Part I - Sudden Cardiac Death in Athletes Pathophysiologic Screening: A Transformative Solution to a Social Imperative

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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 competitive athletes. However, the design and implementation of a proven screening solution remains elusive [2, 3]. To date large scale preparticipation screening has been ineffectual because it is focused on costly disease diagnosis and risk factor associations, and not on pathophysiologic effectors known to quantify a cardiovascular (CV) "risk state". The problem is that disease diagnosis does not quantify risk, [4] and statistical associations do not adequately define cause[5]. Causality can be proven only by demonstrating a quantifiable cause and effect mechanism [4, 6, 7]. A preparticipation examination should be focused on quantifiable features that have been conclusively proven to measure the magnitude of risk, and illuminate a cause-and-effect relationship between the intensity of CV risk (cause) and an emergent CV disease (effect).

The barrier to changing current preparticipation screening lies in the continued acquiescence to existing opinions that are based on risk factor associations [8]. The first step to changing this approach is to break the code of silence, which sustains the status quo [9]. The medical community needs to step out of the box, applying clinical systems biology cause-and-effect prediction for the quantification and management of dynamic disease processes using echo Doppler diastolic parameters. An individual's "pre-emergent risk" state is defined as abnormal diastolic parameters before there is phenotypic expression of disease. The diastolic parameters can be used to distinguish a benign from malignant state. This distinction is an essential component of a "focused" preparticipation screening examination. A "focused" preparticipation screening exam has the capacity to reduce cost, increase quality, and effectively address the social imperative of preventing unanticipated athletic field death across the spectrum of athletic activities and age groups.

Introduction

Athletes are perceived to be the healthiest members of our society. A healthy appearing athlete may harbor an unsuspected

disease process capable of triggering stress-induced sudden death [10, 11]. An unexpected death during training or athletic competition is a particularly tragic occurrence [12, 13]. Although infrequently encountered, addressing athletic sudden death has become a major societal imperative, [14-17] yet there is no universally accepted pre-participation screening exam in asymptomatic athletes [2]. This manuscript is a critical review of this subject.

Screening

Cardiovascular disease (CVD) is the leading cause of death in the developed countries, and many who die suddenly of CVD have no previous symptoms [18]. The definition of screening is a test offered to asymptomatic people who may, or may not, have a disease or disease precursors [19]. The test should estimate the level of "pre-emergent risk" and determine whether a diagnostic test is justified. A screening exam should not be used for disease diagnosis, management, or a substitute for a comprehensive health assessment Table 1.

Literature Review

The incidence of sudden cardiac death in athletes has been extensively studied [20-22]. However, population based studies contain varying interpretations, content, conclusions, and associations [23]. Harmon et al studied sudden death in 273 athletes between 2004 and 2008. Harmon identified that accidents accounted for 51% of the sudden athletic deaths. The second most common cause of death was cardiovascular (16%). However, this manuscript made no mention of the type of cardiac disease associated with sudden athletic field death [20]. Maron reviewed 1866 sudden deaths in young competitive athletes between 1980 and 2006. Maron identified that 56% of the deaths were cardiovascular in nature. In this population hypertrophic cardiomyopathy was attributed to 20% of the deaths and anomalous coronaries 17%. Other associated diagnoses included

Table 1 Characteristics of a Good Screening Test [19].

Objectives	Question and Answers	Essential Characteristics	Essential Pathophysiology
Detect a Preclinical disease	Is Sudden Death in Healthy Athletes a Significant Priority?	Widely available; Echocardiographic Pathophysiology	Low false positives
Characterize and Quantify ARisk State	Pre-emergent disease state treatable?	Safe; Noninvasive	Low false negatives
		Inexpensive; Reasonable Cost	Unambiguous; Discriminates Diseased vs. Non-Diseased Persons
		Prevention: Sudden Death in Athletes	Multifeature Biomarker; No single feature will adequately define risk
		Pre-emergent disease Detection	Causality: Feature state (cause) changes in concert with the emergent disease state (effect)

myocarditis, atherosclerotic coronary artery disease, mitral valve prolapse, aortic stenosis, and channelopathies [21]. In an Italian study (1979-1996) comprised of 269 sudden deaths in young people there was only one patient with hypertrophic cardiomyopathy, but a 22% incidence of arrhythmogenic right ventricular cardiomyopathy [24].

Autopsy Data

The majority of the medical literature on athletic heart disease is empiric, retrospective, and is based upon non-uniform associations. Based upon available autopsy data it is usually assumed to be related to structural heart disease [25]. A small number of events remain indeterminate [16, 25]. Structural abnormalities identified at autopsy have not been consistently validated by physiologic and/or microcellular data, or proven to be the true cause of death. The cause of any individual athlete's death remains an enigma. Current dependence on associations and assumptions do not allow for validated determination of true cause of death.

Something Overlooked

The literature lacks evidence from randomized studies using cardiovascular screening tests based upon causality [4,18]. Disease should not be defined or managed by measurements and ratios in isolation [23,26,27]. The pervasive use of population based *associations*, absence of uniform screening methodology, and the lack of a unified solution to a social imperative deserves a critical review.

Background

The fear of unexpected sudden death in athletes has led to considerable debate regarding the forms of preparticipation screening and sub-specialty medical training in sports medicine [16, 28]. The problem with the status quo is the fact that contemporary views of human disease are based on simple correlations and associations between clinical syndromes and pathological analysis, which have been used since the 19th century [8].

Disease processes are complex, and rarely a consequence of an abnormality in a single effector. Instead they are a reflection

of multi-feature pathobiological processes that interact to yield an emergent disease. The disease process is discernible only by appreciating the conjoined effects of multiple related components [8, 29]. A cardiovascular system remodels in a similar manner from normal athletic activity and disease related stressors[30]. This explains why a normal athlete can have morphologic features that are virtually identical to those identified in an unrelated disease process [29, 31]. The solution to distinguish normal from abnormal pathophysiologic profiles lies in tests designed to test causality [4,6,32]. Sudden death in athletes is a multi-variable puzzle. Individual variations in types of sports, intensity of training, and pre-emergent disease processes create a medical challenge which cannot be effectively quantified by the physician's own inductive reasoning or regression statistics [8]. The only logical solution to this conundrum is to individualize and quantify each athlete's personal pathophysiologic state using diastolic Doppler variables linked to causation [4,6,8].

Current preparticipation screening

There is a broad range of screening recommendations dependent upon the investigator(s), sporting discipline, and level of physical exertion and competition [3]. The overriding challenge is providing a common – sense, integrated strategy for prevention, while accounting for the fact that regular exercise is an activity to be encouraged. Current screening recommendations are not founded on state-of-the-art medical knowledge, but principally on general, expert consensus and associations which cannot effectively assign causation. The approach to clinical care has evolved in conjunction with evolution of the risk factor approach to diagnosis and management of disease processes. However, most of these recommendations are not supported by high quality evidence [33]. As of this date the fundamental cause of sudden death in asymptomatic athletes remains shadowed in uncertainty. An additional challenge, among 10 to 15 million athletes of various ages, is the fact that the incidence of sudden cardiac death is very low [20-22, 31, 34-36]. As a consequence of the low incidence of disease in the athletic population the current literature suggests that all cardiac imaging modalities are inadequate to justify their use as primary screening modalities in athletes, as well as the general population [2, 37].

Outside the athletic community, the medical community has come to the conclusion that routine exams in asymptomatic persons does little to improve health outcomes, and is largely a misappropriation of time and money [38]. A screening electrocardiogram (ECG) or stress testing are currently not recognized as acceptable screening tools in asymptomatic people [2, 21, 39, 40]. Even though screening tests in asymptomatic patients have no firm evidence of utility, these tests are commonly touted as acceptable screening tools for asymptomatic athletes primarily because of lower cost and access [21]. In addition to a lack of utility, a high percentage of positive ECGs and stress test findings will be false positives [41, 42], which result in anxiety and expensive adjudication [43, 44]. As medicine evolves into the 21st century and the new era of cause-and-effect pathophysiology evolves these issues will be resolved.

Experts

Thinking outside the box is difficult when people are in the box [9, 45]. Experts often reside in their domain of expertise, making it difficult for them to determine the limitations, or sources of errors in their paradigms. Experts manage each solution and direct the investigative group's focus on domain explicit strategies, rather than determining how to most effectively solve the whole problem. It's difficult for an expert to look at problems holistically — to step back and think about issues that need broader investigation and how data might be most effectively used. Architecting holistically is necessary if we are to prepare ourselves to address broad, unanswered questions [8, 27]. The synergies of cross-pollination across domains have enormous potential when seeking solutions to complex problems.

One of the greatest barriers to any change lies in the continued acceptance of unproven solutions [9]. These approaches are sustained by a culture of silence. Experts know that current limitations for diagnosis and assessment of sudden death in athletes carry an enormous cost but no consortium of experts have stepped out of their domain to change the existing unproven practice patterns.

Time to Change

Medical risk assessment is about to profoundly change and revolutionize the approach to disease prevention. In the 19th century (*Era of Pathologic Correlations*) medicine focused on Oslerian clinical-pathologic correlation [46]. The Oslerian formulation for human disease links clinical presentation with pathological findings following a disease – centric model. As a result disease is defined on the basis of the principal organ system in which symptoms and signs are manifest and in which gross anatomic pathology and histopathology are correlated.

In the 20th century (*Era of Risk Factors*) medicine further refined pathological markers and devices used for correlation between symptoms, findings and pathology, (biochemical measures; X-ray, ECG, Ultrasound, magnetic resonance imaging (MRI), computed tomography (CT); more recently genomics), yet the general principles based on associations remained the same disease- centric model This approach over-generalizes pathophenotypes, which do not sufficiently take

into consideration susceptibility states or preclinical disease manifestations, and cannot be used to individualize disease diagnosis and therapy [4, 6-8, 33, 47-50].

As we enter the 21st century(*New Era of Pathophysiologic Cause-and-Effect*) we are beginning to recognize that conventional pathophenotypes (risk factors)are too limited to be useful [8, 33, 51]. We are about to move the health care enterprise forward to reduce the burden of disease and suffering. Disease is to be looked upon as the result of the output of a complex network of interconnected *nodes* linked mechanistically to yield a pathophenotype [52]. Human disease is redefined using a combination of approaches to identify systems-based pathophysiologic mechanisms that render one susceptible to preclinical and overt pathophenotypes. The network model can predict disease expression (sudden death in athletes) and quantify the magnitude, or intensity of risk. The nonlinear response of physiologic features under lies the emergent properties of asymptomatic disease. Physiologic networks are not random collections, but clusters of regulatory effectors [53, 54]. All diseases are biological networks that manifest properties, which define those features that are most responsible for a specific pathobiological process or specific disease. These tenants promise to redefine our approach to disease and the field of preventive medicine. We can address sudden death in athletes as small networks of highly related combinatorial data to identify systems-based pathophysiologic mechanisms that render an athlete susceptible to preclinical and overt pathophysiologic risk. This change in medicine is made possible by the simplicity of *network medicine* [47, 49] and computer assisted intelligence [55, 56].

Essentials of a Pathophysiologic Solution

“Simplicity is the ultimate sophistication” Leonardo da Vinci [57].

“The likelihood that one event is the cause of another guides much of what we understand about the world and how we act in it.” Judea Pearl [4]

Definitions

Pathology: Is the medical discipline that describes conditions observed during a disease state, and **physiology** is the biological discipline that describes processes and mechanisms operating within an emerging disease state without phenotypic expression. Combinatorial **pathophysiology** documents physiological processes (**cause**), which define the status of an evolving pathological condition (**effect**).

Essentialism [58]: An “*essential*” screening is an exam focused on those things that are absolutely necessary and indispensable, precluding things that are *extra*, or *needless* [58]. The low incidence of sudden cardiac death and the cost of screening athletes shape current policy decisions. To improve the policy the valued-added essential screening exam must identify those at risk at a low cost [35]. Data without sufficient discrimination, reproducibility, or validation are deemed unnecessary and dispensable. Routine physical exam, ECG, stress

test, blood tests, complete or limited echo cardiography, CT, and MRI exams do not meet the definition of *essential because they are costly and attempt to define disease rather than risk* [42]. In order to markedly increase the power of discrimination (normal vs. abnormal) and substantially lower the constraints of access and cost, each feature of the screening exam must be individually scrutinized for its essential role in determining risk. An exam *focused* on simple essentials requires more sophistication than either a *comprehensive* or *limited* examination [59]. This does not mean that non-essentials are void of empirical content: the structural components of a disease may become relevant post the screening when viewed in conjunction with the pathophysiologic state [4, 34, 35].

Objective

The first objective in screening should be to design a test to obtain a scrutinized set of essential data, which reflect the individual's pathophysiologic state that has the potential to deteriorate during stress [8, 60-63]. Screening designed around essentials does not compromise efficiency, completeness, or accuracy of the exam [29]. Second, the screening exam is not comprehensive, but focused on obtaining and prioritizing the most essential objectives. The acquisition of small numbers of essential data will reduce cost [47] and computer assisted data interpretation will increase exam quality and user intelligence [55, 56]. Third, the screening exam should embrace holistic reasoning and avoid domain specific thinking.

Look Alike Data

Many compensatory morphophysiologic *features look alike*("gray area") [30, 34, 64] and are not distinctive enough to be considered unique attribute essential for a screening examination. The differences between normal and abnormal remodeling lie in the diastolic Doppler assessment and not in individual image features [4, 6, 8, 47, 65]. Precepts of pathophysiologic assessment include those listed in Table 2.

Screening

To date screening markers have marginal clinical benefit in determining risk [66]. Most markers are correlated with traditional risk factors and therefore do not have high independent odds ratios (relative risk). A screening test should not be considered a diagnostic test, but a triage and reclassification test [66, 67]. Triage is a test used before an existing diagnostic test is performed, and only patients with a particular result on the triage test continue down the diagnostic pathway. A triage-screening test does not aim to improve the accuracy of the diagnostic test. It reduces the need for additional testing that may be expensive and invasive [66].

Table 2:
• Single datum will not adequately define complex disease state;
• Population based data do not adequately define risk;
• Pre-emergent pathophysiologic data can quantify risk;
• Individualized risk is essential :risk factorassociations do not suffice;
• Causality : Multi-feature networks are used todefine cause and effect.

Guidelines

Consensus based guidelines focus on risk factor associations that do not address cause-and-effect and do not meet the essential criteria for determination of individualized risk and causality [6,31,68]. Most testing modalities entrenched in consensus guidelines [68] are not capable of identifying near-term risk(occurring within 1 year of assessment), but classify risk over many years (10 years for the Framingham Risk Score) [69, 70]. Most clinical tests are currently known to be of little or no benefit in asymptomatic persons [26] and include: physical exam [42], resting and stress ECG [2, 37, 39, 40, 42, 43], complete, limited and/or screening echo cardiographic exam [2, 18, 26, 71], various imaging modalities such as MRI [37], CT calcium score [37], and serum biomarkers [72-74], lipid profile [75] and genomic testing [75-77].

These tests are commonly embedded in consensus guidelines [68].The imperfect specificity of ECG screening and high incidence of false positive findings [41] actually has the potential for harm through further low yield investigations, psychological stress, and unnecessary disqualifications [37]. The American College of Preventive Medicine does not recommend the ECG, exercise treadmill testing, electron-beam CT, ankle-brachial index, carotid intima thickness, or contemporary risk factors including high-sensitivity C-reactive protein in asymptomatic patients [78].The current potential for imperfect decision-making has led to a continuous debate about a suitable preparticipation athletic screening exam. Because of the enormity of the athletic population and the low incidence of sudden death the challenge is analogous to finding a needle in the haystack [20-23]. In order to definitively address this challenge we must focus on identifying and quantifying imminent risk based on validated causality; not population based associations, or long-term risk prediction.

Echo/Doppler Screening Test

Echocardiography has not been considered seriously as a primary cardiac imaging strategy, or testing modality for large-scale universal preparticipation exam because of cost, inaccessibility, and inter-observer variability [2, 37]. This decision is justified if the echo cardiographic examination is used as an expensive general diagnostic test. A good screening test is not a diagnostic test, [19] but a focused test. Echo attributes for screening are listed in Table 3.

Exams based on 20th century risk factor assessment are fundamentally incomplete [37, 68] and not focused on the essential objective of determining imminent risk of sudden death [70].The art of medicine is based on a vast knowledge base, which can and should be condensed into an exam focused on causality and magnitude of pre-emergent risk [6, 8]. It is predicted that in an asymptomatic athletic population there is a small number of persons who have a demonstrable pre-emergent risk profile, which can be managed with prudent observation, medical management, and reduced exposure to the demands of a field activity.

For the general adult population the American Heart Association guidelines for adults [37, 93] recommend risk

Table 3: Echocardiographic Screening.

• Focused Screening: Triage and classification of CV risk [66, 67]
• High quality pathophysiologic exam [29, 79, 80]
• Low cost focused exam [29, 65, 81-83]
• System Biology Screening [8, 47]
• Accessibility: AHA <i>"the single most useful diagnostic test in the evaluation of patients with heart failure...."</i> [84]
• Most peer reviewed literature (TABLE)
• Essentialism: focused echocardiogram[58]
• Anatomy correlated with function [85]
• Quantification of risk: system biology[8, 47]
• Mature multi-feature biomarker [86, 87]
• Causality (cause and effect test) [4, 6]
• Network remodeling [29, 54, 88-91]
• Computer-assisted, centralized interpretation [56, 82]
• Remote access to expertise [92]

assessment beginning at age 40 years and repeat every 5 years or sooner if there is any emerging risk concern. However, in older competitive athletes (>35 years old) recurring assessment may be more important [31]. For young athletes recommendations include CV screening every 2 years with an abbreviated examination in intervening years [17]. Overall the detection of pre-emergent CV disease has become a polarized public health debate, triggering a large and growing body of literature, including clinical studies, editorials, opinion pieces, proclamations, and reviews on both sides of the question [2]. Most literature is based on population based studies, expert consensus, and risk factor correlations. Although echocardiography is the most robust noninvasive cardiovascular exam and multi-feature biomarker, it is perfunctorily excluded or considered second-tier, because of "inaccessibility, cost, and inter-observer variability"[2]. However, echocardiography is recognized as *"the single most useful diagnostic test in the evaluation of patients with heart failure...."* [84]. This designation of *"most useful test"* would also apply to more than 90% of all remaining conditions associated

Table 4: Disease Types and Echo/Doppler Pathophysiology.

Echo Pathophysiology				
Disease and Sudden Death in Athletes [35]	Incidence %	Echocardiographic Pathophysiology		
Cardiomyopathy (CM)		Abnormal Pathophysiology	Normal Athletic Physiology	Normal vs. Abnormal Pathophysiology
Hypertrophic CM	26.4	[88, 94-98]	[88, 98-106]	Essential: Myocyte relaxation (e') is an important test to distinguish normal vs. abnormal pathophysiology. Tissue Doppler is available on nearly every ultrasound device. Obtainable in nearly 100% of young athletes.
Hypertensive CM	7.5	[107, 108]		
Ischemic CM		[109]		
Restrictive CM		[110]		
Arrhythmogenic RV CM	5	[111]		
Myocarditis	2.8	[112]		
Dilated CM	2.3	[96, 109]		
Sarcoid Heart Disease	0.8	[110]		
Other	0.8	Echo		
Substance Abuse CM	1.0	[113, 114]		
Hypertension, LVH				
Hypertensive Heart Dis		[107, 115, 116]		Essential: See CM physiologic Doppler assessment
Unexplained LVH	7.5	[88]		
Coarctation	---	[117, 118]		Essential: Abdominal aorta PW-Doppler [117]
Congenital Heart Disease				
Anomalous Coronary	14	[98, 119-122]	[21, 29, 81, 123]	Essential: Function: Slow scan of short axis and long axis of the aortic sinuses and aortic valve. Essential: Anatomy: Confirm visualization of the proximal coronary arteries; aortic valve leaflets. Enlarged aortic root --- measure anterior posterior aorta dimensions at multiple levels.
Aortic Aneurysm			[124]	
Marfan Syndrome	3.1	[125-127]		
Bicuspid Aortic Valve (aortopathy)	---	[128-130]		
Cystic Medial Necrosis	---	[126]		
Tunneled Coronary Artery	2.8	[122]		
Complex Congenital	---	[131]	[131]	Cardiac Crux [131]
Coarctation(hypertension)	---	[117, 118]		Essential: Pulse wave Doppler of abdominal aorta for presence and severity [117]

Pulmonary Hypertension		[132-134]		
Athletes ≥35 yrs. old		[37, 135, 136]		
Atherosclerotic Coronary Artery Disease (CAD)		[137-141]		
Risk of Sudden Death	2.6	[135, 138] CT Calcium Score [142]		Essential: Risk of CAD: Cardiac function is best predictor imminent risk Presence of CAD: calcium score, other imaging technologies detect CAD but does not predict imminent risk
Valve Disease			[143-145]	
Aortic valve stenosis	2.6	[143, 146]		Essential: Echo/Doppler function depicts anatomic presence and pathophysiologic burden, can alert need for a more comprehensive exam
Myxomatous Mitral Valve	2.3	[147]		
Other valve disease		[143, 144]		
Complex Congenital Heart Dis.		[131]		
Marfan (Aneurysm Rupture)	3.1	[125]		
Tunneled Coronary Artery	2.8	Not Applicable		Angiography
Cyanotic CHD	-	[131]		
Eisenmenger Syndrome	-	[132]		
Trauma				
Commotio Cordis	19.9	[148]		
Heat stroke	1.6	[149]		
other	0.8	Not Applicable		
Other				
Long QT (channelopathies)	0.8 Rare	History [150]50%, Echo [151] 20%, ECG[41, 150, 152]		Electrophysiology [153]
Ruptured Cerebral Artery	0.8	Not Applicable		
Incidence: Maron BJ, Zipes DP. 36th Bethesda Conference: eligibility recommendations for competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol 2005; 45:1312-13[34]				

with sudden death in athletes Table4. Echo/Doppler is a readily accessible, reproducible *pathophysiologic test*, [53] and *universal biomarker* [86, 87], which complements its role as a first order CV anatomic and hemodynamic tool. The cardiovascular community has consistently acknowledged that echocardiography has the validated potential to be the best all round screening test if the three fundamental impediments of “*access, cost, and inter-observer variability* [2]” were definitively resolved. Part Three of this manuscript will discuss the essential features needed in screening to determine imminent risk and how to implement screening that is accessible, valid, and low cost.

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