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Part 3 - Cardiac Death in Athletes Implementation of a High Quality, Low Cost, Pathophysiologic Screening Exam

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Individualize

Risk must be individualized in an athletic population with diverse activity profiles. An optimal test should meet and exceed present day screening criteria [4]; address variable mechanical, structural and electrical pathobiology [5]; emphasize prognostication (cause-and-effect),not disease detection [6];use *rule out principles* [7] to positively define normal and definitively rule out imminent risk of SCD [8].

High Quality

Essential criteria for quality include: eliminate false positives and false negatives [5, 7]; prioritize pathophysiology [5, 9], causality [10-12], simplicity [13-15], inductive reasoning [16], and "essentialism" [17, 18].

Cost-effectiveness(Cost versus Price)

It is import to understand the relationships between cost and effectiveness [19]. It is tempting to make decisions about selection of a screening test based on *cost minimization*, which is only reasonable if the tests are comparable and the clinical outcomes are the same. This is rarely the case --- for example when testing a simple binary assessment between normal and abnormal risk state one might assume that both ECG and echocardiography are superficially similar, but in reality they are markedly different with respect to the sensitivity (rule-out testing) and specificity (rule-in testing) of Pathophysiologic risk [7, 20, 21]. Absolute cost comparisons are unreliable because the test characteristics and demands are so extremely variable [19].

Cost is the amount paid to deliver the product while price is the actual amount of money required to use the product and all the necessary collateral services. The best solution is a substantial reduction in price while prioritizing quality and efficiencies and reducing procedural inefficiencies [19].For example, the cost of ECG is low,(≈$40) [22] however, the price is prohibitively high because of the low prevalence of diseased athletes and the large number of false-positive and false negative tests [1, 23-29]. Both cost and price of a *complete echocardiogram* is prohibitively high (e.g., $427 Medicare to >$2,275) [30].The cost of a *limited echocardiogram* is much lower (e.g.,$10 to $75) [24, 31, 32], but it does not focus upon the essential features pertinent to athletic screening to determine risk [29, 32, 33]. Small hand held devices have a certain degree of cost effectiveness, [24] but have a high price because this technology currently is incapable of obtaining or quantifying emergent physiologic data.

A logical solution to this dilemma is an essential, *focused echocardiogram* designed to obtain small numbers of related pathophysiologic data[28] and maximize cost-effectiveness [19]. Practice expenses are further reduced by selection of point-of-care ultrasound, remote exam rooms, limited documentation, cloud storage and reduction of costly services [28]. The cost of a focused echo cannot mirror the cost of a limited echo, CPT (93308), because the components and services used are substantially different. The essential, focused screening emphasizes the essentials of simplicity [15, 34-36]:assurance of normal and rule-out of abnormal.

Significant cost efficiencies require explicit design features [2, 19, 37]: results of the test must correlate with result [38, 39] and the outcome managed by change in management. Testing a low risk population mandates the use of fewer resources [28, 40];focus on prognostication, and not diagnosis [6]; ECG and traditional echo cardiographic models are deemed ineffective [28]; non-essential data are excluded [1, 2, 18, 27, 29, 41]; use of lower cost point-of-care ultrasound devices [42, 43]; aggressively reduce acquisition time (≈10 minutes) [43, 44]; emphasize causality [2, 5, 9, 13, 28, 34, 43, 45]; and prioritize the confirmation of normal and there-by rule out the rare abnormal [7].

Additional novel efficiencies include open-access ordering

[21, 46], remote location testing [21, 28, 43, 47] and computer-assisted decision-making [48-50].

Open Access Echocardiography

Is defined as services ordered by a designated health care provider without pre-test assessment by experts [21, 46]. The athletic population represents the essence of normal, which does not justify the expense of pretest experts [21]. Open access and computer-assisted decision-making allow the user to prioritize referral and alleviate unnecessary expenses [29, 51, 52].

Remote Location Echocardiography

[42, 43, 47] is defined as an echocardiographic exam performed outside of a medical facility, which translates into a significant cost savings [42] by reducing the cost of services [28].

Computer Assisted Data Interpretation and Decision-Making

A human-computer data interpretation interface is predicted to become an all-purpose tool for navigating, manipulating and understanding biological systems [6, 36, 45]. There is convincing evidence that whenever we can assist human judgment with technology, we should at least consider it [49]. The American Society of Echocardiography has prioritized the implementation of computer-assisted interpretation of echocardiographic data by 2020 [53]. This directive is based on the premise that for a wide range of general prediction problems, easy-to-implement computer-based software is as reliable as and typically more reliable than, human expert interpretation [48-50, 54]. Immediate on-site test interpretation [6, 42, 49, 53] and automated quality assurance assist appropriate triage [16, 34, 35, 47]. Elective use of web-based physician assistance enhances accuracy and reduces cost [47]. Computer assisted multi-feature systems biology markedly lowers the incidence of false positives, increases access and reproducibility (96%) [43, 55, 56], lowers cost, and increases efficiencies [9, 37, 43].

An essential, *focused echocardiogram* meets and exceeds the criteria of an ideal pre-participation screening exam [4]. We propose a new and stronger pathophysiologic-based echocardiographic screening exam that optimizes cost and maximizes effectiveness by focusing on the nuances of systems medicine and wellness [57].

Prediction Requires Causality [58]

Questions that motivate most health science prediction studies are not associative, but causal in nature. For example, we would ask, what is the cause of the death in an athlete, rather than what was the death associated with? Causality requires some knowledge of the data-generating processes; causality cannot be computed from population data alone, or from the distributions that govern the data [11]. Associations alone can never prove causality, but can show you where to look. Associations infer beliefs or probabilities under static conditions, while causality measures beliefs under changing conditions [58] Table 1.

One cannot substantiate claims of causality from associations alone, even at the population level --- behind every causal conclusion there must be some causal assumption that is not testable in observational studies [11]. For example both diastolic dysfunction and abnormal ECG patterns are predictive features of a cardio myopathy; diastolic dysfunction satisfies the definition of a causal feature, and the ECG is a consequence of a disease process.

Prevention: Influence of Causality and Prediction

Currently the benefits, outcomes, and cost-effectiveness of prevention in athletes remain unresolved [3, 72]. Prediction and prevention are not synonymous, but are co-dependent on causality [57]. An essential, focused screening echo exam is designed to predict an individual's pathophysiologic state, while prevention is modifying and monitoring changes related to disease management [10-12, 73].

In the athletic community there have been three ECG based prevention trials, one positive [22] and two negative [27]. These publications contain controversial interpretations, content,

Table 1: Definition of Invariant Causal Relationships (i.e., Causal-and-Effect)[12].

Phenomenon	Definition	Observation	Echocardiographic Pathophysiology	Reference
Contiguity	Cause and Effect must remain contiguous in time and space	Cause (input) must be simultaneously and equally reflected in Effect (output)	Gradations of diastolic dysfunction evolve contiguously with effect. States of causal data mirror the status of the risk state.	**[38, 59-62]**
Succession	Cause must occur prior to the Effect	Cause occurs before the appearance of Effect. Causal features can be observed in the pre-clinical or emergent phase of a disease.	Causal mechanical, structural and electrical features overlap and grow in number and intensity in succession with the expression of Effect. Small numbers of highly related causal data best define the status of a physiologic state.	**[5, 9, 54, 63-66]**
Constant Conjunction	Constant union between Cause and Effect	Change in Cause must be mirrored in Effect of a disease and vice versa	Worsening, improvement or bidirectional change of a disease state (Effect) is equally mirrored by the state of a Causal module	**[67-71]**

conclusions, and associations [10, 74]. In these epidemiologic studies both prediction and prevention were founded on epidemiologic associations, and not causality [5, 10, 11, 75]. The prediction of risk in athletes requires a measurable pathophysiologic risk profile and treatment strategy and not merely an assumed inevitability [3, 10-12]. Current prevention is thwarted by an emphasis on tests better suited for disease diagnosis [5, 7, 10, 73].

Today

Today most decisions are made subjectively based on insufficient knowledge and resources. Transformative quantitative pathophysiologic risk profiling has the capacity to substantially improve the quality and accuracy of a disqualification decision [16, 34]. Recommendations for disqualification and eligibility are discussed in the 36th Bethesda Conference [51]. This consensus-based document is extensive and far beyond the scope of an essentially, focused screening test. One of the most revealing attestations in the 36th Bethesda Conference is the term "gray zone"[51], which highlights the fact that there is considerable overlap between normal and abnormal cardiovascular remodeling. A usable pre-participation exam must eliminate the "gray zone"[51, 76] and emphasize normal versus pre-emergent disease [8]. The essentially, focused echo exam does this using diastolic Doppler data.

Tomorrow: Monumental Transformation

The basic strategy must be to screen healthy athletes to ensure they are not at risk. Medicine is about to undergo a transformation which will change the healthcare system. We will demystify complex disease processes by: (1) providing deep insights into disease processes; (2)individualize risk; (3) define cause-and-effect relationships; (4) initiate pathophysiologic based disease prevention;(5) transform healthcare metrics [57]; and (6) markedly increase the quality and lower the cost of healthcare [17].

There are two inherent challenges that will consume time and resources:(1) the design of a global, integrated system; and (2) ensuring the system incorporates ethical, social, legal, regulatory and economic values [5, 57]. There are a number of features that will assist the transformation: (1)medicine will be looked upon as an informational science, which provides an intellectual framework for dealing with complex medical problems;(2) diseases are redefined as perturbed networks; (3) digital devices will quantify multi-feature risk; (4) causality will be essential to prediction and prevention; and (5) life-long health is maintenance of a measured cascade of wellness. Illness will be defined as a loss of multi-feature regulatory capacity [5]: the inability to adequately respond to internal, environmental and/or lifestyle factors. Instead of treating a consequence of disease, healing will be defined as treatment of causality [10, 11] and restoration of normal regulatory capacity [57].

Practical Implications

An essential, focused echocardiographic screening exam should take 10 minutes and requires sonographers who with computer assistance, are responsible to interpret and delineate primary, associated, and "incidental" findings that are apparent, or become apparent while obtaining images [28]. Sonographers are responsible for recognizing a predefined list of pathophysiologic data in a specific clinical setting within their scope of practice. A physician's interaction falls specifically within the regular duties of a supervising physician. An essential, focused screening exam is a logical extension of a physician's utilization of evidence-based medical care. The physician will be considered respondent superior for the sonographer team and will therefore have a legal duty to monitor the program to ensure quality and accuracy [11].

Limitations

The greatest challenges to the use of clinical systems biology screening is predicted to be the inertia of change [77], the entrenched notion that athletic restriction improves outcomes [3], the huge volume of conflicted literature on athletic screening[3, 29, 51], and unfamiliar nuances of 21st century network medicine [57]. In spite of these challenges computer assisted systems biology is still predicted to markedly transform every aspect of medicine within a decade.

"*Ideas* (as presented in this manuscript) *can change the world --- but only when coupled with influence ---, the ability to change hearts, minds and behavior* (Quote: Muhammad Yunus, Nobel Pease Prize Winner (back cover [77]))."

Conclusion

Sudden cardiac death in an athlete cannot be considered an event that begins with and ends with a catastrophic event. Rather, it should be thought of in the context of a cascade of pathophysiologic events. The presence of symptoms, associated risk factors, and overt image features has been documented to be insensitive and unreliable indicators of risk. Structural and electrical cardiovascular diseases typically evolve through a sequence of causal preclinical pathophysiologic perturbations. A small subset of primary electrical cardiac diseases may be the exception. An essential pre-participation screening focuses on validating wellness and the exclusion of abnormal causal pathophysiology. It is proposed to be the highest quality, lowest cost means of detecting and managing the risk of sudden death in an individual athlete.

Nearly all events attributed to sudden cardiovascular death in athletes have validated pathophysiologic features, which can be used to confirm wellness and rule out risk Table 2. The exam should take no more than 10 minutes. On site data interpretation can be complemented by computer-assisted intelligence. An essential, focused echocardiographic exam markedly lowers cost, while simultaneously assuring highest quality pre-participation athletic screening.

Essentialism is not about how to get more things done, it's about how to get the right things done. It doesn't mean doing less for the sake of less. It's about making the wisest possible investment in time and energy in order to operate at the highest point of contribution by doing only what is essential [18, 78]. Screening should not be used as a definitive diagnostic or

Table 2: Essentials of a High Quality, Low Cost Athletic Screening Exam.

Test Type	Focus
History and Pretest Data	Asymptomatic personal and family history. Normal blood pressure, heart rate, weight and height
Multi feature Functional Physiology focused on Causality	Unequivocal normal physiology (Rule out Abnormal) 11 data features
Hemodynamics	Normal Pulmonary artery pressure; Normal abdominal aorta physiology
Structural Disease	Normal Proximal Coronary Arteries; Normal cardiac chambers, myocardium, valves and great vessels 3 essential views
Cost-Effective Infrastructure	Markedly Lower Cost Open Access; Focused Exam; Remote Site; Computer-User Interpretation; Cardiology backup and referral only if necessary
Final	Binary Conclusion: Unambiguous Normal and Rule-out Principal

management tool, but a means of identifying the state of a small portfolio of pathophysiologic features, which assure normal and rule-out pre-clinical risk that could be life threatening.

There should be a high degree of trepidation in applying medical management to an asymptomatic, overtly healthy person who is designated by any test as having a potentially life threatening condition. The first essential is to fully document the authenticity of the finding, the magnitude of risk and the desires of the young athlete and entrusted guardians. Ultimately an impartial, trained physician must formulate a disciplined medical opinion, which forms the basis for subsequent decision-making. The greatest challenge lies in the continued acceptance of ill designed decisions and tests. The medical community must share differing views openly without falling victim to ridicule for not honoring the past. This manuscript opens a discussion about creating a norm based on pathophysiologic cause-and-effect.

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