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A dynamic risk management approach to reduce harm in hypertrophic cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is thought to be a leading cause of sudden cardiac death (SCD) in athletes, and while SCD is the most dramatic and feared of all HCM presentations, its exact incidence remains unclear. Current expert opinion and consensus panels that formulated exercise recommendations in HCM to reduce the risk of sudden death by avoiding competitive sport are based on scant, observational, often circumstantial, and sometimes conflicting evidence. These recommendations rely on multiple cross-referencing of few original papers from a limited number of research groups. At the same time, there is accumulating data that recommendations to avoid competitive exercise in HCM come at the price of avoidance of all physical activity which carries its own risks and complications. Consequently, physicians are challenged when asked by concerned parents and children to justify overly restrictive clinical judgements and guidance about permitted exercise levels in HCM. In this manuscript, we review the strength of the evidence underlying current sport recommendations in HCM. We propose that developing a working risk management approach to assist anxious parents and children is imperative and must be customized to the needs of the child and their parents. Rather than a blanket recommendation to avoid competitive sport, we believe that HCM patients deserve to have a robust and real-world risk assessment strategy that is tailored to the individual needs, discussed with the child and their parents, and updated as the child grows and matures.

1. Risk Management Approach Towards HCM

When parents of children with HCM seek medical care, they entrust their health and wellness to us. While life expectancy is generally good in hypertrophic cardiomyopathy (HCM), premature mortality can occur unexpectedly via three modes: heart failure, stroke and sudden cardiac death (SCD). Of these, SCD is the most dramatic and feared of all presentations, especially as it occurs seemingly without warning in young, healthy appearing, and athletic individuals. The response to these rare events is often further fueled by sensationalist media attention. The hypothesized mechanisms underlying SCD in HCM are diverse and powerful, including arrhythmia, ischemia and hemodynamic mechanisms, but none are specific and all are unproven [1]. So, have we really made significant progress in better understanding the 'interlocking factors' that lead to SCD in HCM?

Traditionally, risk has been seen as exposure to potentially injurious events that may threaten or damage the individual or an organization [2]. The variability in risk tolerance by patients and clinicians in medicine is complicated and not well understood. There is a pervasive and troubling belief among advocates of the patient safety movement that all adverse events in a health system are discoverable and preventable. The belief is primarily that having more information at hand will be sufficient to improve health systems and prevent all risk from leading to harmful outcomes [3]. Fortunately, more sensitive analyses based on expertise in accident investigation acknowledges that 'adverse events should be characterized as emergent properties of complex systems, and they cannot always be predicted' [4]. Perhaps our 'explanatory hypotheses' need revision in HCM in order to take into consideration our evolving knowledge about the role of risk mitigation and help to make better observations of SCD and how best to prevent these extraordinary outcomes? Our central hypothesis proposed by the paper is that the affordances of the environment of children with HCM and the thinking it entails resists reduction to stable and standardized risk identification and management methods.

The historical context of the everyday experiences of clinicians treating HCM with children and their parents is not adequately captured by statistical measures employed in evidence-based medicine. The clinical experience with HCM is more nuanced and dynamic than

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the simple cause and effect sequences constructed in observational studies and investigations. This situation warrants a co-production care model [5] which entails open and frank discussions with parents and other clinicians in order to identify more effective models of inquiry and a more robust risk management and mitigation approach to help prevent SCD in these patients [6].

Developing an understanding of the unexpected events in the lives, of children with HCM and their parents, requires a different approach, sets of tools and mental models [7]. We explicitly define the "rare events problem" as a situation where only a small proportion of patients are at comparatively "high risk" of experiencing an event. How can we identify these children at risk? We hasten to reinforce a conceptual distinction: the goal of risk classification is not predicting precisely who will live or die. Rather, the goal is identification of a small subset of high-risk patients.

The lives of parents of children with HCM are not conducted as a controlled experimental environment and the risks are ambiguous, constantly emerging and unpredictable. Risks in the lives of these children are situational and context-specific. The needs of children with HCM might be better understood in their temporal context where managing constraints and negotiating the boundaries of safe and joyful living is a matter of collective expertise and experience [8]. This requires us to reflect on optimal judgement and decision-making by parents and their children when faced with questions about exercise levels and risk exposure. When clinical teams are faced with the complexity of a past SCD or near death event in an HCM child, there is no experimental control, nor any assurance that their recommended actions will reduce the risk of recurrence of the event in the future in these or other children with HCM.

Achieving optimal outcomes in children with HCM, while preventing harm requires a comprehensive and dynamic risk management strategy that includes [1] *identifying risk*—finding out what is going wrong; [2] *analyzing risk*—collecting data and using appropriate mixed-methods to understand what it means; and, [3] *controlling risk*—devising and implementing strategies to better detect, manage, and mitigate the harmful events from occurring [9,10]. This begs the question, do we understand where and when the child with HCM is most at risk?

Essentially, risk is defined as the chance of something happening that will have a negative impact on key elements. It can be measured in terms of consequences and likelihood of outcomes (see Fig. 1). Clinical risk management addresses the culture, process, and structures that are directed towards the effective management and prevention of potential harmful opportunities and adverse events [11]. We measure risk in terms of the likelihood and consequences of something going wrong, which is in contrast to how we measure quality (i.e., the extent to which a service or product achieves a desired result or outcome). The task of the clinician trying to tailor an optimal risk management approach that helps the parents and their children with HCM appreciate the risk management, which is all about having the wherewithal to balance the consequences of risks against the costs of risk reduction.

In general, a risk management model takes into consideration the probability of an event occurring, which is then multiplied by the potential impact of the event. Fig. 1 illustrates a risk management model adapted to HCM that considers the probability of an adverse event (low, medium, or high) and the impact of the consequences on the child (limited/minor, moderate, or significant). Assigning an event in one of the cells is not an exact science, but the matrix offers guidance for clinicians in advising parents and their children a workable approach towards assessing the risk to the child. In the end, the parents, as guardians of their children, are ultimately responsible for accepting the risk. The risk/benefit discussion with the physician should therefore provide the family with as much information as possible, enabling them to make the best decision if they wish to assume the risk and responsibility of rare injurious outcomes.

The most recent available guidelines concerning the recommended risk management approach towards children with HCM related to permissible levels of activities in HCM are from the American Heart Association (AHA)/American College of Cardiology (ACC) in 2015 where the general statement regarding exercise in cardiac disease is that: "hypertrophic cardiomyopathy being the most common (cause of sudden cardiac death (SCD)), accounting for at least one-third of the mortality in autopsy-based athlete study populations" [12]. Indeed, the guidelines preamble goes on to say that the three Bethesda, Maryland Conferences 16 (1985), 26 (1994), and 36 (2005), published and used over a 30-year period; and the current 2015 AHA/ACC scientific statement was driven by the tenet that "young trained athletes with underlying cardiovascular abnormalities are likely at some *increase in risk* for sudden cardiac death usually on the athletic field [4–8]". [12] We will subsequently review the supporting literature for those statements. However, the intuitive logical risk management inference from such a tenet is that avoidance of any vigorous activities or competitive sports in young patients with HCM will reduce the risk of SCD. Do we know that to be true?

The recommendations of all three Bethesda evidence-based conferences over a 30-year period, and the recommendations of the most recent 2015 AHA/ACC guidelines are that: "Athletes with a probable or unequivocal clinical expression and diagnosis of HCM (i.e. LV hypertrophy on echocardiography) should *not participate* in most competitive sports, with the exception of low intensity class IA sports such as golf and yoga. (Class III; Level of Evidence C)" [13]. This recommendation is independent of age, sex, magnitude of LV hypertrophy, sarcomere mutation, or absence of LV outflow obstruction (at rest or with exercise), prior cardiac symptoms, late gadolinium enhancement on CMR, surgical myectomy or alcohol ablation. A class III recommendation generally indicates that an intervention is not recommended. This inherent confusion in the meaning of the recommendation itself adds to the widespread ambiguity among clinicians on how best to advise parents and children regarding sport participation. A level C evidence statement indicates expert consensus, as opposed to the stronger evidence of data derived from evidentiary sources such as randomized or controlled clinical trials. This recommendation is at the lowest strength level and based on the lowest level of evidence raises important and troubling implementation questions about how best to support the request of families for expert guidance.

Participation in competitive athletics, for asymptomatic, genotype-positive HCM patients, without evidence of LV hypertrophy by 2-D echo and CMR, is stated as reasonable, particularly in the absence of a family history of HCM-related sudden death (Class IIa; Level of Evidence C) [13]. The European Society of Cardiology guidelines from 2014 have a Class 1, level of evidence C recommendation to parents and their children to avoid most competitive sports in HCM [14]. This recommendation is supported by a single reference, itself a consensus document statement, rather than any original evidence, that recommends avoidance of all sports in patients with HCM [15]. The document states that: "Sports participation increases the risk for SCD in HCM patients and this disease is the most common cause of athletic field death in young athletes in the USA". Again, this implies that avoidance of sports is protective and only two references are provided to support this over-reaching statement. One of these references is a literature review that aims to clarify and summarize the relevant clinical issues and to offer an overview of the rapidly evolving concepts regarding HCM [16]. The authors performed a 'systematic analysis of the relevant HCM literature, accessed through MEDLINE (1966-2000), bibliographies', and extensive 'interactions with investigators'. They assimilated the data into a 'rigorous and objective contemporary description of HCM, affording the greatest weight to prospective, controlled, and evidence-based studies'. The conclusions of the study based on review of the literature were that: a) HCM is the most common cause of cardiovascular sudden death in young people, including trained competitive athletes. b) Sudden death occurs most commonly during mild exertion or sedentary activities but *is not infrequently* related to vigorous physical exertion. c) Intense physical exertion constitutes a

sudden-death trigger in susceptible individuals. d). Disqualification of all athletes with unequivocal evidence of HCM from most competitive sports has been prudently recommended by a national consensus panel.

The other reference is a retrospective review of the clinical, demographic, and pathological profiles of young competitive athletes who had experienced sudden death [15]. This reference (17) was designed as a 'Systematic evaluation of clinical information and circumstances of SCD; interviews with family members, witnesses, and coaches; and analyses of post-mortem anatomic, microscopic, and toxicological data'. This paper reviewed 158 sudden deaths in trained USA athletes over a 10-year period between the years 1985 and 1995. Of the 158 sudden deaths, 134 cases had cardiovascular (CV) causes of SCD. One hundred and twenty-one (90%) collapsed during or immediately after a training session (78 cases) or an athletic contest (43 cases) and HCM was found to be the most common CV disease identified at autopsy as the primary cause of death (36%). The study concluded that SCD in young competitive athletes usually is precipitated by physical activity that may be due to a heterogeneous spectrum of CV disease, and most commonly HCM. It is interesting that in this last study [18] the authors found that most deaths occurred during intense exercise whereas another reference from the 2002 JAMA review [16] found contrary findings. This latter study combines populations from 3 regional centers in Minnesota, US, Tuscany and Genoa, Italy, respectively, to assemble a combined cohort study of 744 patients that were evaluated between the years 1975 and 1998 with a follow-up period of approximately 8 years. It is noteworthy, that (some) portions of these databases had been used in other clinical studies making it difficult to ascertain what de novo conclusions could be drawn from this cohort. Nonetheless, of the 744 study patients, 125 (17%) died during the follow-up period. In 86 of these cases, the death was judged to be probably or definitely as a result of the underlying HCM, although three of these patients also had extensive atherosclerotic coronary artery disease. The most interesting finding of this study may be that 84% of the patients died during *mild or sedentary* activities. In fact, seven patients (16% of cohort) died while asleep in bed. What should we make of these conflicting findings?

This proportion is the same as the seven patients (16%) who died during moderate to severe exertion, including only one patient who experienced cardiac arrest during burst exertion competitive athletics –a 33-year-old man who ultimately survived [18]. These findings stand in contrast to the previous study that found that most experienced SCD during intense activities. Indeed, another study [19], also referenced in the 2002 JAMA review [16], suggested that most SCD happens during mild exercise or sedentary activities. This study reviewed autopsy records of the Pathology Branch and patient records from the Cardiology Branch of the National Heart, Lung, and Blood Institute, National Institutes of Health, between the years 1960 and 1980 [19]. At the time of the cardiac catastrophe, 71% of patients were less than 30 years of age; while 54% were without functional limitation, and, 61% were performing sedentary or minimal physical activity [19].

Intense, especially burst, exertion is thought to invoke SCD through a de novo arrhythmia, this begs the question whether arrhythmias are provoked during exercise. The answer, frustratingly, remains unclear. Two conflicting studies exemplify this heated debate. The first is an older study showing that continuous heart rhythm (Holter) monitoring was superior to exercise testing for exposing arrhythmias, suggesting that cardiac arrhythmias occur more frequently during regular activities rather than during vigorous exercise [20]. In contrast, a more recent prospective study in a cohort of 1380 subjects [21] found that 27 of these patients experienced either non-sustained ventricular tachycardia (NSVT, $n = 24$) or ventricular fibrillation (VF, $n = 3$) during exercise. Eight of these patients (~30%) patients who experienced ventricular arrhythmia during exercise died or experienced a serious cardiac event defined as SCD/appropriate ICD discharge or heart transplant. This was in comparison to 150 (~11%) patients who did not experience NSVT/VF during exercise ($P = 0.008$). Consequently, patients who had exercise induced NSVT were exposed to a 2.82-fold increased risk of SCD/appropriate ICD discharge (HR 95% CI: 1.02–7.75, $P = 0.049$). However, in multivariable analysis, exercise NSVT or VF, but not NSVT alone, was independently associated with an increased risk of SCD/appropriate ICD discharge [HR 3.14 (CI: 1.29–7.61, $P = 0.01$)]. Thus, although the data seem to suggest that exercise provokes arrhythmia, the significance of the multi-variate analysis rests on only *three cases of VF* [21].

Let us return now to the literature referenced above to support the most recent 2015 AHA/ACC guidelines. The general preamble [12] references five papers to support the recommendation to avoid competitive or vigorous exercise [17,22–25]. One of these references is a scientific statement [22] with no primary data and another reference is a literature review article [23]. The remaining three references are original articles, one of which we have already reviewed above [17]. The 2015 guidelines from taskforce number three which specifically addressed the issue of HCM [13], states that: "Therefore, in HCM, the most common cause of sudden death in young athletes, engagement in intense competitive sports is itself an acknowledged modifiable risk factor." Again, this implies that exercise is a risk factor and it is modifiable by avoiding intense competitive sports. As noted above, this statement is supported by only three references, two of which are literature review articles, and the third reference, is an original paper - referenced in the general preamble [24]. Thus, we are provided with only two additional empirical research papers [24,25] to support the guidelines that suggest significant major lifestyle restrictions, particularly in children.

The first of these two studies investigated 1866 sudden deaths in young competitive athletes between the years 1980 and 2006 [24]. The data were derived from a wide variety of public databases including 1) the LexisNexis archival database (news, business, legal, public records (5 billion documents culled from thousands of sources)), 2003–2006 (457 cases) [2]; Media accounts (Burrelle's Information Services), 18,000 US and international media sources daily, 1990-to 2006 (847 cases); [3] Internet searches, (eg., Google, Yahoo), 2003 to 2006 (200 cases); [4] US Consumer Product Safety Commission reports 1988–2006 (15 cases); [5] Center for Catastrophic Sports Injury Research, 1985–2006 (187 cases); [6] NHLBI Pathology Branch archives, 1980 to 1990 (68 cases); and [7] reports submitted to the Minneapolis Heart Institute Website (www.suddendeathathletes.org) or personal reports from physicians, attorneys, coroners/medical examiners, high schools/colleges, and patient advocacy and support organizations, 1980 to 2006 (92 cases). Of the 1866 cases of SCD, 251 were attributed to HCM, which was found to be the most common cause of SCD (36%). The authors found that 82% of the patients died during competitive exertion or training, which notably, stands in contradistinction to findings from a previous study, 9-years earlier, that found that most SCD in HCM were during mild or sedentary activity [18].

So what is the other evidence to support a role for strenuous versus sedentary activity in provoking SCD, given its etiological role in recommending for children with HCM to avoid vigorous or competitive sports?

Most of the evidence concerning the exercise-associated risk of SCD is circumstantial and conflicting making it difficult for clinicians to comfortably offer optimal guidance and recommendations to restrict all sports activity in already anxious parents of children with HCM. Burke et al. from Baltimore, Maryland, found that exercise-related deaths were more likely due to HCM ($P = 0.0007$) compared with age-, sex-, and race-matched controls in the non-exercise group [26]. In contrast, a population based study in a German-speaking Swiss canton found that 20% of SCD during recreational sports were from HCM, which is a larger proportion than the 9.5% of SCD that occurred during competitive sports, and the 9.8% of HCM SCD which were not related to sports [27]. These percentages are similar to the 7% of HCM related SCD among 8862 Spanish SCD cases that occurred during recreational activities [28]. A Danish nationwide review of all cases of SCD between ages of 12 and 49 years found that the incidence rates of sports-related

SCD in non-competitive and competitive athletes are no different and that SCD in the general population is much more prevalent than SCD in sports-related cardiac arrests in all age groups [29].

Perhaps the most relevant study that offers substantive guidance to address the question of whether exclusion from competitive or vigorous sports prevents SCD in HCM is the study from Corrado et al. [25] This study is from the Veneto region of northern Italy, the only other original research study quoted in the 2015 AHA/ACC guidelines. The study evaluated the incidence of SCD in the Veneto region between the years 1979 and 2004 after a mandatory program to screen athletes by ECG prior to participation in competitive sports was instituted in 1982. The authors found an 89% decrease in the incidence of SCD in screened athletes, from an incidence of roughly 3.5/100,000 person years in 1979, to an incidence of less than 1/100,000 person years in 2004. This decrease in reported incidence contrasted to the low but unchanged incidence of around 1/100,000 person years of SCD in non-screened non-athletes over the study period. The authors attributed the decrease in SCD in athletes to the initiation of a mandatory pre-sport screening program yet fail to address the many reasons why this association might not be causal but may be confounded by other reasons. Remarkably, the percent of disqualified athletes remained unchanged from the early to the late study periods. One of the reasons for this apparent discrepancy in the data is that the decrease in SCD from cardiomyopathy was partly attributable to a decrease in SCD from arrhythmogenic right ventricular cardiomyopathy, where the percentage of individuals *excluded* over the study period grew, rather than from a decrease in SCD from HCM.

Of note, the same group of investigators had published eight years earlier a study where they found that 3.5% of all disqualified individuals from sports had HCM, and that among the 17 patients who died suddenly with HCM, only 1 was an athlete and the remaining 16 were non-athletes [30]. Their interpretation of these observations was that the low prevalence of HCM among young competitive athletes who died suddenly was most likely the result of pre-participation screening ('screening of 33,735 young competitive athletes in the Padua area identified and disqualified 22 athletes with HCM, thus protecting them from the risk entailed by athletic activity'). However, they only provide indirect evidence to support their assertion that the screening (and subsequent recommendation to avoid sport) reduced SCD from HCM. They first observed that the prevalence of HCM among young non-athletes who died suddenly (7.3%) was similar to the 3% prevalence in the aforementioned study of Burke et al. in the United States [26]. In contrast, among young athletes who died suddenly, the prevalence of HCM was very different in the two studies (2 vs. 24%). The authors inferred that a selective reduction in SCD from HCM among athletes who underwent pre-participation screening was causal and related but again provide no further data or deliberations as to whether this association is confounded by other reasons.

These deductions based on the comparison of the incidence between different regions stand in contradiction to a study from Steinvil et al. who reviewed the incidence of SCD before and after a mandatory resting and exercise ECG pre-participation screening of competitive athletes that was enacted in 1997 in Israel [31]. The data collection was done through a systematic search of the two main newspapers in Israel. The difference in average yearly incidence of SCD or cardiac arrest in pre-screening vs. screening period was not significant (2.54 and 2.66/100,000 person-years, respectively). Substantial limitations and potential confounders of this study, acknowledged by the authors, included the retrospective nature of the data collection methods given the uncertain number of cardiac events and the need to calculate a rough estimation of the population of competitive athletes [31].

Only two prospective trials aiming to test exercise in HCM patients are available online and listed on ClinicalTrials.gov. The first study was a randomized, controlled trial of moderate intensity exercise training in hypertrophic cardiomyopathy (RESET-HCM) from the University of Michigan to determine the safety and potential benefits of moderate intensity exercise in patients with HCM. In this study, moderate-intensity exercise compared with usual activity resulted in a small increase in exercise capacity at 16 weeks [32]. There were no occurrences of sustained ventricular arrhythmia, sudden cardiac arrest, appropriate defibrillator shock, or death in either group.

The second study is from Israel and involves exercise training in patients with hypertrophic cardiomyopathy with the aim of examining the safety and feasibility of a structured exercise training program in symptomatic HCM patients. However, the recruitment status of this study is listed on March 29th, 2018 as unknown as of 2012 on ClinicalTrials.gov.

Some authors have suggested that exercise may worsen myocardial hypertrophy. However, at present, there is little evidence to associate exercise intensity with disease progression in HCM. Some experimental data, albeit in a different CV disease, suggests that in adults, the data may actually support the opposite [33] in which exercise intensity is seen as an important factor for reversing LV remodeling and improving aerobic capacity, endothelial function, and quality of life in patients with post-infarction heart failure. In mice HCM models that had not yet developed the HCM phenotype, exercise prevented fibrosis, myocyte disarray and induction of markers of hypertrophy; while, in mice that already express the HCM phenotype, exercise appeared to reverse myocardial disarray and induction of markers of hypertrophy although not the fibrosis [34].

2. Building a Risk-management Informed Body of Knowledge About HCM Long Term Outcomes

At a universal level, the questions posed by clinician investigators about preventing SCD relate to what can be *known* generally about adverse events in children with HCM. In contrast, parents deal with everyday interactions in context and relate knowledge construction to the dynamic of particular situations in which children with HCM live, play and thrive. In order to address what is *known* or *unknown* about the risks and vulnerabilities in children with HCM, methods are needed that enable the discovery of previously unrecognized risks using methods uniquely suited for rare events such as in predicting airline crashes, nuclear power meltdowns or wrong sided surgeries (e.g., failure modes effect analysis, fault tree analysis, human reliability analysis, and probabilistic risk assessment) [35–37]. Questions at a contextual level relate to gaining a better understanding of operational matters across the life of an HCM child. When making sense of an SCD or adverse event it is important to find out what was *known* about the particular problematic situation *by the people involved* [38]. An incident investigation draws on the experience of clinicians working on the frontline in the setting in order to reconstruct the event. In summary, the three different ways of risk knowing represent three basic approaches to constructing knowledge about adverse events in children with HCM:

1. *Knowledge as transferring data*. Policy makers and national guideline writers look for what is known generally, from aggregated reports,
2. *Knowledge as learning about systems*. Hospital and ambulatory quality and safety programs seek to discover what is unknown or better understand known risks, and,
3. *Knowledge as an ongoing dynamic*. Local incident investigation work with what is knowable about an event from the circulating information about everyday clinical and non-clinical interactions from the people that support and live with the child.

The points of intersection in the diagram (Fig. 2) represent the current state of knowledge about actual or potential problems in HCM. In practice, knowledge varies from situation to situation, is highly context dependent, and mediated through a process of translation by multiple people at different levels across the life of the child, in their complex systems [39].

At the same time, there are accumulating data that recommendations to avoid competitive exercise in HCM come at the price of avoidance of all physical activity leading to less happy children and

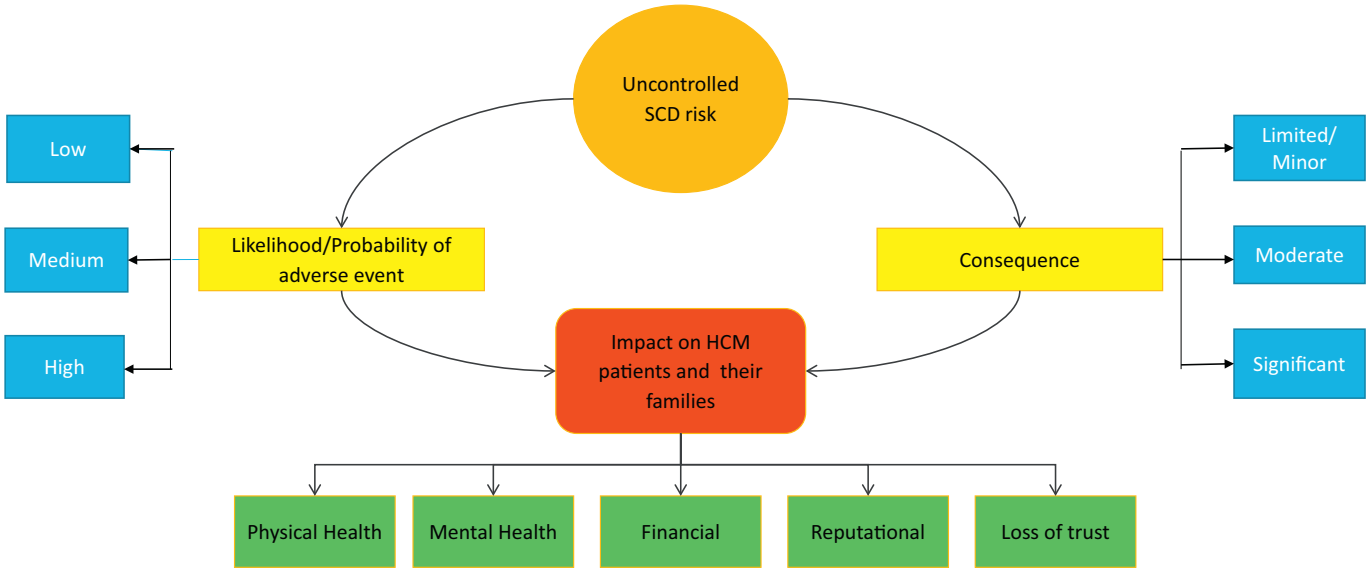

Fig. 2. Different inquiry methods produce different types of knowledge.

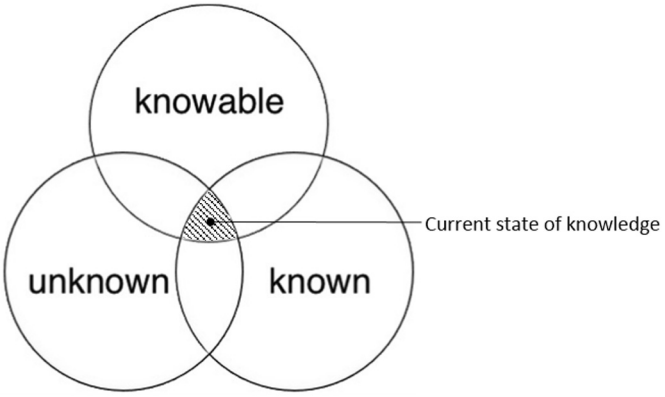

Fig. 1. Dynamic patient risk assessment and impacts.

parents. While the recommendation is to avoid vigorous exercise and competitive sports due to the risk of SCD, the highly variable response to these recommendations in practice and how they are implemented in patients with HCM is poorly understood. A recent study found that 55% of individuals with HCM did not meet minimum guidelines for physical activity due to multiple perceived barriers [40].

3. Concluding Thoughts and Recommendations

HCM is thought to be a leading cause of SCD in athletes, but the exact incidence of SCD in HCM remains unclear. Any single measure remains unlikely to provide enough information to holistically evaluate predictive model performance for rare SCD events. Though perfect prospective discrimination remains an unattainable goal, incremental improvements in how we identify children at risk may still advance us towards a more personalized medicine approach for children with HCM. The search for causes of SCD is pervasive but when applied to understanding biological behavior in response to changes in the daily life of children with HCM, it tends to ignore the complexity and produces a reductionist approach of universal explanations independent of the context in which the risk emerges [8]. Developing a working risk management approach to assist anxious parents and children is imperative and must be customized to the needs of the child and their parents. The incidence of SCD is probably low, and is estimated at less than 1% per year. The overall risk of SCD, considering the incidence of SCD among athletes and prevalence of HCM in the general population, in actively competing HCM athletes, is likely less than 0.1% per year [1]. It is hard to support firm recommendations given that the evidence for avoidance of competitive sport is based on a very limited number of observational studies/registries (with variable quality data sources) on causes of death and a change in prevalence of SCD after implementation of screening. There are conflicting data and methods, supportive data are deductive, open to interpretation and largely based on the comparison of SCD prevalence between widely different eras or between different geographic regions with different cultures, genetic profiles and clinical practices. Professionally and in the lay culture, HCM is thought, although rare, to be a leading cause of SCD in athletes with recommendations to avoid competitive exercise. Physicians are challenged when asked by concerned parents and children to justify seemingly overly restrictive clinical recommendations and to provide guidance about what exercise should be permitted in children with HCM [41]. On the one hand, despite the weak evidence and retrospective data, strenuous exercise may be deleterious to children with HCM, and is thought to increase the risk of life-threatening arrhythmias and syncope. Conversely, overzealous restriction of physical activity can lead to heart and body deconditioning, demoralized and poorly socialized children, and deleterious effects on the mental and physical health and wellness in patients with HCM. Based on this review we believe that HCM patients deserve to have a robust and real world risk assessment strategy that is tailored to their individual needs and discussed with the child and parents, and updated as the child grows and matures and can appreciate the inherent risks and benefits of exercise.

Children should be permitted to exercise with risk recommendations customized to their lifestyle and needs, and in full disclosure about the risk with the patient and family about the lack of conclusive evidence that strenuous exercise indeed increases the risk for SCD or that avoidance of exercise reduces this risk. We suggest that a change in the risk communication of AHA and other guidelines, in which the wording and recommendations of consensus/expert guidelines be based and justified on actual evidence. This rational risk management approach may facilitate a change in practice. We suggest that the limitations to the present guidelines that we have detailed above be added to any present and future guidelines. We believe that this may enable safer levels of exercise for HCM patients, reduce parent anxiety levels, and allow the children to reap the physical and emotional benefits of exercise. Further studies, both on the mechanisms of sudden death in HCM and interventional clinical trials on exercise intervention, will

further inform this complex problem and facilitate a change in the risk communication of guidelines and practice.

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Conflicts of Interest

Authors declare there is no conflict of interest.

References

[1] Hindieh W, Adler A, Weissler-Snir A, Fourey D, Harris S, Rakowski H. Exercise in patients with hypertrophic cardiomyopathy: a review of current evidence, national guideline recommendations and a proposal for a new direction to fitness. J. Sci. Med. Sport 2017;20:333–8.
[2] Walshe K, Rundall TG. Evidence-based management: from theory to practice in health care. Milbank Q 2001;79:429–57. [IV–V].
[3] Leape L Is. Hospital patient care becoming safer? A conversation with Lucian Leape. Interview by Peter I. Buerhaus. Health Aff. 2007;26:687–96.
[4] Dekker S. New frontiers in patient safety. Patient safety: a human factors approach Taylor & Francis. 2011. p. 213–39.
[5] Batalden M, Batalden P, Margolis P, et al. Coproduction of healthcare service. BMJ Qual. Saf. 2016;25:509–17.
[6] Cassin BR, Barach PR. Making sense of root cause analysis investigations of surgery-related adverse events. Surg. Clin. North Am. 2012;92:101–15.
[7] Senge P. The fifth discipline: Crown business. 2006.
[8] Hollnagel E. Thinking about accidents. Barriers and accident prevention ashgate. 2004. p. 36–67.
[9] Dickson G. Principles of risk management. Qual Health Care 1995;4:75–9.
[10] Cassin B, Barach P. How not to run an incident investigation. In: Sanchez JA, Barach P, Johnson JK, Jacobs JP, editors. Surgical patient care: improving safety, quality and value. Springer International Publishing; 2017.
[11] Barach P. The end of the beginning: lessons learned from the patient safety movement. J. Forensic Legal Med. 2003;24:7–27.
[12] Levine BD, Baggish AL, Kovacs RJ, Link MS, Maron MS, Mitchell JH. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 1: classification of sports: dynamic, static, and impact: a scientific statement from the American Heart Association and American College of Cardiology. J. Am. Coll. Cardiol. 2015;66:2350–5.
[13] Maron BJ, Udelson JE, Bonow RO, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 3: hypertrophic cardiomyopathy, Arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132:e273–80.
[14] Authors/Task Force m, Elliott PM, Anastasakis A, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur. Heart J. 2014;35:2733–79.
[15] Pelliccia A, Fagard R, Bjornstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the study Group of Sports Cardiology of the working Group of Cardiac Rehabilitation and Exercise Physiology and the working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Eur. Heart J. 2005;26:1422–45.
[16] Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287:1308–20.
[17] Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. JAMA 1996;276:199–204.
[18] Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858–64.
[19] Maron BJ, Roberts WC, Epstein SE. Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. Circulation 1982;65:1388–94.
[20] Savage DD, Seides SF, Maron BJ, Myers DJ, Epstein SE. Prevalence of arrhythmias during 24-hour electrocardiographic monitoring and exercise testing in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation 1979;59:866–75.
[21] Gimeno JR, Tome-Esteban M, Lofiego C, et al. Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. Eur. Heart J. 2009;30:2599–605.
[22] Maron BJ, Friedman RA, Kligfield P, et al. Assessment of the 12-lead electrocardiogram as a screening test for detection of cardiovascular disease in healthy general populations of young people (12-25 years of age): a scientific statement from the American Heart Association and the American College of Cardiology. J. Am. Coll. Cardiol. 2014;64:1479–514.
[23] Maron BJ. Sudden death in young athletes. N. Engl. J. Med. 2003;349:1064–75.
[24] Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006. Circulation 2009;119:1085–92.
[25] Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA 2006;296:1593–601.
[26] Burke AP, Farb A, Virmani R, Goodin J, Smialek JE. Sports-related and non-sports-related sudden cardiac death in young adults. Am. Heart J. 1991;121:568–75.
[27] Asatryan B, Vital C, Kellerhals C, et al. Sports-related sudden cardiac deaths in the young population of Switzerland. PLoS One 2017;12:e0174434.
[28] Suarez-Mier MP, Aguilera B, Mosquera RM, Sanchez-de-Leon MS. Pathology of sudden death during recreational sports in Spain. Forensic Sci. Int. 2013;226:188–96.
[29] Risgaard B, Winkel BG, Jabbari R, et al. Sports-related sudden cardiac death in a competitive and a noncompetitive athlete population aged 12 to 49 years: data from an unselected nationwide study in Denmark. Heart Rhythm. 2014;11:1673–81.
[30] Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. N. Engl. J. Med. 1998;339:364–9.
[31] Steinvil A, Chundadze T, Zeltser D, et al. Mandatory electrocardiographic screening of athletes to reduce their risk for sudden death proven fact or wishful thinking? J. Am. Coll. Cardiol. 2011;57:1291–6.
[32] Saberi S, Wheeler M, Bragg-Gresham J, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. JAMA 2017;317:1349–57.
[33] Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation 2007;115:3086–94.
[34] Konhilas JP, Watson PA, Maass A, et al. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. Circ. Res. 2006;98:540–8.
[35] Cassin BR, Barach PR. Balancing clinical team perceptions of the workplace: applying 'work domain analysis' to pediatric cardiac care. Prog. Pediatr. Cardiol. 2012;33:25–32.
[36] Barach P, Apostolakis. Lessons from nuclear power. In: Youngberg BJ, Hatlie M, editors. The patient safety handbook. Aspen Publications; 2003. p. 205–25.
[37] Zaitseva E, Levashenko V, Kvassay M, Barach P. Healthcare system reliability analysis addressing uncertain and ambiguous data. 2017. International conference on information and digital technologies (IDT). 2017. p. 442–51.
[38] Barach P, Phelps G. Clinical sensemaking: a systematic approach to reduce the impact of normalised deviance in the medical profession. J. R. Soc. Med. 2013;106:387–90.
[39] Dekker S. Theorizing drift. Drift into failure: from hunting broken components to understanding complex systems. 121. Ashgate Pub; 2011.
[40] Sweeting J, Ingles J, Timperio A, Patterson J, Ball K, Semsarian C. Physical activity in hypertrophic cardiomyopathy: prevalence of inactivity and perceived barriers. Open Heart 2016;3:e000484.
[41] Montgomery K. Clinical judgement and the interpretation of the case. How doctors think: clinical judgment and the practice of medicine OUP USA. 2006. p. 45–53.