

Mechanisms of right heart failure—A work in progress and a plea for failure prevention

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The right ventricle (RV) of the heart, which pumps blood through a low pressure, low resistance “lesser” circulation, is now receiving more attention by researchers and clinicians, after many years of benign neglect.^[1-7] Some of the many reasons for neglecting the RV assumed that (1) In the context of global cardiac performance, the RV was not very important;^[2] and (2) The cellular and molecular mechanisms of RV failure (RVF) were not different from those responsible for LV failure. Perhaps the biggest knowledge gap originated from the lack of experimental studies modeling the development of RVF, and from attempts to extrapolate mechanisms of chronic RVF from studies originally designed to study acute RVF. These likely explain why “pressure overload” is the most frequent—and sometimes exclusively—quoted mechanism of RVF. Indeed, patients with chronic, progressive pulmonary vascular disease most frequently die of RV failure.^[8,9] However, as we enlarge our knowledge of in the pathobiology of RVF, we should also begin to consider RVF as a “progressive,” but not necessarily “chronic,” phenomenon.

THE CASE FOR INVESTIGATING RV FUNCTION AND DYSFUNCTION

We propose that the outcome of the patient with pulmonary arterial hypertension (PAH) is not fundamentally determined by pathophysiological characteristics germane to the lung disease (e.g., vasoconstriction and pulmonary vascular remodeling), but rather by the response of the RV to increased afterload and to additional mechanistically important factors imposed on the RV such as neuroendocrine system activation,^[3,10] and, perhaps, factors released from a “sick-lung circulation”^[11] (Fig. 1). In the management of patients with severe PAH, we still face (as a barrier) the fact that prevention of RV failure is not a realized treatment goal. For the past 15 years,

clinical studies have utilized vasodilator drugs expecting to significantly reduce pulmonary arterial pressure, halt or delay the progression of the lung vascular disease, reduce RV afterload, and prevent the development of RVF. However, this goal is not often accomplished in the clinical setting, as a recent meta-analysis of PAH clinical trials reported a weighted mean reduction in mean pulmonary arterial pressure of 3 mmHg after treatment.^[2] Moreover, it has been demonstrated that even after many years of prostacyclin therapy (at least with epoprostenol treatment), pathological lung vascular remodeling does not stop.^[12] Lastly, a recent cardiac MRI study from the Netherlands’ pulmonary hypertension center reported that the survival of medically-treated patients with PAH was not determined by a vasodilator-induced decrease of the pulmonary vascular resistance, but rather by an improved RV ejection fraction (RVEF).^[13] Thus, if current vasodilator drugs have failed to reverse the vascular disease, should we not start thinking about RV-targeted therapies while we wait for new PAH lung-specific therapies to get in the pipeline?

Altogether, current data highlights unmet needs in the current concepts of the pathobiology of RVF: (1) We lack detailed cellular and molecular mechanistic elements to explain RV failure (“RV failure program”); and (2) we do not fully understand the pathobiology behind the transition from compensated RV hypertrophy to RV failure. Possibly the most compelling argument in support of RV failure investigations is based on the postulate that RV failure is reversible: the end-stage RVF of PAH patients fully recovers after lung transplantation, usually within weeks. Unfortunately, we do not have any mechanistic studies to help explain how the RV recovers during the post-transplant period.

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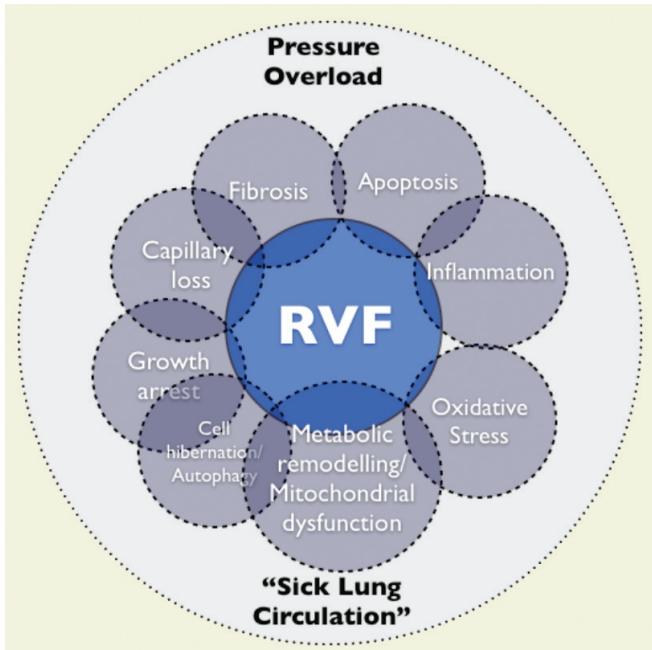


Figure 1: The right ventricle between “a rock and a hard place”, challenged by the pressure overload and the sick lung circulation (). The grey circles symbolize cellular and molecular mechanisms. **RVF:** right ventricular failure.^[3]

MECHANISMS CONTRIBUTING TO RV FAILURE

The prevailing paradigm holds that increased RV afterload is sufficient as an explanation of RV failure, but there are several problems with this view:

- Under most circumstances, the RV adequately adapts to chronic pressure overload (in contrast to acute pressure overload). On average, at least 55% of incident patients with PAH live (with chronic progressive pressure overload) for three years.
- Even in the prepulmonary hypertension “drug era” (prior to 1991) there were long-term PAH patient survivors,^[14] most prominently patients diagnosed with aminorex- (appetite suppressant) induced PAH.^[15]
- There are patients with severe PAH that remain highly functional (NYHA Functional Class I) for many years without developing RV failure.^[12]
- Patients with Eisenmenger physiology live prepulm. hypert.drugera number of years with strikingly elevated pulmonary arterial pressure but do not develop failure until later in life.^[16]
- Experimental studies show that after pulmonary artery banding (PAB), the RV develops adaptive hypertrophy which is more resistant to pressure overload and does not necessarily develop failure.^[17]

In the aggregate, there seems to be solid evidence to suggest that chronic, progressive pressure overload might be the initial component responsible for triggering maladaptive

changes in the RV; however, it is not necessarily the only one. Other factors such as ischemia, inflammation, oxidative damage, epigenetics, and abnormal cardiac energetics could equally contribute to the development of RVF (Figure 1).

Right ventricular ischemia

Patients with severe PAH can develop chest pain which may be due to RV ischemia. Wolferen et al.^[18] have shown changes in the right coronary artery blood flow pattern in patients with PAH, while Gómez, Sandoval, and collaborators employed stress myocardial scintigraphy using technetium sestamibi to demonstrate RV ischemia associated with an RV end-diastolic pressure elevation.^[6] Unfortunately, human histological studies of the RV from patients with chronic severe PAH are unavailable, and it has never been demonstrated that the ratio of RV muscle-to-capillary density, in patients with severe PAH, is altered as it has been reported in LV failure or in experimental RVF. Hein et al. studied LV tissue biopsies obtained at the time of heart surgery for aortic stenosis valve replacement, and described capillary rarefaction and discuss their finding of autophagy. In order to explain RV ischemia in the setting of PAH, investigators have pointed toward increased RV-wall stress^[19,20] and myocardial fibrosis, but it is presently unclear whether impairment, RV wall stress, RV fibrosis—or all these factors in combination—contribute to RV myocardial ischemia.

In the SU5416/ chronic hypoxia (Su/Hx) model of severe PAH and RV failure,^[10,17] we have demonstrated a dramatic reduction of the number of perfused myocardial capillaries using in vivo tomato-lectin endothelial cell (EC) labeling (Fig. 2B). Histologically, we have also showed diffuse myocardial fibrosis.^[17] Capillary rarefaction has also been reported in the monocrotaline (MCT) model of PAH.^[21] Surprisingly, the capillary density in the RV from rats with pulmonary artery banding (mechanically induced RV hypertrophy) is only mildly decreased.^[17] We asked whether the Su/Hx model of PAH presents with additional functional alterations of the remaining RV capillaries. Thus, we used electron microscopy to show damaged EC in cardiac capillaries (Fig. 2C). By immunohistochemistry, we found regional loss of proteins associated with normal EC function (unpublished data).

Based on our results, we propose three mechanisms that could account for the capillary rarefaction observed in experimental RVF: 1) EC apoptosis, and/or 2) endothelial cell mesenchymal transformation, as proposed by Zeissberg et al.,^[22] and 3) insufficient angiogenesis in a context of rapid myocardial hypertrophy. EC death could be partially explained by a decreased expression of the angiogenic protein vascular endothelial growth factor (VEGF), as it has been observed in the failing RV from Su/Hx animals.^[17] This hypothesis is largely based on

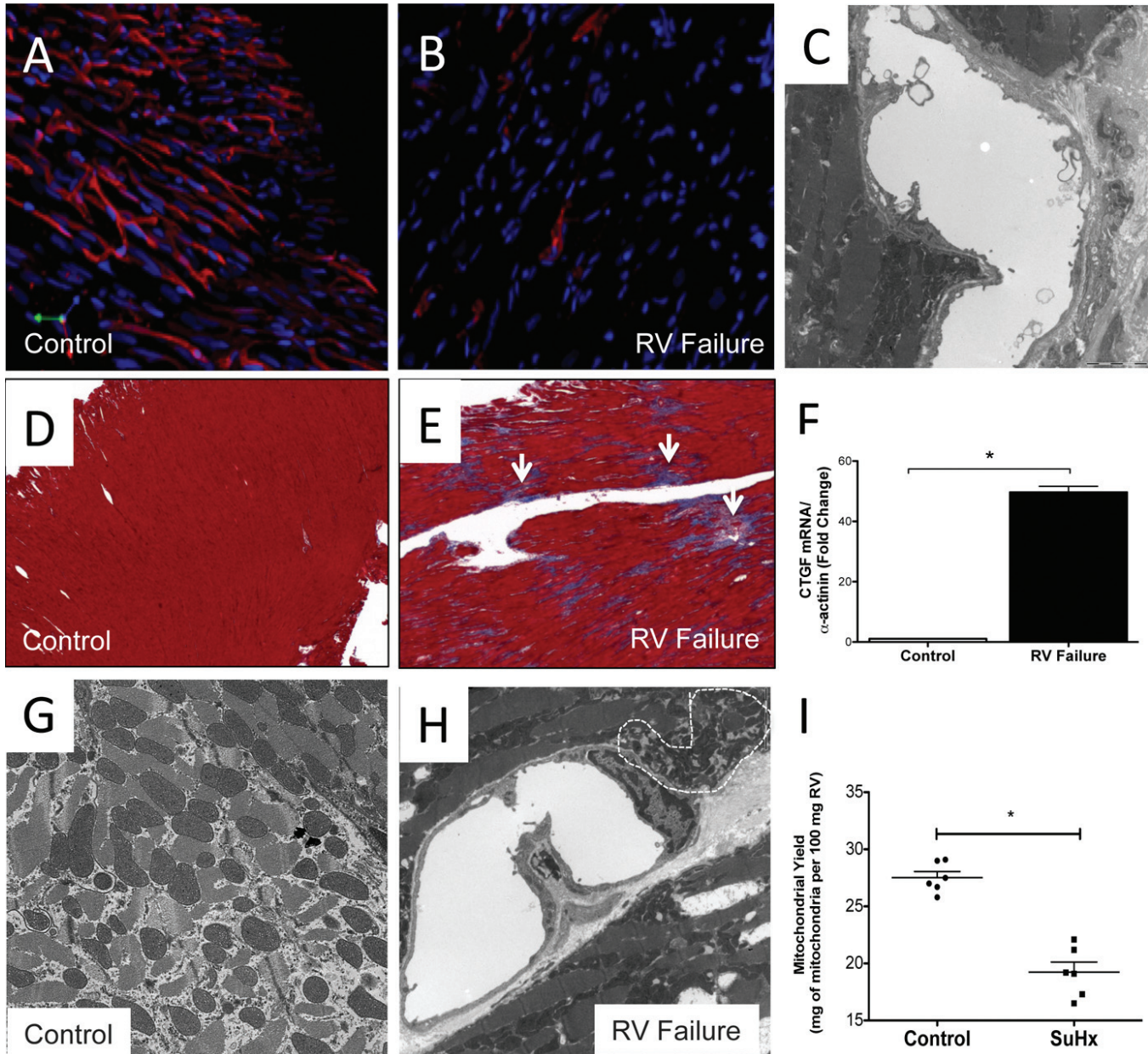


Figure 2: “Right ventricle; changes of the microcirculation (A-C). Confocal microscopy of in vivo labeled right heart muscle capillaries; immunohistochemistry, tomato lectin stain = red (A,B). One single capillary lumen, electron microscopy, in vivo fixation. The image shows destruction of the endothelial cell with bleb formation (C). Trichrome stain (D,E), expression of connective tissue growth factor (CTGF) gene in the failing (Su/Hx) right ventricle (F). Electron microscopy, normal right ventricle mitochondrial morphology (G), small, dense mitochondria in the Su/Hx failing right ventricle (H). Reduction of mitochondria (mitochondrial yield) in the Su/Hx failing right ventricle.

the data generated by Eli Keshet’s group, which have shown that genetically engineered, reversible reduction of VEGF expression in the mouse myocardium results in capillary rarefaction, suggesting that VEGF signaling is necessary for the maintenance of myocardial capillaries.^[23] Handoko et al. have also reported decreased VEGF and RV-capillary rarefaction in rats treated with MCT.^[21,24] Taken together, it appears that the work from several laboratories supports the notion that there are microcirculatory problems in the failing RV. However, whether impaired

microcirculation function is sufficient to explain the rest of maladaptive changes observed in the failing RV remains to be investigated.

Inflammation

Inflammatory cells have been localized in the RV from rats with monocrotaline-induced PAH;^[25] however, data relating to human RV failure are lacking and no systematic study has been undertaken to examine the role of inflammatory cells or inflammatory mediators in RV failure. A recent

experimental study of LV failure in mice generated a novel concept of a toll-like receptor 9 (TLR-9)-dependent failure component. In this model of chronic severe LV pressure overload, mitochondrial DNA from damaged heart cells generated a cardiac inflammatory response via TLR 9.^[26]

Oxidative stress

Oxidative cell damage and oxidant-dependent transcriptional control occur and participate in inflammatory organ and tissue responses. Little is known about the role of oxidant stress in RV failure with the exception of the important study of Yet et al.^[27] These authors exposed hemoxygenase 1 KO mice to five weeks of chronic hypoxia and found that the RV, but not the LV, was damaged and dilated. Thus, it appears that the HO-1 function is required for a successful adaptation of the RV to pressure overload. The expression of HO-1 in the RV tissue from the Su/Hx pulmonary hypertensive rats is reduced, perhaps reflecting an impaired response to oxidant stress.^[17]

MicroRNA

Several recent publications have demonstrated microRNA dependent regulation of gene expression in association with pulmonary artery cell growth^[28-30] and plasma microRNA expression patterns after acute myocardial infarcts or in patients with heart failure^[31,32] (Table 1). In mouse models, miRNAs play a role in the development of heart failure and the literature on cardiac microRNAs is still expanding.^[33-35] The transition of the RV from hypertrophy to failure has been investigated in the rat Su/Hx model and we reported a decrease in miR 21,34c, 133a, and 139-3p in Su/Hx-induced RV failure when compared to PAB-induced RV hypertrophy.^[36] More recently, Reddy et al. reported RV-specific microRNA expression changes in a murine model.^[31] Unfortunately, the mechanisms by which miRNAs could affect gene and protein expression during RVF are incompletely understood.

Mitochondrial energy metabolism

Abnormal cardiac metabolism has long been recognized as a problem in chronic left heart failure.^[37,38] Similarly, data derived from experimental models of PH suggest that the failing RV is also characterized by a certain degree of “metabolic remodeling.” In the SU/Hx rat model, the

RV exhibits increased expression of glycolysis-related genes,^[36] whereas dysfunctional RV hypertrophy in the monocrotaline rat model of PH is associated with increased glycolysis enzymatic rates.^[39] Unfortunately, a complete characterization of RV “metabolic remodeling” in human PAH is still lacking. Positron emission tomography studies have shown increased accumulation of the glucose analog 18F-2-Deoxy-2-Fluoro-D-Glucose (18-FDG) in the RV of PAH patients.^[40,41] However, 18-FDG uptake studies have multiple limitations and the physiological interpretation is not straightforward (i.e., 18-FDG uptake studies do not directly measure glycolysis). RV oxygen consumption can also be measured by [11C]-acetate PET scanning.^[42] However, such studies are limited to a few specialized centers and are difficult to perform.^[8] Based on experimental models, there is now evidence to suggest that the machinery required for fatty acid metabolism in the failing RV is compromised on multiple levels (fatty acid transport, oxidation and upstream transcriptional regulation).^[43] Furthermore, there is evidence to suggest important alterations of mitochondrial structure and function. The expression of multiple critical transcription factors involved in the regulation of mitochondrial biogenesis, including the mitochondrial transcription factor A (TFAM) and the peroxisome proliferator-activated receptor (PPAR)- γ coactivator-1 α (PGC-1 α), is significantly downregulated in the failing RV.^[44] In accordance, RVF seems to exhibit a net loss in the mitochondrial number per gram of RV tissue^[10] (Fig. 2I). The remaining mitochondria demonstrate abnormal ultrastructure on electron microscopy (Fig. 2H), as well as decreased oxidative capacity.^[10] Akin to chronic left heart failure, the data support that dysfunctional RV hypertrophy, in the setting of severe PAH, is characterized by a metabolic switch from aerobic to anaerobic metabolism. Whether this switch is an adaptive or maladaptive mechanism remains elusive. However, multiple studies have shown that the rate of fatty acid oxidation is preserved or increased in physiological/adaptive left ventricular hypertrophy, and that it decreases during the progression of heart failure.^[45] Similar results have been reported for the nondysfunctional, mechanically-induced RV hypertrophy from rats with pulmonary artery banding, which exhibit high rates of fatty

Table 1: microRNA in PAH

Human PAEC and PASMC	BMP-control of angiogenesis	miR-21	(Drake et al ^[28])
Human EC		miR424 \rightarrow HIF-1 α	(Gosh et al ^[51])
Human PASMC		miR-204	(Courboulin et al ^[30])
Mice, rats, chronic hypoxia		miR-17	(Pullamsetti et al ^[29])
Heart muscle injury		miR133, miR499-5p, miR-208b, miR126	(Xu et al ^[32])
Rat right ventricle	Hypertrophy/failure		(Drake et al ^[36])
Mouse right ventricle	Hypertrophy/ failure		(Reddy et al ^[31])

PAEC: pulmonary artery endothelial cells, **PASMC:** pulmonary artery smooth muscle cells

Table 2. Gene expression changes during right ventricular failure and after treatment with carvedilol

Category/Gene	Normal heart	RVF (SuHx)	RVF + Carvedilol	Reference
Angiogenesis				
VEGF	+++	+	+++	Bogaard <i>et al</i> [10]
Angiopoietin-1	+++	+	++	Drake <i>et al</i> [36]
Apelin	+++	+	++	Drake <i>et al</i> [36]
Glucose Metabolism				
Hexokinase-1	+	+++	+	Drake <i>et al</i> [36]
Glut-1	+	+++	+	Gomez-Arroyo <i>et al</i> [43]
Fatty Acid Metabolism				
PGC-1 α	+++	+	+++	Gomez-Arroyo <i>et al</i> [43]
PPAR- α	+++	+	+++	
ERR- α	+++	+	+++	
CD36	+++	+	+++	
ACSL1	+++	+	+	
CPT1 α	+++	++	+++	
CPT1 β	+++	++	+++	
CPT2	+++	++	+++	
ACADM	+++	+	+++	
Mitochondrial Biogenesis				
TFAM	+++	+	+++	Gomez-Arroyo <i>et al</i> [44]
NRF-2	+++	++	+++	
Cell growth				
IGF-1	+++	+	+	Drake <i>et al</i> [36]
KLF-5	+++	+	++	
Tissue remodeling				
Adducin-3	+	+++	++	Drake <i>et al</i> (REF)
BNP				Drake <i>et al</i> [36]
ANP	+	++++ (200 fold change)	++++ (600 fold change)	Bogaard <i>et al</i> [10]
α -MHC	+++	+	+	
β -MHC	+	++	+++	
SERCA2a	+++	++	++++	

α -MHC: alpha-myosin heavy chain; β -MHC: beta-myosin heavy chain; **ACADM**: Acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain; **ANP**: Atrial natriuretic peptide; **ACSL1**: Acyl-CoA synthetase long-chain family member 1; **BNP**: Brain natriuretic peptide; **CD36**: Trombospondin Receptor/Fatty acid translocase; **CPT**: Carnitine palmitoyltransferase; **ERR**: Estrogen-related receptor; **Glut**: Solute carrier family 2 (facilitated glucose transporter); **IGF-1**: Insulin-like growth factor 1; **KLF-5**: Krueppel-like factor 5; **NRF**: Nuclear respiratory factor-2; **PGC-1**: Peroxisome proliferator-activated receptor gamma coactivator-1; **PPAR**: Peroxisome proliferator-activated receptor; **SERCA2a**: sarco/endoplasmic reticulum Ca²⁺-ATPase; **TFAM**: Mitochondrial transcription factor A; **VEGF**: Vascular endothelial growth factor

acid oxidation.^[46] In addition, pure mechanical pressure overload is insufficient to change the expression of PGC-1 α , PPAR- α or the expression of the estrogen-related receptor- α ^[43] which, along with PGC-1 α , are the main transcription factors that coordinate fatty acid oxidation in the heart.^[47] Thus, it appears that decreased fatty acid oxidation may contribute to the development of RV failure, along with fibrosis, capillary dysfunction and, oxidative stress (Fig. 1). It is clear that pressure overload alone is not sufficient to explain RVF,^[17] or the metabolic switch.^[43] Whether capillary dysfunction (or the consequent tissue hypoxia) is sufficient to explain the metabolic remodeling remains to be investigated. Whereas the role of metabolic modulators for the treatment of RVF in PAH is of potential interest, their efficiency could be limited by underlying mitochondrial abnormalities. If the mitochondrial machinery is not working adequately, it would not matter which substrate is being oxidized. Finally, we have begun to investigate the mechanisms whereby carvedilol improves RV function in Su/Hx RVF model. Some of the changes in the RV gene expression pattern as they relate to mitochondrial function are listed in Table 2. Interestingly, treatment of normal rats with carvedilol is sufficient to induce gene expression changes

in the heart, and carvedilol has been shown to be cardio-protective in cultured cardiomyocytes.

SUMMARY AND CONCLUSION

Right heart failure is characterized by morphological and functional changes. We wish to advance the concept that the RV afterload by itself is insufficient as an explanation of the mechanism of RV failure and that RVF prevention and preservation of RV function are important treatment goals for patients with severe PAH. We also take the position that RVF is potentially reversible. This has been shown experimentally in the Su/Hx rat model of severe RVF, where carvedilol treatment has reversed RVF without reducing the RV afterload.^[10] This “proof of principle” investigation has stimulated the search for mechanisms and molecular targets of RVF reversibility (Table 2). Mitochondrial energy metabolism is compromised during RVF and β -adrenergic receptor blockade^[43] and perhaps diet or exercise may improve cardiac mitochondrial function.^[48,49] Both the positive and negative impact of neuroendocrine factors^[3,50] on a right ventricle “under pressure” deserve detailed studies.

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