, 7 were <24 hours and 18 were >24 hours. Nine patients had consulted a cardiologist. None was diagnosed with myocarditis, but rather with premature ventricular contractions or "palpitations."

Heart weights were 383 g ± 88 (range, 224 to 580). Inflammatory cells were predominantly lymphocytic (n = 65, 67%), mixed cellular (lymphocytes and/or other cell types) (n = 15, 15%), and other cell types or not specified (n = 17, 17%) (Figure 1). Distribution of infiltrates (when specified) were most often multifocal or diffuse (n = 57), but also isolated (n = 29). Of the 29 isolated infiltrates, 19 were present in the conducting system (atrioventricular node or HIS bundle). Of 58 cases in whom the conduction system was specifically examined, foci of inflammatory cells were identified in 37 (64%) (Figure 1A and 1B).

Associated diseases, not considered the primary cause of death, included: Hypertrophic cardiomyopathy (n = 3), atherosclerotic coronary artery disease (n = 1) congenitally anomalous right coronary artery origin (n = 1), myxomatous mitral valve (n = 1).

Discussion

Based on 2 large athlete and cardiovascular registries comprised of thousands of cases acquired over several decades, this report provides a profile of myocarditis as a cause

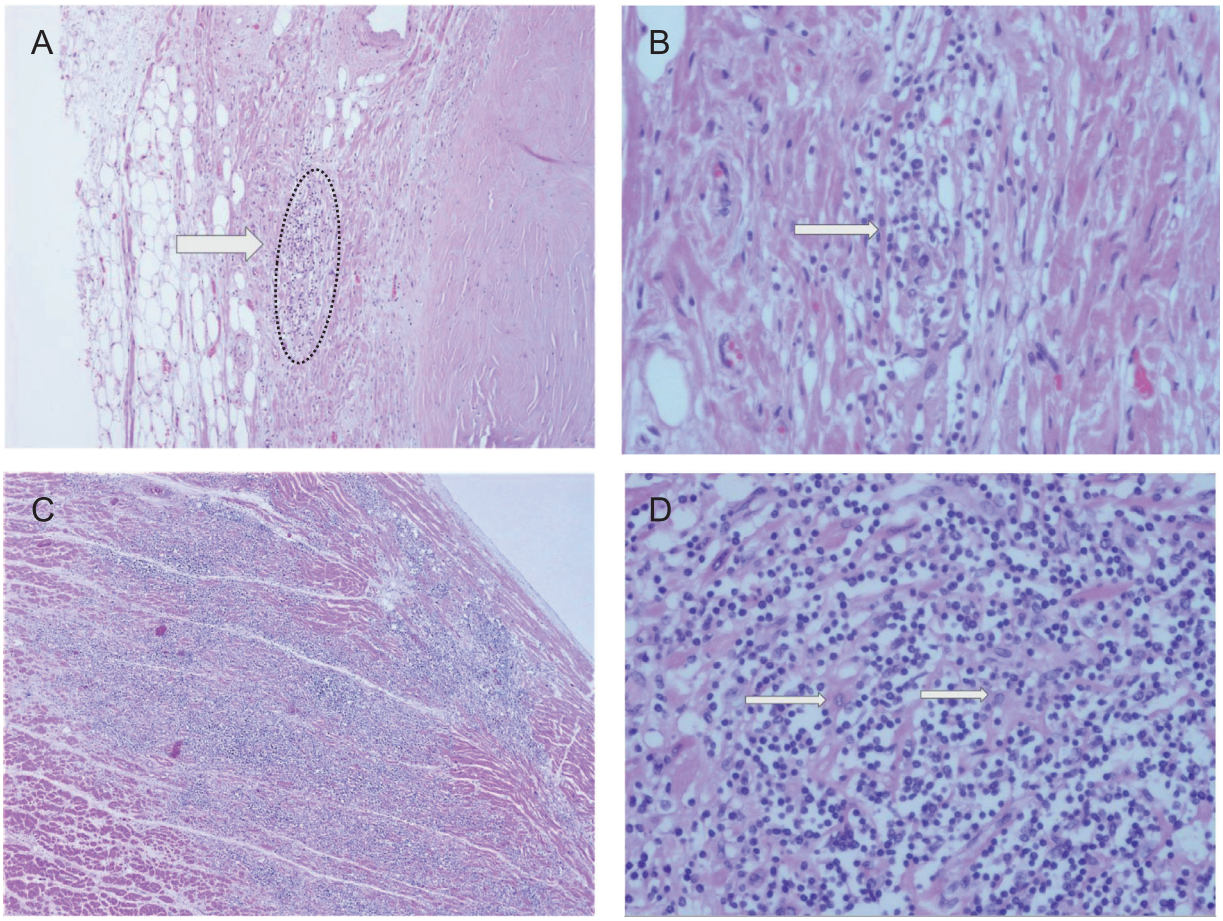

Figure 1. *(A)* Single large focus of myocarditis in subepicardium *(arrow, circled)* prominent within the atrioventricular node from a 26-year-old woman found dead at home. H&E stain; Magnification × 20.
(B) Focus of myocarditis within the atrioventricular node in panel A, shown at higher power. Arrow indicates area of injury and death. H&E ×200.
(C) Diffuse myocarditis with numerous lymphocytes, associated with loss of myocytes in 17-year-old boy found dead at home. H&E ×40.
(D) Higher power view of panel C of florid lymphocytic myocarditis. Arrows indicate injured myocytes. H&E ×400.

of death in young people. Whereas some individuals had sought medical attention for nonspecific symptoms, including apparent viral syndromes, chest pain and syncope, none were diagnosed premortem with heart disease or myocarditis.

Whereas the clinical spectrum of myocarditis includes acute coronary-type syndromes and heart failure, the presentation in young apparently healthy people with sudden unexpected death is underappreciated.[8–11] In contrast to many causes of sudden death in the young (including athletes), myocarditis is an acquired condition which easily eludes even rigorous history and physical examination screening. Complicating recognition, a viral prodrome may coexist in only 10% of myocarditis cases[9,11] and nonspecific symptoms occur in 40% as reported here. Therefore, for clinicians assessing young athletes, these data highlight the importance of clinical vigilance, a high index of suspicion and referral for diagnostic testing including with cardiac MRI.[9]

Our finding of inflammatory histopathologic changes consistent with myocarditis in two-thirds of cases after careful examination of the conduction system is notable. This observation provides a potential novel mechanism for some sudden catastrophes presumably mediated by complete heart block.[9,10] Recent cardiac MRI data showing myocarditis involvement of anteroseptum associated with increased sudden death risk may potentially be explained by involvement of the conduction system such as in our cases.[12]

Once myocarditis is recognized, restrictions on athletic participation during recovery have been recommended by the AHA/ACC consensus panel.[3,13] The panel recommendations advise that the athlete may return to play once left ventricular function and markers of inflammation, heart failure, and injury have normalized and clinically relevant arrhythmias are absent.[3,13] Indeed, it is notable that almost 90% of the athletes in the present study were known to be physically active near the time of death. Because COVID-19 myocarditis is becomming increasingly prominent in this population it may be an additive concern for sports eligibility.[3,13–16]

Although this study, to our knowledge, constitutes the largest series of myocarditis cases leading to sudden death it does have certain inherent limitations. Access to certain clinical data was restricted, including ECGs. In a small number of cases with hypertrophic cardiomyopathy, there were coexistent conditions, and the precise cause of death (or possible dual causality) could not be determined. Cardiac conduction systems were not routinely studied as part of autopsy examinations.

Due to the referral nature of the Jesse Edwards Registry, an estimate of the incidence of myocarditis could not be calculated reliably but was 7% in the Sudden Death in Athletes Registry.

In conclusion, myocarditis is an important under-recognized cause of sudden death in young people including competitive athletes. For the sports medicine community evaluating young active individuals, clinical diagnosis of myocarditis is challenging since associated symptoms are usually nonspecific and often ignored, requiring a high index of suspicion for diagnosis. When the diagnosis of myocarditis is suspected, cardiology referral and imaging with MRI is indicated.

This report provides support for AHA/ACC guidelines withholding participation from sports in those athletes suspected or diagnosed with myocarditis. Several cases of conduction system involvement with myocarditis suggest a potential novel pathophysiologic mechanism for sudden death in this population.

Credit Author Statement

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Disclosures

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