Avalanches in cardiology

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ABSTRACT

Sudden cardiac death (SCD) accounts for 15%–60% of mortality in patients with heart disease. Generally, this has been attributed to ventricular tachyarrhythmia. However, ventricular tachyarrhythmia has been documented or strongly suspected on clinical grounds in a relatively small proportion of SCD patients (8%–50%). Attempted prophylaxis of SCD by implantation of cardioverter-defibrillator is associated with variable success in different subsets of high-risk cardiac patients (30%–70%). A significant number of SCD, therefore, appear to be due to catastrophic circulatory failure. Multiple interdependent compensatory mechanisms help to maintain circulation in advanced cardiac disease. Rapid, unexpected, and massive breakdown of the compensated state can be precipitated by small and often imperceptible triggers. The initial critical but stable state followed by rapid circulatory failure and death has been considered to be analogous to snow avalanches. It is typically described in patients with left ventricular (LV) dysfunction (ischemic or nonischemic). It is now recognized that SCD can also happen in conditions where the right ventricle (RV) takes the brunt of the hemodynamic load. Advanced pulmonary arterial hypertension and operated patients of tetralogy of Fallot with pulmonary regurgitation are of particular interest to pediatric cardiologists. A large amount of data is available on LV changes and mechanics, while relatively little information is available on the mechanisms of RV adaptation to increased load and RV failure. Whether the triggers and the decompensatory processes are similar for the two ventricles is a moot point. This article highlights the currently available knowledge on the pathophysiology of SCD in RV overload states, with special reference to RV adaptive and decompensatory mechanisms, and therapeutic measures that can potentially interrupt the vicious downward course (cardiac avalanches).

Keywords: Circulatory collapse, nonarrhythmic death, sudden death

INTRODUCTION

KM (age 22 years) died soon after he walked out of the consulting room. Since the diagnosis of severe idiopathic pulmonary arterial hypertension (PAH) was made 10 years ago, he had remained stable (New York Heart Association Class II) on therapy with dual PAH drugs. The right ventricle (RV) was enlarged and impaired (fractional area change 22%). However, there was no worsening in effort tolerance, clinical parameters, 6-min walk test distance, or NT-pro brain natriuretic peptide level. When he collapsed, the monitor showed slow sinus rhythm with narrow QRS and normal ST-T complexes. A brief trans-thoracic echocardiography study did not show any pulmonary artery (PA) rupture, PA dissection, or effusion. One can only guess the mechanism of his death. Known complications such as worsening heart failure, syncope, arrhythmia, hemoptysis, PA dissection, PA rupture, myocardial ischemia, and embolism were not found. Although the PA was enlarged, there was no indication of left coronary artery compression and left ventricular (LV) systolic function was normal. The terminal event

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suggested acute failure of cardiac function with electromechanical dissociation. In large studies of PAH patients, the common causes of death were progressive heart failure (40%–49%), vascular complications (20%), and sudden cardiac death (SCD) (13%–26%).[1-4] SCD is generally attributed to ventricular tachyarrhythmia. A review of 13 papers on PAH showed a prevalence of 24% for ventricular arrhythmia.[5] However, the initial ECG during cardiac resuscitation in patients with PAH showed ventricular fibrillation in only 8% of cases. The common rhythms noted during cardiac arrest in PAH patients were bradycardia (45%), electromechanical dissociation (28%), or cardiac asystole (15%).[3] The exact mechanism of SCD in PAH, therefore, remains a mystery in a significant proportion of patients.

In a recent editorial, Packer described a similar phenomenon in patients with dilated cardiomyopathy.[6] Nearly 30%–50% of deaths are sudden and unexpected among patients who have reduced LV ejection fraction (EF). Since ventricular tachyarrhythmia has been considered as the likely mechanism, implantation of cardioverter-defibrillator (ICD) is recommended for patients who have persistent symptomatic LV impairment (EF ≤35%) despite adequate medical treatment and do not have any other life-threatening diseases.[7] However the efficacy of ICD in preventing SCD has been only about 50% in nonischemic cardiomyopathy[8] and 60%–70% in ischemic cardiomyopathy.[9] Technical factors were excluded as cause of ICD failure.[10] Analysis of the rhythm revealed that many sudden deaths were nonarrhythmic in nature. The commonly observed rhythms were sinus rhythm, sinus bradycardia, and electromechanical dissociation.[11] Severe remodeling of the LV and advanced functional class were more likely to be associated with SCD. However, the absence of severe symptoms or heart failure did not exclude SCD.[9] Packer pointed out the analogy between the sudden catastrophic mechanical circulatory failure and an avalanche in snow-clad mountains.[6] As snow keeps accumulating on the slopes, many interdependent factors (gravity, friction, mass, movement, and others) interact to maintain the delicate stability. A slight trigger can precipitate collapse of the snow pile and result in a devastating avalanche. The points of interest here are the gradual build-up of stressful factors, apparent stability, and sudden irreversible breakdown. Similarly, a big pile of sand stands erect because the grains support each other by their weight, friction, and other factors. The contribution of each grain is critical, but at the same time, all the grains are interdependent. A similar mechanism allows us to build a tower of playing cards. Addition or removal of a single card or the slightest imperceptible movement of even one grain of sand can bring down the tower of cards or pile of sand, respectively, in a dramatic collapse. Physicists have used the term self-organized criticality while explaining the mathematical basis of dynamic systems characterized by the spontaneous interaction of multiple interdependent elements to maintain a critical equilibrium.[12]

Unexpected collapse and death are typically described in patients with LV dysfunction. It is now recognized that sudden circulatory collapse can also happen in conditions where the RV is mainly affected. Patients with PAH, operated tetralogy of Fallot with pulmonary regurgitation (TOF-PR) and congenital heart diseases (CHDs) with systemic RV are of special interest to pediatric cardiologists. Many of these patients appear relatively well, and SCD at a prime age is a tragic event. The estimated risk of SCD in adult CHD is relatively low at 0.09%–0.2%/year.[13,14] Nonetheless, this represents a significant increase over that of comparable populations. The frequency of late SCD has exceeded heart failure as cause of mortality in some reports.[15-17] Risk stratification using conventional methods, and even electrophysiologic testing and cardiac magnetic resonance study, remains imperfect. Late survivors of TOF-PR represent the largest and most analyzed group among adult CHD patients at risk of SCD. About 0.1%–0.8% of TOF patients die suddenly on late follow-up after correction.[18] The incidence of SCD rises as the duration of follow-up extends beyond 25 years after repair.[19] Ventricular tachyarrhythmia is suspected to be the cause. However, the results of ICD in adult TOF (for either primary or secondary prophylaxis) have been disappointing. Only 30% received appropriate ICD shocks, while 25% and 35% presented with inappropriate shocks and ICD-related complications, respectively.[20] Interestingly, the all-cause mortality remained high, and 50% of the deaths were sudden despite the ICD. It is possible that the ICD shock is not effective in treating ventricular tachycardia or ventricular fibrillation occurring in a severely dysfunctional RV. On the other hand, it is also possible that the deaths were secondary to a cascade of hemodynamic failure, with a transient ventricular or atrial tachyarrhythmia, bradyarrhythmia, or a hypotensive episode acting as the initial trigger.

PATHOPHYSIOLOGY OF SUDDEN CARDIAC DEATH

The LV myocardium is significantly abnormal in patients who die with dilated cardiomyopathy.[6] It shows varying combinations of hypertrophy, dilatation, fibrosis, dysfunction, and pathological remodeling. The circulatory dynamics are markedly deranged with severe neurohormonal activation. In addition, multiple systems in the body showed biochemical and/or functional changes. This situation possibly acts as a substrate for abrupt arrhythmic or nonarrhythmic collapse. While a large amount of data has been

accumulated on LV changes and mechanics, relatively little information was available until recently on the mechanisms of the RV adaptation.[21] Recent research in PAH has provided insights into the hemodynamic, cellular, and metabolic effects of increased afterload on the RV.[22] However, studies on the effects of volume overload on RV myocardium are still inadequate.

HEMODYNAMIC REMODELING OF RIGHT VENTRICLE

The gross hemodynamic changes in the RV associated with increased load appear similar to those in the LV[23-25] [Figure 1]. The normal RV circulation is a low resistance and high compliance circuit. Although the stroke volumes of the two ventricles are almost equal, the RVEF is lower than LVEF. A gradual increase in afterload as in PAH causes hypertrophy and homeometric adaptation without much increase in cavity dimension. This is associated with better RV-PA coupling and maintained output. No symptoms may be noted at this stage, although stress testing can show diminished aerobic exercise capacity. As the degree of hypertrophy increases, mild exertional dyspnea and fatigue may appear.[23] The volume-loaded RV in TOF-PR is characterized by a combination of hypertrophy with enlargement of cavity. Such heterometric adaptation also occurs in chronic severe rise in afterload and during acute rise in afterload. RV-PA coupling is not efficient in heterometric RV adaptation.[22] With persistently high load, the RV enlarges displacing the interventricular septum into the LV. Increased

interstitial tissue impairs RV wall compliance and diastolic filling. Dilatation of the right atrium and appearance of tricuspid regurgitation are common at this stage, correlating with clinical findings of raised venous pressure and fluid accumulation. Systemic output and perfusion begin to suffer as a result of LV underfilling, which aggravates poor oxygen delivery and myocardial perfusion [Figure 1].[24,25] The circulatory failure at advanced stages is not entirely dependent upon the increased load, and RV pathological changes may decide the outcome. Hence, it is imperative to identify and apply RV-specific measures, if possible, in addition to treating the cause of increased load. It is also interesting to note that RV dysfunction due to severe PAH, even if severe in degree, is not irreversible. This is typically demonstrated after lung transplantation for PAH, when the severely remodeled RV often returns to normal function.[21] On the other hand, in chronic severe TOF-PR, the RV may not recover its function after correction, once it is significantly dilated and impaired.[26]

MOLECULAR REMODELING OF RIGHT VENTRICLE

Significant differences at the cellular and metabolic levels have been observed between the LV and RV when they are under high afterload stress [Figure 2].[22,23] The RV shows evidence of increased oxidative stress with reduced antioxidant enzymes. It also shows an earlier switch to glycolysis from fatty acids as source of energy. The capillary density in the RV myocardium is low
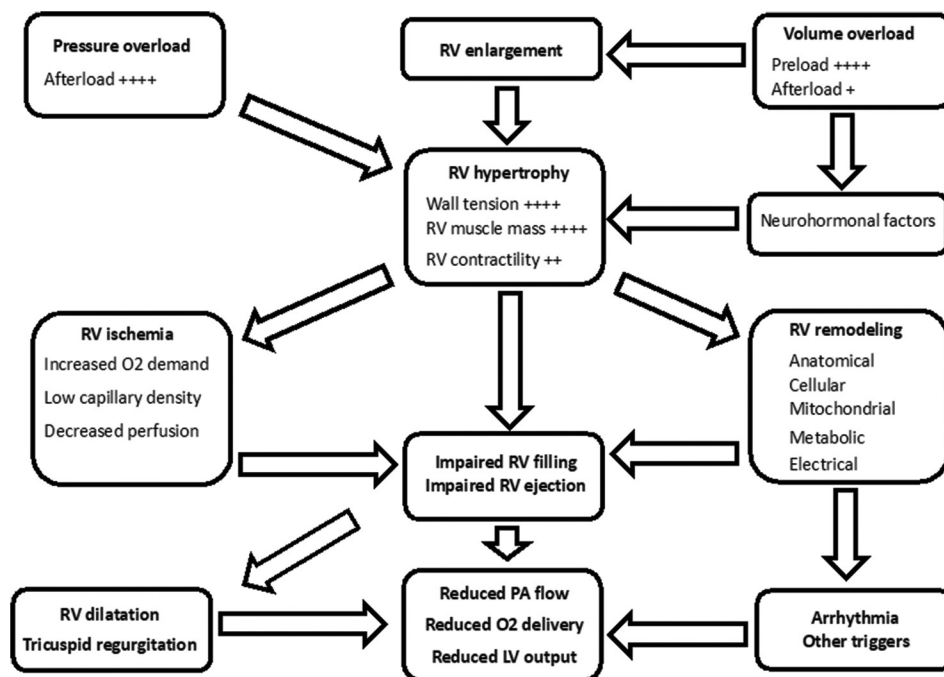

Figure 1: Pathophysiology of RV overload and failure. LV: Left ventricle, PA: Pulmonary artery, RV: Right ventricle
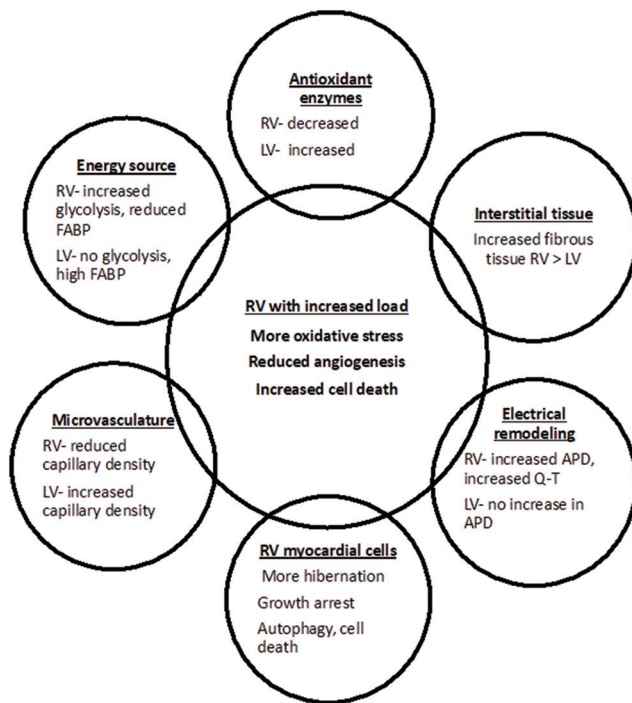
Figure 2: Cellular and molecular changes in failing RV and LV.
APD: Action potential duration, FABP: Fatty acid-binding protein,
LV: Left ventricle, Q-T, Q-T interval, RV: Right ventricle

indicating reduced angiogenesis. This is accompanied by more myocardial cell loss and increased fibrous tissue.[21-23] The adrenergic receptor signal mechanism shows similar changes in the failing LV and RV, with downregulation of β1-, α1-, and DA1-receptors.[22] However, β-adrenergic blockade does not produce any beneficial effect in the failing systemic RV or in the dilated RV associated with TOF-PR. On the contrary, β-blockade may actually worsen symptoms in systemic RV failure. This is in contrast to the marked benefit seen in the failing LV.[27-29] Catecholamines such as dobutamine and norepinephrine increase RV output in experimental situations, but their clinical efficacy is limited unlike the response seen in LV failure. The role of renin–angiotensin–aldosterone system (RAAS) activation in RV failure is not well defined yet, although RAAS activation has been noted in patients with PAH.[22,23] However, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) in PAH[30,31] and in CHD with failing systemic RV or TOF-PR[32-34] have produced equivocal results. The exact significance of the RV-specific changes is not yet known, but they suggest that the RV may be more prone to diminished energy production, more ischemia, more electrical instability, and less inotropy.[22] Understanding them may provide clues to the processes involved in sudden RV decompensation and possibly provide new targets for therapeutic intervention.[23-25]

MECHANISM OF SUDDEN CARDIAC DEATH IN A REMODELED RIGHT VENTRICLE

A large number of conventional risk factors (clinical and hemodynamic) have been identified related to SCD in both PAH and adult CHD patients.[35,36] However, their predictive value is relatively low, and they are not very helpful in anticipating sudden collapse in an individual patient.[14] More studies are required, possibly using multiple complex and larger data sets to look for novel indicators of risk. Figure 3 depicts the possible sequence of events in acute deterioration of RV-dependent states. The actual trigger remains unknown in the vast majority of victims. However, based on information available on hemodynamics and pathophysiology of the ventricles, the initial event is likely to be either an episode of hypotension or an acute rise in pulmonary vascular resistance (PVR).[23-25] Fall in blood pressure and reduced perfusion can occur due to transient arrhythmia, cardio-inhibitory reflexes, systemic vasodilatation, volume redistribution, hypovolemia, medications, or stress. Acute increase in PVR may result from thromboembolic occlusion of PA branches, PA wall dissection, hypoxia, hypercapnia, acidosis, respiratory diseases, and other unknown factors [Figure 3]. Irrespective of the triggering event, it is likely that a vicious cycle of low blood pressure, reduced perfusion, reduced oxygen delivery, RV ischemia, rise in PVR, reduced RV output, and fall in LV output is set in motion.[24] The downward trend is often aggravated by aggressive resuscitative measures such as epinephrine administration and inappropriate ventilation.

EMERGENCY TREATMENT OF SUDDEN CARDIOVASCULAR COLLAPSE IN PULMONARY ARTERIAL HYPERTENSION AND CONGENITAL HEART DISEASES

Despite many advances in recent years, our understanding of the mechanisms of RV avalanches and its treatment remains incomplete. Only about 21% of patients are successfully resuscitated even if the collapse occurs in hospital.[3] The currently available measures for the emergency treatment of acute RV hemodynamic collapse are summarized in Figure 3. The goals of treatment are as follows: maintain systemic blood pressure for coronary-systemic perfusion, correct the precipitating factor, optimize RV preload, reduce resistance to RV output, augment RV contractility, improve LV filling and if necessary, provide extracorporeal mechanical support (ECMS) to bypass the RV.[24,25] Although the broad principles are similar to those applied in LV failure, it is essential to apply measures which are more specific for the RV.[21,24] A α-adrenergic agonist like phenylephrine is
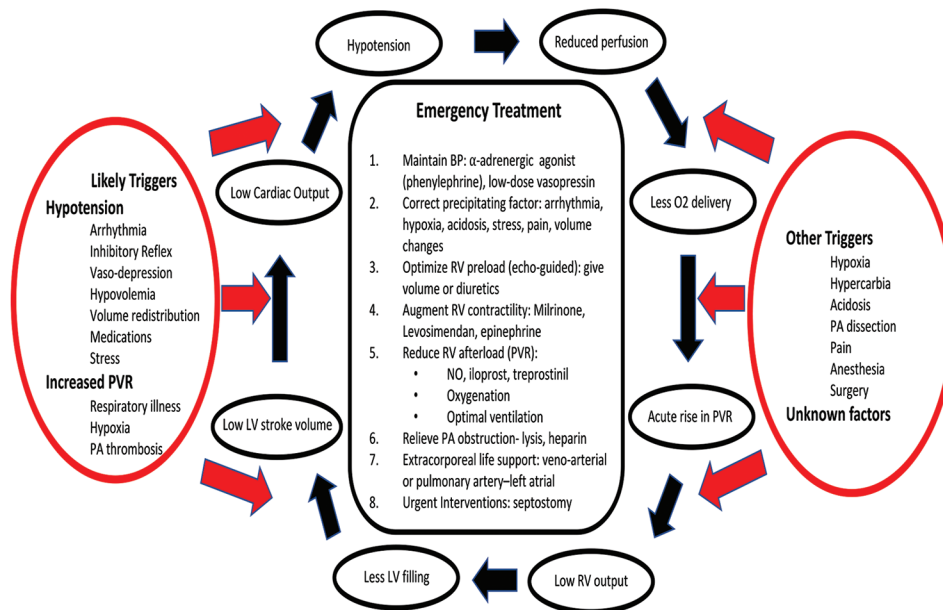
Figure 3: Mechanisms and management of acute RV hemodynamic failure. BP: Blood pressure, LV: Left ventricle, NO: Nitric oxide, PA: Pulmonary artery, PVR: Pulmonary vascular resistance, RV: Right ventricle

the drug of choice for treating hypotension as it produces vasoconstriction without excessive tachycardia. Low-dose vasopressin can also be used, but higher dose produces pulmonary vasoconstriction and reduced coronary flow. Adequate oxygenation and pulmonary vasodilators by inhalation are important to reduce RV afterload. Inhaled nitric oxide and aerosolized prostacyclins (iloprost or treprostinil) have the advantages of direct delivery to target organ, quick action, better ventilation-perfusion matching, low dose requirements, shorter half-life, and minimal effect on systemic blood pressure.[37] Intermittent positive pressure ventilation (IPPV) should be avoided if possible. If tracheal intubation is considered necessary, spontaneous respiration with low-pressure support is recommended. When needed, IPPV can be used with minimum intrathoracic pressure, tidal volumes, and optimal positive end-expiratory pressure. The aim is to achieve adequate ventilation and oxygenation without increasing the PVR.[24] There is a major difference between LV and RV in the use of inotropic medications. Adrenergic agonists like adrenaline, dobutamine, or dopamine are preferred for LV inotropy. However, they are not useful for increasing RV contractility and may cause undue tachycardia and arrhythmia. β-adrenergic stimulants are best avoided in case of RV failure, except for short-term use during resuscitation. Among currently available inotropic drugs, either milrinone (phosphodiesterase 3 inhibitor) or levosimendan (calcium sensitizer) appears to be most suitable. Off-label use of inhaled milrinone has also been used to avoid the systemic vasodilatory side effect.[24] Correction of acidosis, tachycardia, and other aggravating factors increases the efficacy of the above measures. If, however, the downward spiral of events

continues, an early decision to initiate RV bypass by either venoarterial or PA-LA ECMS pump offers the best chance of survival.[25] If ECMS is not available one can consider urgent catheter intervention such as balloon atrial septostomy, although it is not proven to be effective in this situation.

PREVENTION OF SUDDEN CARDIOVASCULAR COLLAPSE IN PULMONARY ARTERIAL HYPERTENSION AND CONGENITAL HEART DISEASES

This is a very important aspect and would involve timely detection and prevention of arrhythmic as well as nonarrhythmic forms of SCD. The following steps provide a guideline.

1. It is imperative to identify new indicators of impending RV decompensation to identify at-risk patients and take preventive action
2. Adequate preventive measures must be undertaken to avoid the aggravation of RV load and function. Early diagnosis is important in this respect, especially in conditions like idiopathic PAH. In addition to conventional screening methods, artificial intelligence is now being investigated as a tool for the early diagnosis of PAH[38]
3. Since adverse ventricular remodeling of both ventricles appears to be the common substrate, aggressive reverse remodeling should be the goal of preventive medical treatment besides relief of symptoms.[6]

In dilated cardiomyopathy, whether ischemic or nonischemic in etiology, treatment with beta-blockers

and neurohormonal antagonists (ACEi, ARB-neprilysin inhibitor) has been shown to significantly reduce mortality in adult patients with or without ICD.[39-42] In patients with PAH, evidence of RV stress should be considered as a strong indication for aggressive combination therapy to reduce PVR to near-normal ("treat to target" approach). The emphasis needs to shift from symptom relief to reverse remodeling of RV and PAs. The use of multiple drug combinations including oral or parenteral prostacyclins, at maximally tolerated doses, has been reported to be associated with higher survival rates in PAH. [43-46] More RV-specific medications need to be developed to improve the failing RV myocardial function.[21,22] In late survivors of operated TOF-PR with dilated RV preemptive management includes: (1) correction of PR and TR, (2) relief of obstruction in the outflow tract and PAs, (3) maintenance of low PVR, (4) prophylaxis of arrhythmia by ablation or ICD and (5) prevention of LV disease.[18,47]

In summary, biological avalanches are often the causes of death in cardiac patients. They may strike when least expected without much warning and are devastating. In cardiac patients with significant underlying abnormalities, clinical stability and absence of worsening are not sure signs of good outcome. The complex interdependent mechanisms of compensation and breakdown are still not entirely understood. In many cases, a critical equilibrium may actually mean that the patient is on the brink of collapse. The results of emergency treatment are still unsatisfactory. Further research is necessary to improve currently available methods of preventing and treating cardiac avalanches.

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Conflicts of interest

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