Part 2 - Sudden Cardiac Death in Athletes Focused Cause-and-Effect Screening

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Abstract

Sudden death in an athlete is a tragic event. There is a strong social imperative to implement effective means of predicting and preventing sudden death in athletes. However, the design and implementation of a solution seems unobtainable [2]. Part Two discusses how novel attributes of systems biology and digital technology are capable of delivering high quality, low cost athletic screening. The merit of a transformative idea does not necessarily predict its adoption. The greatest barrier to change lies in the acquiescence to familiar practices even in light of new ideas and technology. The current thought in athletic screening is more centered on specific disease associations (*rule-in principle*), [3-5] and much less about the sensitivity of pathophysiologic causality (*rule-out principle*) [5-8].

A solution will languish until the expert community takes direct action to embrace 21st century systems based medicine, causality, and digital technology [7,9,10]. The *first step* is to break the code of silence by open public discourse (publish and speak about the transformative attributes of systems based medicine). The *second step* is to make everyone accountable (causal prediction and prevention must be 100%). The *third and final step* is to focus on how to define the components of systems based medicine, determine how these components interact with one another, and delineate the dynamics of these components in determining pre-emergent disease states [10].

Introduction: Why and How

Why? [11] Although sudden cardiac death in athletes is rare, most of these individuals are young, healthy and otherwise would have long productive lives. Their loss is shocking and can be prevented.

How? Every essential screening test must detect normality, and on the other hand alert the presence and intensity of a potential life threatening abnormality with a very low rate of false positives. An essential screening exam should emphasize prognostication and not the permutations of disease detection [12]. Athletes are known to have normal to hyper-normal physiology, while life-threatening diseases have distinctly abnormal physiology.

Echo/Doppler screening should be looked upon as a strategy used in a select population of healthy, asymptomatic individuals to identify pre-emergent disease. Using focused echo/Doppler screening the incidence of a cardiovascular finding in athletes has been reported to be roughly one case in every 170 athletes screened with a "false positive" finding in only 8 of 508 athletes [2, 10, 13-15]. We describe how to provide a highest quality, exceptionally low cost pathophysiologic athletic screening test, which is validated to differentiate the status of a normal state from an abnormal life-threatening pathophysiologic state.

Matching pre-emergent disease (without phenotypic expression) "*associated*" with sudden death through diastolic parameters is the key to differentiating normal from abnormal pathophysiology [5, 9, 16-24]. These data are focused on two principal objectives: detect an imminent life-threatening state at a time when the opportunity for prevention is optimal [25, 26], and define the magnitude of imminent risk that enlightens physician decision making and management [23, 26-28].

Rule-Out vs. Rule-in Screening

A sensitive screening approach must be distinguished from a specific screening methodology [5, 6]. The current trend in athletic screening is searching for an "abnormal" disease feature in a low risk population. This fact alone (searching for a specific rare event) is a major contributor to the controversies and shortfalls surrounding athletic screening [5, 6].

The most optimal screening test for a large, asymptomatic athletic population prioritizes testing to confirm wellness and rule out disease. An abnormality in screening would be referred for comprehensive evaluation. The rule out principle is important because the penalty for missing a disease has the potential for athletic death. This principle reduces the number of specific diseases to be considered during screening. All cardiomyopathies are grouped as having abnormal diastolic tissue Doppler examination. Conversely, ruling in a disease is more applicable when confirming a high frequency disease. Confirming wellness

and ruling out disease is most applicable to large, asymptomatic athletic population [5, 6].

The testing that depicts pre-clinical disease is diastolic function [29]. Primary diastolic dysfunction occurs early in the emergence of cardiomyopathies, hypertension, valvular, and ischemic heart disease Table 4. Doppler-echocardiography is recognized as the most useful tool to routinely and economically quantify diastolic and systolic function [29-34].

Causes of Sudden Death

Sudden cardiac death is most commonly due to a quiescent pathophysiologic “trigger” that can become malignant if the “trigger” is disturbed. There are 3 principal types of triggers: cardiomyopathies, channelopathies, and structural heart disease. The nature of individual and overlapping triggers vary not only by an underlying disease state, but also by pathophysiologic state, genetic determinants, and environmental factors [33, 35]. People with cardiomyopathies commonly die an arrhythmia death[36]; people with channelopathies may experience arrhythmia death [37]; and people with structural diseases may experience cardiac dysfunction and arrhythmia deaths [38]. The causes of sudden cardiac death promote blunted micro and macro-vascular ischemia and replacement fibrosis, which cause electrical heterogeneity, and induced arrhythmias [39, 40]. The state of a “trigger” can be measured as an aggregate of multiple related features [7-9, 41]. In athletes a quiescent “trigger” can suddenly transition into a malignant state due to the physiologic stress of exercise [29, 42-44]. In vulnerable athletes exercise changes LV compliance, rather than LV systolic function[45]. The distinction between a normal and abnormal “trigger” lies in the aggregated pathophysiologic profile of small groups of highly related features of diastolic function [9] Table 1 and 2.

Cardiomyopathies

Normal CV function can be effectively and reproducibly measured as a small set of related echo/Doppler data [30, 46, 47] Table 1 and 2. Essential screening for cardiomyopathies is not designed to define a specific disease, but should be focused on the imminent risk of sudden death. Risk is most easily and accurately defined as a weighted expression [22, 23] of a small group [16, 17, 28, 48] of linked diastolic parameters [9, 49]. The essential focused echocardiographic approach has been validated to have a very low incidence of false positive and false negative interpretations[9, 14, 48, 50]. Outliers within a disease module can be appropriately classified [48]. In most circumstances only 2 to 4 aggregated diastolic features (e' , E/e' ratio, DT, E/A ratio) will suffice to differentiate normal vs. abnormal pathophysiology [51].

Asymptomatic diastolic myocyte dysfunction followed by systolic myocyte dysfunction and microvascular ischemia emerge early in the pathophysiologic continuum, while structural and electrical remodeling (electrical heterogeneity, arrhythmogenesis, and fibrosis) and symptoms occur later [60]. The prognostic importance of asymptomatic pre-emergent pathophysiology has only recently been realized [61, 62]. Asymptomatic athletes commonly engage in activities that

can accentuate pre-emergent pathophysiology that could be acutely detrimental to myocardial function. For screening purposes “cardiomyopathy” can theoretically apply to almost any disease affecting the heart in which the heart muscle is structurally abnormal. Essential screening should be focused on *prognostication* of risk, and not *detection*, or characterization of a disease type [12, 63]. An essential exam requires the acquisition of a small number of essential data, which define the presence and intensity of emergent cardiac dysfunction Table 1. Disease risk is always defined by more than one datum feature. Hypertrophic cardiomyopathy (HCM) is an exemplary candidate for pathophysiologic screening. HCM rarely has any premonitory symptoms [35], even under exertion [35], ECG has a high rate of false positives [64-67], ejection fraction (EF) is rarely abnormal,[32] and anatomic remodeling is variable, and typically occurs late in the pathophysiologic cascade [68]. However, associated diastolic dysfunction can be detected and measured early in the HCM cascade [68-70] and is capable of detecting pre-clinical HCM risk [68, 69, 71]. An essential screening exam is the one designed to affirm the existence of an abnormal physiologic profile, and identify individuals with an abnormal risk profile, independent of morphology Table 2 [9, 21, 28, 72]. The algebraic summation of a small aggregate of related data (E/A , DT, e' , E/e') define causality [28, 41] which mirrors the status of an individual's risk state in both a positive and negative direction during serial screening, management, and follow-up [7, 8, 73].

Cardiomyopathy-screening needs to take a focused approach to potential emergent cardiac dysfunction and risk [36, 74]. Each cardiomyopathy disease (hypertrophic [68, 75], restrictive [76, 77], dilated[78], ischemic [79, 80], hypertensive [81, 82], arrhythmogenic right ventricular [83], myocarditis [84], left ventricular non-compaction [85, 86]) each has validated pathophysiologic features that can confirm a risk state [52, 87]. Averaged features have a very low incidence of false positives and false negatives results [9, 14, 48, 50].

Hypertensive Heart Disease

The essential pathophysiologic data used to depict the risk of hypertensive heart disease [81, 82] and “pseudo-HCM” [48, 91, 92] are identical to those of general *cardiomyopathies* [60] **Table 1&2**. Screening blood pressure and increased LV wall thickness serve only as benchmarks that require physiologic classification as normal compensatory physiology versus emergent heart disease [91]. The overlapping features of normal [9, 54, 93] myocardial remodeling can mimic the features of HCM, hypertensive heart disease, and infiltrative diseases [81, 94]. These overlapping features have been referred to as the “gray zone”. The overlapping features are not essential to an essential, focused examination attempting to determine risk. The goal of essential screening is to affirm normal and rule out abnormal disease related remodeling [5].

Ischemic Heart Disease

Although considerable attention is focused on young athletes, the risk of sudden death from coronary artery disease (CAD) is much greater among sports participants older than 35 years

Table 1: Mechanical Features [30, 47].

• E = early transmitral filling velocity related to the time course of active LV relaxation, which generates a gradient from left atrium through the left ventricular inflow.
Lateral e' = early diastolic annular velocity measured in the lateral region of the mitral annulus; Most patients with lateral e' ≥8.5 cm/s have normal myocardial relaxation [30].
Septal e' = early diastolic annular velocity measured in the septal region of the mitral annulus; reflects longitudinal diastolic myocardial relaxation; Most patients with septal e' ≥8cm/s have normal myocardial relaxation [30];
E/e' ratio: E/e' ratio is a surrogate measure of LV filling pressure [43]. Average of lateral and medial E/e' <8 would have normal myocardial relaxation and LV filling pressure [30].
• S' = systolic velocity of mitral annulus
• A = late transmitral filling velocity
• DT = Transmitral Deceleration Time; tends to be prolonged by impaired LV relaxation and shortened by increased filling pressure.
• EF = Ejection Fraction
• GLS = Systolic Global Longitudinal Strain
• LAVI = Left Atrial Volume Index [51]

Table 2: Normal Multi-feature Screening Physiology [30, 47].

Diastolic Function	Normal				Reference
Mitral inflow E (cm/s)	60±12				[47]
Diastolic velocity MV annulus	Normal e' by Age group (y)				
	16-20	21-40	41-60	>60	
Septal e' (cm/s) [†]	14.9 ± 2.4	15.5 ± 2.7	12.2 ± 2.3	10.4 ± 2.1	[30]
Lateral e' (cm/s) [†]	20.6 ± 3.8	19.8 ± 2.9	16.1 ± 2.3	12.9 ± 3.5	
E/e'	NormalE/e' (& Normal e')	AbnormalE/e' (& Abnormal e')			
Septal E/e' ratio	7.05±6.0	8-10	11-14	≥15	[30, 47]
Lateral E/e' ratio	6.18±1.53	>8-9	10-11	≥12	
Average E/e' ratio	<8	9-12		>13	[30]
MV inflow E/A ratio if the e' is normal	>0.8 to <2*	If e' is abnormal these same data ranges would be abnormal (i.e. pseudonormal)			[30]
MV inflow DT if the e' is normal	>140 to <240*				
Left Atrial Morphology	Normal	LA overload			[51]
LA Volume Index (mL/m2)	16 to 28 22±6	Mild 29-33	Moderate 34-39	Severe ≥40	[52]
		Benign if e' is Normal			[51, 53]
		Malignant if e' is Abnormal			
Systolic Function	Normal				
EF %	≥55	Athletes with Large LV; EF can appear mildly reduced; if diastolic function is normal the low EF is likely an artifact			[54]
Artifactual EF %*	50-55				
Global Longitudinal Strain %	-19.7	(As the negative number increases the function improves)			[55, 56]
Tissue Doppler s' (cm/s)					
Septal	>7.5				[57]
Lateral	10±1.5				
RV systolic Function (cm)					
Tricuspid Annular Displacement					
TAPSE (cm)	≥1.8				[58]

[†] Data are expressed as mean ± SD. Note that a normal e' velocity in subjects aged 16 to 20 years, values overlap with those for subjects ages 21 to 40 years. This is because e' increases with age in children and adolescents. Therefore, the e' velocity is higher in a normal 20-year-old than in normal 16-year-old, which results in a lower e' value when subjects aged 16 to 20 years are considered [30].

*EF between 50-55% [54] (LV cavity enlargement in normal athletes can be associated with a modest lowering the EF). The presence of normal diastolic function would strongly suggest normal athletic CV remodeling and not physiologic dysfunction.

[†] GLS (Global Longitudinal Strain) is a measure of sub-clinical systolic function.

There is a universal pathophysiologic cascade in primary and secondary cardiomyopathies [39, 59]

and is greatest in the fifth decade [95-97]. The incidence of fatal CAD is reported to be 0.7 per 100,000 person - years for athletes <35 years of age, and 13.7 per 100,000 persons-years for those ≥35 years of age [98]. Ischemic risk represents the cumulative impact of a cascade of pathophysiologic events [59]. The focus on the late stage features of CAD (ECG abnormalities, angina, wall motion abnormality and infarction) needs to be redirected to the more fundamental underlying pathophysiologic factors (sub-clinical diastolic and systolic dysfunction) that emerge earlier in the pathophysiologic cascade [59]. The essential objective of screening asymptomatic athletes is to disclose imminent pathophysiologic risk (occurrence of an event within 1 year [99], and not the presence of long-term risk (Framingham Score 10 year risk profile [100]). Screening stress testing [67, 101-103] and CT coronary angiography [104] are considered inadequate means of assessing CAD risk in asymptomatic adults. Coronary calcium score may be helpful to determine the burden of CAD, but at this time the risk associated with a particular calcium score is unknown [105] and deemed an inappropriate marker for those at low risk [106]. In an asymptomatic population, echocardiographic physiologic dysfunction as an indicator of asymptomatic life threatening cardiac dysfunction is often underappreciated [69]. In asymptomatic adults, resting echo/Doppler diastolic function assessment Table 1&2 is reported to be an excellent independent predictor of imminent CAD risk [107-111].

There is controversy regarding the means of quantifying imminent CAD risk in asymptomatic athletes (92). At present, recommendations for the assessment of imminent risk are limited, inconsistent, or nonexistent [101, 108, 112]. However, echo/Doppler determination of an individual's physiologic state is a logical general predictor of imminent risk, including the risk of ischemic heart disease. If the physiologic risk was sufficiently abnormal further assessment of coronary anatomy and physiology would be clinically indicated particularly in individual's ≥35 years old. As the population ages, the incidence of pre-clinical risk associated diastolic dysfunction increases [61, 62]. This fact supports the use of essential screening in the general population just as screening is used with other disease processes (e.g., colonoscopy [113]; mammography [114]; and often CV disease [115]).

Channelopathies

Channelopathies are considered unique and are variably classified as a primary electrical disease or cardiomyopathy [36, 60]. Various forms of electrical cardiomyopathy affect about 1 in 1000 people [116]. Channelopathies are the assumed culprit in cases of undefined sudden death [65]. Randomized and/or blinded studies do not exist in this field. All recommendations are based on consensus opinions [117]. An important clinical finding is that 50% of these sudden death victims have preceding "warning signs": exercise /auditory triggered fainting/seizures, family history of premature CAD (<40 years of age), or unexplained accidents, and near drowning [116].

Proper recognition of these warning signs may significantly reduce primary electrical deaths and initiate a more comprehensive electrophysiology workup [65, 118]. Currently

technical and logistical challenges preclude the use of ECG as a robust tool for universal screening in asymptomatic population [116,119]. One of the biggest challenges with ECG is the high incidence of false positive findings [66, 118]. Interestingly in recent research subclinical Doppler pathophysiologic changes were identified in nearly 20% of Long QT syndrome patients [120]. These findings prompt speculation that electrical dysfunction (abnormal cardiac repolarization and rhythm) may precipitate macroscopic structural and functional changes visible on focused echocardiograms [120, 121].

Structural and Hemodynamic Cardiac Disease

Pulmonary Hypertension

Pulmonary artery pressure (PAP) can be estimated in nearly 100% of patients using any one of three simple techniques [122]: (1) *Systolic PAP* using the Tricuspid Regurgitant Velocity (TRv) (Normal TRv ≤2.8 m/s corresponding to a right atrioventricular gradient ≤31 mmHg) is considered a reasonable cutoff to define elevated PAP in healthy persons; (2) Normal *Diastolic PAP* using the end-diastolic Pulmonary Regurgitant Velocity (PRv) (PRv <1.1 m/s corresponding to an end-diastolic pressure of <5 mmHg) is correlated with normal pulmonary pressure.; and (3) normal *mean PAP* using pulmonary flow acceleration time (AcT) (AcT defined as the time interval from the onset of forward flow in the PA to peak velocity of this flow). AcT >100 ms equates a mean PAP < 20-39 mmHg and AcT <75 ms equates to a mean PAP ≥40 mmHg [123,124] Table 3.

Coarctation of aorta

Is a rare cause of hypertension. It should be excluded in every patient with elevated blood pressure, or in the presence of a BAV [126]. Coarctation cannot be effectively detected by random blood pressure measurements or a cursory physical exam [24], but can be detected and quantified by a simple echo/Doppler signal in the abdominal aorta [127]. In the presence of coarctation the overall aortic velocity is blunted, systolic upstroke is delayed and there is continuous forward flow consistent with a diastolic and systolic gradient and/or collateral flow. These abdominal aortic pulsed-wave Doppler signals were recorded in a normal patient (upper panel) and a patient with severe coarctation of the aorta (lower panel). The normal tracing (upper) shows a rapid systolic upstroke and return to baseline at end-systole. The early diastolic reversal of flow associated with a widely patent aortic arch. Elastic recoil of the ascending aorta causes the low velocity, late-diastolic forward flow seen after the early diastolic reversal.

Table 3: Pulmonary Artery Pressure Screening (125).

Measure	Equivalent PAP	Normal Values	Reference
TRv m/s	(Systolic PAP)	≤2.8 m/s (>31mmHg)	[122]
PRv m/s	(End Diastolic PAP)	≤1.1 m/s (≥5 mmHg)	[122]
Pulmonary AcT	(Mean PAP)	>100 ms (<20-39 mmHg) <75 ms (≥40 mmHg)	[122-124]

PAP: Pulmonary Artery Pressure; TRv: Tricuspid Regurgitant Velocity; PRv: Pulmonary Regurgitant Velocity; AcT : Acceleration Time

In contrast, in the presence of coarctation (lower panel) overall velocity is blunted and the systolic upstroke is delayed. Although the systolic velocity is decreased, the diastolic velocity is actually greater than normal. This case shows continuous forward flow, consistent with both systolic and diastolic gradients across the coarctation.

Anomalous Coronary Artery

An essential component of every athletic screening examination is the visualization of the origin of the proximal coronary arteries, which can be accomplished with transthoracic echocardiography in 70 to over 95% of young athletes [14, 66, 128-130]. Other technologies (e.g., MR and CT) do not fit the essential qualifications of a focused screening exam principally because of limited access and cost [131]. Although the anomalous origin and course of the left or right coronary artery has been reported to be exceedingly rare in young athletes [129], others have reported that coronary artery anomalies are the second most common association with sudden death in athletes (i.e., ~17%) [128]. The most life-threatening anomaly is left or right coronary artery originating from the contralateral sinus of Valsalva and coursing between the aorta and proximal pulmonary artery Figure 3 [3, 132, 133]. The management of the coronary anomalies is controversial [133]. If an anomalous coronary is identified or suspected further diagnostic and clinical assessment would be indicated.

A. Echocardiogram [135]. Anomalous right coronary artery (RCA) arising from a common orifice with the left main coronary artery

Computed tomography [134]. Single right coronary artery with an inter arterial path of the left main coronary stem. Left coronary artery (white arrowheads) originates for the proximal part of the right coronary artery (black arrow) then follows an inter-arterial path between the ascending aorta and the pulmonary trunk. The white arrows indicate the inter-arterial part of the circumflex coronary artery. AO: Ascending Aorta; LA: Left Atrium LV: Left Ventricle.

Echocardiogram [135]. Anomalous origin of the left anterior descending (LAD) coronary from the proximal right coronary artery (RCA).

Aortic Aneurysm

Another essential component of a focused screening CV exam is documentation of the anterior-posterior aortic diameter [e.g., leading edge to leading edge, at end-diastole [52] at the level of aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta. An aortic root dimension >40 mm in highly conditioned male athletes and >34 mm in female athletes is uncommon; is unlikely to represent the physiological consequences of exercise training; is most likely an expression of a pathological condition [136]; and mandates size-based surveillance [137] Table 4. Although there are multiple types of aortic aneurysms [137] there are three syndromic aortopathies of particular concern in asymptomatic athletes: Marfan syndrome [138, 139], BAV [140-142], and cystic medial necrosis [143]. The

presence of any aortic valve regurgitation in a young athlete should alert the examiner to a possible structural abnormality of the aortic valve [140]. The pathophysiology and genetics of these aneurysms are similar and should be recognized as having a life-long enhanced risk of an aortic pathology [144]. In focused screening Marfan syndrome body habitus is variable and not discriminating enough to be essential. Both Marfan syndrome and cystic medial necrosis have a characteristic sinus of Valsalva aneurysm (i.e., Erlenmeyer flask configuration) [139, 143] Figure 4. The aortopathy associated with BAV is different and is usually a fusiform ascending aortic aneurysm [140] Figure 5. Risk of rupture of a non-syndromic aortic aneurysm is expressed as an indexed relative size (i.e., diameter indexed to body surface area) [145-147] Table 4. However young patients particularly with a syndromic aortic aneurysm approaching 5.0 cm should be considered surgical candidate. Counseling and CV evaluation of all first-degree relatives is strongly recommended [142]. In older men who have ever smoked an abdominal aortic aneurysm (AAA) should also be ruled out [148]. A ruptured AAA is usually catastrophic. Screening in women for AAA has not been shown to provide benefit [149].

Valve Disease

Echo/Doppler is a validated approach for evaluating both asymptomatic [150-152] and symptomatic valvular heart disease [150]. Early echocardiographic screening of valve disease in the general population does not translate into reduced risk of death or cardiovascular events [153, 154]. The essential objective of pre-participation athletic screening is early detection of imminent risk [48, 99, 155] and not a comprehensive echo anatomic and Doppler hemodynamic exam [155]. A multi-feature diastolic physiologic profile best reflects the magnitude of imminent risk Table 1&2 and guide to clinical care in patients with asymptomatic valve disease [156]. An athlete with an unremarkable history, normal physiologic profile, and mild anatomic valve disease may be eligible for physician monitored athletic activities.

Congenital Heart Disease

Congenital heart disease (CHD) is not a benign condition at

Figure 1: Pathophysiologic Cascade.

Figure 2: Coarctation[127].

Figure 3: (Anomalous Coronary).

any age [38]. Pathophysiologic risk assessment is usually more informative than the nuances of structural abnormalities Table 1&2. Although there is no evidence that sudden death due to CHD in athletes and non-athletes has increased in frequency [119]. The prevalence of young and older CHD survivors now exceeds the incidence of pediatric CHD [157]. CV mortality is increased particularly in young persons with a history of CHD [38] (median age at death 48.8 years; chronic heart failure (26%); sudden

death (19%)). Athletic activity should be individualized and based on sound lifelong periodic pathophysiologic assessment. Patients with known CHD are not candidates for a focused screening exam [38, 90, 158]. It is recommended that all patients with known CHD have knowledgeable provider and a least one overreaching visit with a cardiologist with advance training and experience with CHD [158].

Unanticipated Congenital Heart Disease in Athletes

The most important attribute of a pre-participation screening exam is not diagnosis but determination of imminent risk and assisted decision-making [158]. The incidental finding of CHD should not be considered a definitive test but an alert for further evaluation. Persons performing a screening examination should have a general understanding of important normal versus suspected congenital anatomy and pathophysiology [159].

Shunt lesions are inferred in otherwise healthy individuals by increased pulmonary blood flow, asymmetric heart chamber enlargement, arrhythmias and increased pulmonary pressure.

Figure 4: Large aneurysm of the aortic sinus in an adult patient with Marfan syndrome. The aortic sinus aneurysm is often considered analogous to an Erlenmeyer flask configuration (i.e., flat bottom, bulbous body and cylindrical neck). LA: Left Atrium; LVO: left Ventricular Outflow; MV: Mitral Valve; RVO: Right Ventricular Outflow; VS: Ventricular Septum.

Figure 5: Left panel: Composite image of the ascending aorta in a child with early morphologic features of Marfan syndrome. Note the bulbous aortic root (Erlenmeyer flask appearance). The remainder of the aorta appeared normal. Right panel: Bicuspid valve associated aortopathy

Stenotic lesions are suggested by characteristic chamber remodeling and pathophysiologic risk assessment.

Complex lesions are recognized by pathognomonic structural variations. Essential anatomic landmarks include [74, 135].

Apical 4-Chamber Internal Cardiac Crux

The internal crux is the four-quadrant intersection of the atrial and ventricular septum and septal leaflets of the mitral and tricuspid valve [160] **Figure 7**. Many complex congenital anomalies will have an abnormality of the internal cardiac crux (e.g., Ebstein's Anomaly, Corrected Transposition, atrioventricular canal, etc.). Patients with irregularities of the internal cardiac crux should be referred for further CV evaluation.

The internal cardiac crux is one of the most infallible cardiac landmarks (118). The apical 4-chamber view of the heart allows identification of the crux of the heart. The morphologic tricuspid valve consistently inserts lower on the ventricular and the morphologic mitral valve inserts higher. The internal crux anatomy unambiguously confirms the commitment of the morphologic tricuspid valve to the morphologic right ventricle. Many complex congenital anomalies distort the internal cardiac crux (Ebstein Anomaly, corrected transposition). The internal cardiac crux is one of the most infallible cardiac landmarks (118).

(Left panel) Normal internal cardiac crux of the heart: The morphologic tricuspid valve consistently inserts lower on the ventricular and the morphologic mitral valve inserts higher. The internal crux anatomy confirms the commitment of the morphologic tricuspid valve to the morphologic right ventricle. Many complex congenital anomalies distort the internal cardiac crux (e.g., Ebstein Anomaly, corrected transposition) (142,293). **(Right panel)** Abnormal Atrial-Ventricular Discordance: This patient has a complex congenital abnormality where the morphologic tricuspid valve and the morphologic right ventricle are on the left side of the heart (atrial-ventricular discordance). This patient had corrected transposition of the great arteries where the morphologic right ventricle functions under system blood pressure, which commonly leads to progressive ventricular dysfunction (morphological right ventricular failure).

Figure 7: (Left panel) Normal internal cardiac crux of the heart: The morphologic tricuspid valve consistently inserts lower on the ventricular and the morphologic mitral valve inserts higher. The internal crux anatomy confirms the commitment of the morphologic tricuspid valve to the morphologic right ventricle. Many complex congenital anomalies distort the internal cardiac crux (e.g., Ebstein Anomaly, corrected transposition) (142,293). **(Right panel)** Abnormal Atrial-Ventricular Discordance: This patient has a complex congenital abnormality where the morphologic tricuspid valve and the morphologic right ventricle are on the left side of the heart (atrial-ventricular discordance). This patient had corrected transposition of the great arteries where the morphologic right ventricle functions under system blood pressure, which commonly leads to progressive ventricular dysfunction (morphological right ventricular failure).

Figure 6: Morphology of the aortic valve.

Table 4: Aorta Size in Athletes.				
(Reference)		Abnormal (Athletic Aortopathy)		
	Normal	Recommendation (130)		
[136]	Very Low Risk	Mild Restriction	Moderate Restriction	Consider Surgery
Male	≤40 mm	>40 mm	>45 mm	
Female	≤34 mm	>34 mm	To Be Determined	≥50 mm
[145-147]		Risk of Aorta Rupture (Indexed Diameter cm/m ²)		
Risk of Rupture		<2.75 cm/m ² ≈4% rupture/yr	≥2.75 to 4.24 cm/m ² ≈8.5% /yr	≥4.25 cm/m ² ≈20% /yr

This patient has a complex congenital abnormality where the morphologic tricuspid valve and the morphologic right ventricle are on the left side of the heart (atrial-ventricular discordance). This patient had corrected transposition of the great arteries where the morphologic right ventricle functions under system blood pressure, which commonly leads to progressive ventricular dysfunction (morphological right ventricular failure).

Non-Cardiovascular Causes of SCD

A significant proportion of sport related SCD occurs in persons with known or previously unrecognized structural or functional cardiac abnormalities. However, more than 50% of sudden death in athletes is due to other causes [161]. The most common of these are suicide and drugs, which were responsible for 29% of all sudden deaths [161]. Approximately 5-15% of cardiac arrest victims are classified as *autopsy negative* lacking

necropsy findings to establish the cause or manner of death [162]. These observations support a wider dissemination of prevention measures. First a screening test is purposefully designed to affirm an individual's normal physiologic state [63]; a screening exam should be used for *prognostication* and not *detection* of a particular disease [12]. A pathophysiologic profile will depict general risk. The risk of heat stroke [163], substance abuse [164-166], and cardiac trauma are specific to the particular situation. The risk may increase in the setting of abnormal diastolic function [167] Table 1&2. Conversely, individuals with a history of CV disease or first-degree relative are not appropriate candidates for a focused screening exam [41, 63, 66, 117, 119, 162, 168].

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