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Mitochondria and Metabolism in Right Heart Failure

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Abstract

Heart failure (HF) is a clinically complex and heterogenous disease characterized by an inability of the heart to pump sufficient blood to the periphery. As such, it has historically been thought of and studied as a disease of the left ventricle (LV). While LV failure is the most common form of HF, it is the ability of the right heart to function that predicts survival in many clinical settings. Extrapolation of mechanisms of left HF to the right ventricle (RV) has yet to prove fruitful in identification of therapeutic approaches, in large part due to a lack of basic mechanistic understanding of the RV which is embryologically, anatomically, and physiologically distinct from the LV. The failing LV is characterized by mitochondrial dysfunction and a metabolic switch, both of which contribute to an energetically starved heart with poor contractile ability. These mechanisms, however, are far less described in the failing RV. The purpose of this chapter is to present the current literature examining the role of mitochondria and metabolism in the healthy right heart, treatments to target deficits in the failing RV, and to identify knowledge gaps for future research in this clinically important area.

Keywords: heart failure, right ventricle, mitochondria, metabolism, ventricular dysfunction, pulmonary hypertension

1. Introduction

Cardiovascular disease is the leading cause of death worldwide, of which heart failure (HF) constitutes a growing public health concern. In the United States alone, close to 6 million individuals currently suffer from HF, accounting for nearly one of out every nine deaths [1]. Morbidity and mortality from HF are high, with 50% mortality within the first 5 years of diagnosis. HF is also a financial burden on the healthcare system, with direct costs estimated at \$32 billion per year in the United States [2], roughly 2–3% of total global healthcare spending.

While HF constitutes a complex syndrome of diseases, it generally refers to the inability of the heart to pump sufficient blood to the periphery. As such, historically HF has been studied as a disease of the left ventricle (LV), and most treatments for HF are designed to improve function of the failing LV. Hallmarks of current HF therapies include neurohormonal targets, vasodilators, and/or reducing heart rate- all of which should reduce myocardial oxygen consumption and workload and rebalance energy supply and demand in the heart. However, these therapeutic approaches are largely based on symptom management and have not significantly changed the clinical course of the disease, as the staggering HF morbidity and mortality statistics have remained largely the same over the past 15 years [3]. These data suggest new therapeutic strategies are needed for successful HF therapy, and targeting the bioenergetic deficit through restoration of mitochondrial abnormalities has recently emerged as a promising strategy [4].

While LV-centered pathology constitutes the largest number of HF cases, it is ability of the right ventricle (RV) to function that predicts survival in many cardiovascular disease contexts including pulmonary hypertension [5], (which will be reviewed in much greater detail below), heart failure with preserved ejection fraction [6], and dilated cardiomyopathy [7]. However, no RV-directed therapies exist, and far less is known about the pathophysiology of the failing right heart than the LV. So, while considerable progress has been made to elucidate the metabolic and mitochondrial derangements that underlie LV failure, basic understanding of mitochondrial and metabolic derangements in RV dysfunction continues to be ill-defined. Here, we will present what is known about RV failure and the role of mitochondria and metabolism in models of experimental RV failure and in human populations with right HF. We believe successful HF therapies must target the failing RV for significant improvement in clinical and therapeutic outcomes.

2. The healthy right and left ventricles

Although many similarities exist between the ventricles, and they work in concerted effort to efficiently contract and relax for sufficient blood delivery, important embryological, physiological, and pathophysiological differences exist between the right and left ventricles [8]. We will briefly discuss a few of these differences, with a specific focus on mitochondria and metabolism.

2.1. Embryology, anatomy, and physiology

The RV and LV have different embryological origins and diverge early in development. The RV derives from the anterior (secondary) heart field, while the LV derives from the early heart tube (primary heart field) [9]. This early divergence is transcriptionally regulated, and several transcription factors have been identified which are responsible for the chamber-specific development including *Hand2* and *Tbx20* [10]. During gestation, the RV functions as the systemic pump. After birth, the RV becomes coupled to the low-pressure pulmonary circulation. As the ductus arteriosus and foramen ovale close, peripheral vascular resistance (PVR) decreases,

leading to an increase in RV compliance, regression of muscle mass, and shifting of the inter-ventricular septum toward the RV, resulting in a concave shape of the ventricle in adulthood. Consequently, right sided pressures are significantly lower than the systemically-coupled left sided pressures. Due to its coupling to a low-pressure circuit, the RV is approximately 1/3 the thickness of the LV. As a result of lower pressures and wall stress, the RV has a lower O₂ requirement both at rest and during exercise. Consistent with a lower workload, coronary blood flow and O₂ delivery to the RV are comparatively lower than the LV [11]. At rest, the LV extracts 75% of O₂ and the RV ~50% of the available coronary O₂. These basal differences in oxygen uptake are important under periods of physiological or pathological stress, particularly those in which oxygen availability changes. Further, the ventricles can adapt to changes in oxygen availability through different mechanisms, with the RV meeting O₂ demands by either increasing coronary flow or by increased O₂ extraction [12], whereas the LV primarily increases coronary flow to match demand [13]. These data are consistent with the response of the ventricles to pathological insult, which will be discussed in greater detail below.

2.2. Mitochondrial function and metabolism in the healthy heart

2.2.1. Cardiac metabolism

In healthy states, the heart derives energy from multiple sources to match the demand of contractile function, and can serve as an energetic omnivore based on substrate availability. When given a choice, however, the heart prefers lipid, based on significantly higher ATP production per carbon molecule compared to glycolysis. The first report of the heart's preference for lipid was published in 1953 [14], with subsequent studies confirming that fatty acids constitute 60–90% of cardiac ATP sources with carbohydrates supplying the remaining 10–40% [15]. Fatty acids are transported into cardiomyocytes through fatty acid transporters and subsequently into the mitochondria by carnitine palmitoyltransferase-1 into the matrix where they undergo β -oxidation. The successive oxidation of fatty acid chains provides acetyl CoA that enters the Krebs's Cycle to produce energy to supply the demand of contraction. Glucose is transported into cardiomyocytes by facilitated diffusion mediated by glucose transporters GLUT1 and GLUT4 (insulin-dependent). Once inside the cell, glucose is phosphorylated by hexokinase as the first step in glycolysis. Nine steps later, pyruvate is either decarboxylated by pyruvate dehydrogenase (PDH) to form acetyl CoA to be transported into the mitochondria to begin Krebs's Cycle, or reduced to form lactate and subsequent anaerobic metabolism.

Assuming similar metabolism and mechanisms of control of these pathways between the ventricles might be overly simplistic. As discussed above, the RV is thinner and has a different shape than the LV, which contributes to differential responses to pathological load (discussed below). Transcriptional profiles, including those which regulate metabolism, differ between ventricles, as a comparative gene expression of mRNA and microRNA between control RV and LV samples identified numerous genes with differential expression between the ventricles [16]. These genes spanned a wide variety of biological processes including metabolism, with carbohydrate metabolism (three differentially expressed genes), lipid, fatty acid and steroid metabolism (11 genes), nucleic acid (30 genes) and protein metabolism (22 genes), as well as other metabolic genes (11 genes) significantly varying between ventricles [16].

2.2.2. Mitochondrial content, dynamics, and function

The heart is an extremely energetically active organ. Despite accounting for less than 1% of body weight, it consumes roughly 8% of total ATP [4]. The process of energy production and consumption is incredibly dynamic, as the heart only stores enough energy to supply a few beats and turns over the entire metabolite pool every 10 seconds [17]. To meet this costly energy demand, the heart is the most mitochondrially-dense tissue, with mitochondria comprising 25–30% of cardiac myocyte cell volume [18]. Mitochondria are responsible for the majority of ATP production in the healthy heart, with some estimates suggesting that close to 95% of cardiac ATP production occurs through mitochondrial oxidative phosphorylation [19]. Mitochondria are double membrane-bound organelles which are tightly regulated within the myocardium to facilitate efficient energy production. ATP is produced through oxidation of metabolic fuel to provide reducing equivalents (NADH and FADH₂) that are coordinately used to generate a proton motive force across the inner mitochondrial membrane to drive ATP synthesis. Successive electron transfer through complexes I through IV of the electron transport chain culminates in ATP synthesis through complex V (ATP Synthase) in an oxygen-dependent manner.

It has been recognized for quite some time that mitochondria exist in a dynamic reticulum and not as isolate organelles [20]. This network not only allows for efficient ATP production, but also facilitates mitochondrial quality control. The maintenance of this network occurs through continuous mitochondrial fusion and fission, a process mediated by both inner and outer mitochondrial membrane proteins. Fusion, the elongation of the mitochondrial network, increases mitochondrial mass and is regulated mainly by mitofusin-1 and mitofusin-2 (Mfn1 and Mfn2) of the outer mitochondrial membrane and optic atrophy-1 (Opa1) of the inner membrane. Fission, the fragmentation of the mitochondrial network, results in a greater number of smaller mitochondria, and is mediated in part by dynamin-related protein-1 (DRP-1) and fission protein 1 homolog (Fis1) [21]. Fusion and fission are critically necessary for cardiac development as loss of any of these proteins is embryonically lethal [22–24]. Substantial evidence suggests they are also important in the adult heart, as genetic manipulation of these proteins has profound impact on cardiac function.

In addition to regulating mitochondrial shape and size, mitochondrial fission and fusion proteins also regulate mitochondrial quality control through mediating mitophagy, the cellular process of removing damaged mitochondria through autophagy [25]. Autophagy, a highly conserved lysosomal-dependent process of removing damaged cargo and recycling long-lived proteins and organelles, plays a pivotal role in a number of disease states, including cardiovascular diseases [26]. Though the exact mechanisms of mitophagy are far from resolved, it is generally believed that too much mitophagy results in cardiomyocyte death and can contribute to cardiac dysfunction [27] while too little may impair the removal of damaged mitochondria, causing the accumulation of damaged mitochondria which lose mitochondrial membrane potential, produce excess reactive oxygen species, and impart cellular damage [28]. Microtubule associated protein light chain 3 (LC3) is often used as a marker of autophagy; LC3-I (the cytosolic isoform) is converted to LC3-II during the formation of autophagosomes. Additional mitochondrial specific regulators of this process include PINK1 and Parkin [28]. In addition to these protein markers of mitophagy, the process can also be visualized by electron microscopy (EM).

In addition to dynamically undergoing fission and fusion to regulate the mitochondrial network, mitochondrial turnover or biogenesis, creates new mitochondria. Mitochondria have their own DNA (mtDNA) and genetic code that is distinct from nuclear genetics. The biogenesis of mitochondria is a cooperative effort between mitochondrial and nuclear-encoded genes to synthesize all proteins which comprise the five electron transport chain complexes. Biogenesis is transcriptionally regulated by peroxisome proliferator-activated receptor- γ coactivator 1- α (PGC-1 α), the “master regulator” of biogenesis [29], transcription factor of mitochondria (TFAM), and nuclear respiratory factor 1 (NRF1) [30]. Biogenesis of mitochondria also requires the synthesis of cardiolipin, a mitochondrial-specific phospholipid located on the inner mitochondrial membrane which regulates respiratory enzyme super complex assembly [31]. The transcriptional assessments of TFAM, PGC-1 α and NRF1 or markers of mitochondrial content are often used as surrogates of biogenesis, a cumulative process which is truly represented by net synthesis of mitochondrial proteins and/or lipids into functioning organelles [32].

Mitochondrial biology and physiology are further complicated when we consider the arrangement of mitochondrial populations within the adult heart. Three distinct cardiac populations have been identified: the subsarcolemmal mitochondria (SSM), located along the perimeter of the cell, interfibrillar mitochondria (IFM), located between the myofibrils [33], and perinuclear mitochondria which are arranged in clusters surrounding nuclei and are presumably involved with transcriptional activity. Although never directly tested, SSM are hypothesized to provide ATP for basic cell functions, whereas IFM provide energy for the contractile apparatus. The original description of IFM and SSM populations identified differences in biochemical and respiratory properties, as well as ultrastructural differences [33]. Following years of debate as to whether these two populations were different and discrepancy over the causal role of isolation procedures in obscuring differences, consensus seems to have been reached regarding important physiological differences in IFM and SSM. It should be noted that these differences have only been identified in LV mitochondria, and to our knowledge, subpopulations of SSM and IFM have never been described in the RV.

Indeed, most of what we know about mitochondrial structure and function in the healthy heart derives from studies of the LV, and only a few studies have compared healthy right and left ventricles. However, a small report suggests differential expression of autophagy and mitophagy regulators in the RV compared to LV [34]. A proteomic analysis of healthy rabbit and porcine LV and RV free walls demonstrated similar cellular aerobic capacity, mitochondrial volume, mitochondrial electron transport chain content (complexes I, III, IV, and V), as well as mitochondrial enzyme activity [35]. Our group assessed mitochondrial content and electron transport chain activity, as well as protein markers of mitochondrial dynamics in the RV and LV from healthy 2-week old cows (**Figure 1**). While we generally found similar mitochondrial profiles between the ventricles, there were some subtle differences including higher relative copy number of COXI (mt/nDNA) and higher expression of Mfn1 in the RV compared to the LV. Together, the few published papers comparing the LV and RV and the data from our group suggest that though small or subtle, differences exist in mitochondrial physiology in the RV and LV, consistent with the different energetic and functional capacities of the ventricles. A more careful description of interventricular differences will aid in understanding pathological adaptations that occur within these organelles, and the contribution they play in development of cardiac disease.

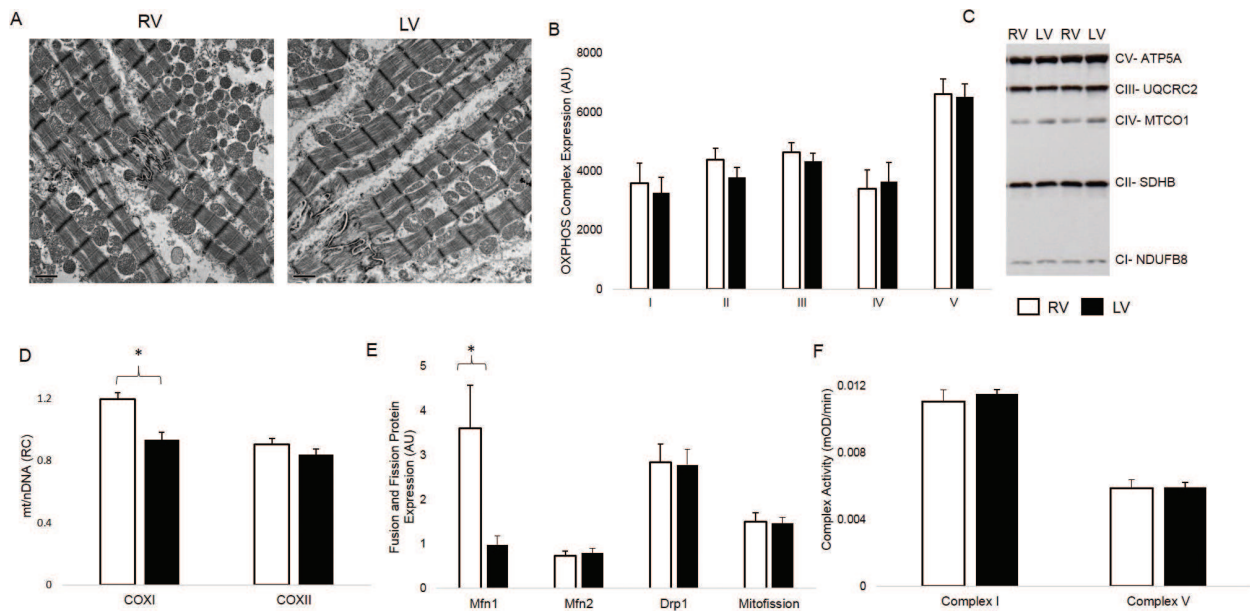


Figure 1. Mitochondrial content, dynamics, and activity in healthy right ventricle (RV) and left ventricle (LV) from neonatal cows. (A) Representative electron micrographs of the mid-RV and LV of control cows. (B) Expression of electron transport chain complexes does not differ in the healthy ventricles. OXPHOS complex expression was assessed by immunoblotting using an antibody against one subunit of each complex. (C) Representative image. (D) Mitochondrial content, as assessed by mt/nDNA copy number, is slightly different between ventricles, as COX1 copy number is higher in the RV than the LV. (E) Mitofusin-1 (Mfn1) expression is significantly higher in the RV than the LV, with no differences in other mitochondrial dynamics markers. (F) Complex I and V activity do not differ between healthy RV and LV, as assessed by spectrophotometric assay. All comparisons were assessed by Student's *t*-test. **p* < 0.05, *n* = 10 in each ventricle. White bars: RV; black bars: LV. Adapted from Bruns, DR et al. *AJP-lung*, 2014.

2.2.3. Non-energy producing roles for mitochondria in the healthy heart

Mitochondria are a major source of cardiac reactive oxygen species (ROS), and the largest producer of ROS within the cell [36]. Several labs have identified superoxide ($O_2^{\bullet-}$) as the primary mitochondrial source of ROS. Superoxide formation occurs on the outer mitochondrial membrane, in the matrix, and on both sides of the inner membrane. The relative contribution of each site to total $O_2^{\bullet-}$ varies from tissue to tissue and depends on respiration state of the mitochondria. In heart mitochondria, complex III appears to be most responsible for $O_2^{\bullet-}$ formation [37]. When mitochondria are functioning normally, ROS production is low. Although a physiological amount of ROS are produced for oxidant-sensitive cell signaling, these ROS are balanced by both mitochondrial and cytosolic scavenging systems to prevent oxidative damage. The matrix contains a specific form of superoxide dismutase (SOD) with manganese in the active site (MnSOD, or SOD2) [38]. SOD2 dismutates $O_2^{\bullet-}$ into hydrogen peroxide (H_2O_2), which is catalyzed to water and molecular oxygen by catalase, a major detoxifying enzyme present in heart mitochondria [39]. In addition to these enzymes, other enzymes including glutathione peroxidases, as well as non-enzymatic molecules like vitamins C and E, help to attenuate excess ROS production. However, if ROS production exceeds the ability to remove them, oxidant damage occurs in the form of lipid peroxidation (including oxidation of both inner and outer membranes, and cardiolipin), mitochondrial protein oxidation, and oxidant damage to mtDNA.

In addition to damaging macromolecules, excess ROS can trigger apoptosis. The observation that mitochondria trigger cardiomyocyte apoptosis was first described in 1999 [40]. This study demonstrated that when cardiomyocytes are exposed to hydrogen peroxide, Bad, a pro-apoptotic family member of Bcl-2 family, translocates to the mitochondria, resulting in the release of cytochrome c into cytoplasm which leads to the activation of caspase 3 and programmed cell death. Furthermore, both pro-apoptotic proteins Bax and Bak co-localize with Mfn2 on the outer mitochondrial membrane [41]. Drp1 is also recruited by Bax in response to apoptotic stimuli, and colocalizes with Bax at the outer mitochondrial membrane [41]. Conversely, OPA1 is strongly anti-apoptotic by preventing cytochrome c release independent from modulation of fusion [42]. Taken together, these findings suggest that in addition to their roles as primary energy producers, the mitochondria are key contributors to redox homeostasis and regulation of programmed cell death, both of which contribute to healthy and pathological cardiac function.

While little is known regarding basal differences in ROS production, antioxidant defenses, and apoptotic signaling between the healthy LV and RV, two recent studies suggest differences may exist between the ventricles in healthy hearts and in response to cardiac stress. Schreckenber and colleagues [43] used a model of systemic nitric oxide (NO) depletion in rats by administration of the pharmacological nitric oxide synthase inhibitor L-NAME. They evaluated cardiac antioxidant capacity in response to L-NAME and in a control (untreated) group. Chronic NO deficiency is associated with oxidant stress, however it appears to do so in a ventricle-specific manner. Dihydroethidium staining, used to detect ROS, showed elevated free radical load in untreated RV control samples compared with the LV, as well as elevated peroxynitrite, both of which were further increased during L-NAME treatment. To identify mechanisms underlying the differential formation of ROS in the LV and RV, the authors examined expression of antioxidant enzymes and found that L-NAME treatment induced SOD2 expression in the LV by 51%, but depressed SOD2 by 30% in the RV. The authors concluded that while the LV increases SOD2 to compensate for increased oxidant load with NO deficiency, the RV does not. Importantly, these biochemical differences in redox status were correlated with changes in RV geometry and function indicative of cardiac dysfunction. A second small study of ischemia-reperfusion injury in a bi-ventricular isolated working heart preparation suggests that mechanisms of myocardial apoptosis also differ between the ventricles. While both ventricles saw similar upregulation of apoptosis in response to ischemia as assessed by cleaved caspase-3 expression, the RV downregulated anti-apoptotic regulator Bcl, while the LV did not [34]. Though this study was small, and performed no follow-up of additional apoptotic regulators or ROS signaling in the healthy heart, it does suggest that different mechanisms may underlie the ability of the two ventricles to regulate ROS production, antioxidant defenses, and apoptosis. Together, this work suggests that inherent differences between the ventricles with respect to these signaling pathways may be especially relevant in response to stresses which promote redox dys-homeostasis including ischemia, reperfusion, and hypoxia.

3. Cardiac remodeling and heart failure

In response to pathological stress, the heart remodels, resulting in changes in structure, shape, or physiology of the heart and its cellular components. While remodeling can occur

physiologically such as in response to exercise or pregnancy, pathophysiologic remodeling is a maladaptive process that occurs with stress such as myocardial infarction or hypertension (chronic pressure overload). Adaptations evidenced at the organ level can occur at the level of myocyte, as well as within other cardiac cell types including fibroblasts and endothelial cells. Typically, remodeling is not an acute event, but rather occurs as a continuum of changes both adaptive and maladaptive, first evidenced by ventricular hypertrophy, dysfunction and abnormalities in filling and contraction. In the continued face of stress and/or adverse signaling modalities the heart continues to remodel resulting in overt failure - the inability of the heart to supply sufficient circulation for the needs of the body. The response of the RV or LV to pathological stress is complex and is likely a cumulation of the nature, severity, and chronicity (acute versus chronic) of the insult. In addition, the timing of the insult (newborn, juvenile, adult, or aged) likely has a large impact on cardiac remodeling. Insults that are initiated early in life tend to be better tolerated than those in adulthood [44]. Though cardiac aging research and RV aging are understudied, the aged heart has been suggested to perform even poorer in response to pathological stress, an area which warrants future research efforts.

It should come as no surprise given the physiological differences between ventricles, that the ability to adapt to pathological load greatly varies between the left and right heart. While it is generally accepted that the RV is able to tolerate volume overload well [45], it poorly tolerates pressure overload (afterload). Experimentally, an increase in pulmonary artery pressure of 20 mmHg compared to a similar increase in systolic afterload resulted in a 30% decline in RV stroke volume, compared to only a 10% reduction in LV stroke volume [46]. Mechanistically, the thin wall of the RV along with reduced elastance is thought to reflect this poor tolerance for increases in afterload. This observation is clinically highly relevant, as patients with systemic hypertension compensate for the increased load for many years before diagnosis or treatment of cardiac disease, but patients with pulmonary hypertension (PH, which will be discussed in greater detail below), often rapidly progress to right heart failure.

3.1. Right heart failure

Right heart failure (RHF) is a syndrome reflecting the inability of the RV to fill or eject properly. Clinically, it manifests as fluid retention (peripheral edema) and decreased systolic reserve or cardiac output, which often presents as exercise intolerance [47]. In the case of RV geometry, the ventricle becomes more concentric, and the interventricular septum flattens. In humans, right heart failure is diagnosed through a combination of clinical findings, laboratory tests and imaging. Similarly, in larger animal models of RV failure (below), it can be measured by echocardiography, whereas in mouse models it is generally demonstrated by morphometric changes including RV/LV ratios and myocyte size.

3.2. Models of right heart failure

Understanding RV failure requires the use of animal models that are primarily or predominantly right-sided. Therefore, although the most common cause of RV failure in humans is left-sided heart failure, it is more helpful to study the RV in diseases and models in which it is primary. For reasons including methodological constraints, clinical relevance, and the

sensitivity of the RV to increased afterload (compared to the insensitivity of the RV to volume overload), most groups use models of RV pressure overload. However, we should mention that other causes of RV failure include valvular insufficiency, congenital disease including tetralogy of fallot, pulmonary atresia, truncus arteriosus, and hypoplastic left heart syndrome, RV ischemia/infarct, and amyloid and sarcoid [44]. Below, we'll briefly overview common animal models of RV failure and how they recapitulate human disease, which are summarized in **Table 1**.

Pulmonary artery banding (PAB) involves surgical constriction of the pulmonary artery, in a manner equivalent to the commonly used transaortic constriction (TAC) model of LV pressure overload. Administration of a band around the pulmonary artery results in pulmonary constriction, increased afterload, RV hypertrophy, and eventually failure. While similar methodologically and conceptually to TAC, an RNA-seq experiment comparing the RV and LV in isolated TAC or PAB suggests that the two ventricles do not respond in an entirely similar manner [48]. Of the nearly 3600 genes identified, only 192 were commonly expressed in both ventricles, 565 were unique to the RV, and 327 were unique to the LV. Canonical pathway enrichment only revealed oxidative phosphorylation as similar between the two ventricles [48]. Therefore, despite being methodologically and conceptually equivalent models of isolated pressure overload, TAC and PAB do not elicit identical molecular signatures, again suggesting that important differences between the ventricles may explain disease trajectory and prognosis.

A more clinically relevant model of RV afterload is pulmonary hypertension (PH). The World Health Organization classifies five distinct groups of PH based on etiology, prognosis, and therapy. However, they're all linked by an increase in mean pulmonary artery pressure of >25 mmHg at rest [49]. The increased pulmonary pressures cause pressure overload in the RV, isolated RV

Human RHF	Experimental RHF
LV failure	Pulmonary artery banding (PAB)
Pulmonary hypertension	Pulmonary hypertension: chronic hypoxia, MCT, SuHx, BMP2R
Congenital disease: hypoplastic left heart syndrome, tetralogy of fallot, pulmonary atresia	Not available
Amyloid sarcoid	Microbial infection, genetic knockout
RV Ischemia/infarct	Right coronary ligation (sheep)
Valvular disease	Not available

Legend: LV failure is the most common cause of RHF in humans. Pulmonary hypertension is a heterogenous disease, classified into five groups by the World Health Organization, but generally refers to an increase in pulmonary arterial pressure, causing increased RV afterload. Congenital diseases, amyloid, sarcoid, RV ischemia and infarct, and valvular disease (tricuspid, pulmonic) also contribute to RHF. In experimental RHF, pulmonary artery banding/constriction causes an isolated increased RV afterload, similar to transaortic banding in left heart failure. Animal models of PH (rats, mice, cows) are also frequently used to cause predominant RHF. MCT: monocrotaline, SuHx: Sugen hypoxia, BMP2R: bone morphogenetic peptide receptor models (BMP2R plays a critical role in the pathogenesis of familiar idiopathic PH).

Table 1. Selected causes of clinical right heart failure (RHF) and the corresponding experimental model.

hypertrophy, dysfunction, and eventual failure. PH can be modeled in animals by different approaches including chronic exposure to hypoxia, pharmaceuticals which accelerate pulmonary dysfunction, or their combination. Here, we will briefly discuss the most common laboratory approaches to PH, but refer readers to an extensive review of animal models of PH [50].

Exposure to chronic hypoxia while causing systemic reduction in oxygen supply, selectively induces pressure overload on the RV. Animal models of chronic hypoxia are often driven by normobaric hypoxia, accomplished by nitrogen replacement to reduce partial pressure of oxygen, or by hypobaric hypoxia (simulated ~14,000–17,000 feet), reducing overall atmospheric pressure and thus reducing oxygen partial pressure in the inhaled air. Animal models of hypoxia-driven PH have been used at least since the early 1960s [51] and can be used to elicit predictable and reproducible PH within many animal strains. However, there are some unique differences between species worth noting. Bovine models produce robust responses to simulated altitude and hypoxia, and were among the most common model used in early research [52]. Neonatal calves exposed to chronic hypobaric hypoxia develop severe PH with striking remodeling of the pulmonary vasculature [52]. Rodent models of hypoxia are also common in the literature, with certain strains of rats developing more severe PH, and mice developing the least severe perivascular remodeling [50].

In addition to hypoxia exposure, other models of PH include monocrotaline (MCT) injection, a pyrrolizidine alkaloid oxidized in the liver to a bioactive molecule which selectively injures the lung vascular endothelium, causing PH [53]. MCT as a model of PH has been in use for almost 50 years, and can be produced by a single subcutaneous or intraperitoneal injection of the drug. Within hours of injection, pulmonary damage occurs, by 2 weeks PVR has increased, and by 3 weeks, increased RV mass is often reported [54]. Some reports also describe liver and kidney damage [55], as well as myocarditis of both the RV and LV [56], limiting the use of MCT to study isolated RV hypertrophy and failure. A relatively recent model to the PH literature is a model of severe PH that combines chronic hypoxia plus a pharmaceutical vascular endothelial growth factor (VEGF) receptor inhibitor. This model, coined the Sugen hypoxia (SuHx) model after the VEGF receptor inhibitor Sugen 5416, has been modified for both mice and rats, and is characterized by persistent pulmonary vasculature disease and right heart failure [57]. Alternative animal models of PH worth mentioning include bleomycin injury and single gene mutations. Bleomycin, an antibiotic, is a common model for pulmonary fibrosis in mice. A single intratracheal dose results in PH after 2–5 weeks, a doubling of right ventricular systolic pressure, and a drop in cardiac output [58]. Lastly, several human mutations have been linked to elevated pulmonary pressures and PH, with the bulk of experimental PH studies using models with mutations of bone morphogenetic protein receptor type II [59].

4. Molecular mechanisms of left heart failure

All cell types within the heart respond to stress, including in response to chronic pressure overload [60]. However, the majority of research has focused on changes within the myocytes as they are the primary cell type responsible for contraction and heart failure is a disease of impaired cardiac function. The hallmark molecular change of myocyte remodeling is hypertrophy. In

response to pathological load such as pressure overload, myocyte size increases via synthesis of new sarcomeres. Myocytes also reactivate a fetal program of gene expression, now often referred to as the hypertrophic gene program [61]. While initially characterized in the failing left heart, the fetal (hypertrophic) gene program has now been shown to also occur in RV failure [62]. While believed to be compensatory at first, over time this is maladaptive, and likely contributes to the energy deficit of the failing heart.

4.1. Metabolic remodeling and mitochondrial dysfunction in left heart failure

Mitochondrial and metabolic abnormalities are well-established in left-sided HF. Since this topic will be more extensively covered elsewhere, we will just briefly discuss mitochondrial dysfunction and the metabolic switch in the failing left heart. Considerable evidence exists for an energetic deficit in HF, both in pre-clinical animal models of disease, and in studies from explanted human hearts (reviewed in [4]). One of the hallmarks of the hypertrophied or failing heart is a metabolic switch [63]. As the heart remodels, it undergoes a switch from fatty acid oxidation (FAO) to glycolytic carbohydrate metabolism. Although it is still a matter of debate whether this switch is causal, associative or compensatory, it is clear that the energy starved heart no longer produces the majority of its ATP from lipid sources. It has been suggested that this switch is designed to allow more efficient energy production with respect to oxygen since under states of low oxygen availability carbohydrate metabolism produces more ATP per mole of oxygen [64].

Due to their primary role as ATP generators, mitochondrial dysfunction has been mechanistically linked to the energy starved failing heart. Mitochondrial dysfunction is well described in the failing LV across many different pre-clinical models including guinea pigs [65], rats [66], rabbits [67], and dogs [68] with dilated, ischemic, and diabetic heart failure. Similarly, decreased respiration and respiratory control ratios, associated with an overall loss of oxidative capacity [69], have been observed in human explanted hearts from patients with ischemic and dilated cardiomyopathy. In addition to depressed oxidative phosphorylation, mitochondrial biogenic signaling is depressed in HF, with PGC-1 α downregulated in different models of HF [70, 71]. Together, substantial data links mitochondrial respiratory deficits with the failing LV and suggests interventions aimed at preservation of mitochondrial function may have therapeutic potential. Observations of changes in the shape of mitochondria in HF spurred the idea that the major proteins regulating mitochondrial dynamic could be causally involved in development of the disease [72–74].

As discussed above, ROS production in the healthy heart is countered by enzymatic and non-enzymatic scavenging of ROS to prevent cellular damage. However, increased ROS and oxidant stress have been reported in many types have cardiovascular disease, including early in the development of pressure overload-induced left HF [75]. In addition to damaging cellular macromolecules, increased ROS can activate several cell-signaling processes including apoptosis and opening of the mitochondrial transition pore (mPTP) which are known to correlate with adverse health outcomes. Opening of this pore is associated with oxidant stress and mitochondrial dysfunction, and increased opening is observed in HF [75]. Although apoptosis of cardiomyocytes is rare in the healthy heart, it is well-established that apoptosis increases

in human HF [76]. As adult cardiac myocytes have limited regenerative capacity, the loss of these cells is often counteracted by replacement with non-myocytes, promoting fibrosis and cardiac dysfunction.

5. Molecular mechanisms of right heart failure

The bulk of the research thus far in the field of RV failure and mitochondrial function has focused on PH-associated changes within the pulmonary vasculature (pulmonary artery smooth muscle cells, endothelial cells, and fibroblasts [77]) and metabolic changes that underlie activated inflammatory cells (reviewed in [78, 79]). In addition, a systemic metabolic and mitochondrial hypothesis has been put forward, based on similar changes in mitochondrial function observed in skeletal muscle in models of PH [80]. However, a few RV-specific investigations of changes in metabolism and mitochondrial function exist, and we'll review this evidence below.

5.1. Metabolic remodeling in right heart failure

Although the data are less extensive than in the LV, the metabolic switch that occurs during LV hypertrophy and dysfunction also occurs in models of RV dysfunction [81, 82]. Several groups have reported upregulated glycolysis with suppression of FAO, and associated global changes in gene expression favoring glucose oxidation and downregulation of PPAR α target genes [62]. Mechanistically, pyruvate dehydrogenase kinase (PDK) has been linked to the metabolic switch. PDK, an inhibitor of pyruvate dehydrogenase, is upregulated in RV hypertrophy. This PDK-mediated metabolic switch is associated with decreased RV myocyte contractility and cardiac output [81]. The shift to aerobic glycolysis has several consequences for the heart. First, greater amounts of lactate are produced, shifting redox status and other homeostatic outcomes, and second, fewer ATP molecules/glucose molecule are produced (32 during glucose oxidation, and 2 during glycolysis). To compensate for increased glycolysis, glucose uptake is accelerated, and can be assessed by positron emission tomography, both in experimental PH and RV dysfunction [83, 84], and in patients with pulmonary arterial hypertension [85].

As in left heart failure, researchers have attempted to explain the metabolic switch based on energy production relative to oxygen availability. The pressure overloaded RV is oxygen deprived. In the setting of an oxygen limited hypertrophic RV, energy production which favors a high ATP/O₂ ratio would benefit the working heart, and FAO uses 12% more oxygen than glucose oxidation to generate the same amount of ATP [86]. Some experimental data support this hypothesis, with reports of systolic perfusion gradients limiting coronary artery flow [87], coupled with increased metabolic demands in the hypertrophied heart, which result in a localized RV ischemia. However, the question of oxygen supply in RV hypertrophy is insufficiently answered. While it may be true that angiogenic potential in the failing RV is attenuated, resulting in ischemia [88], methodological difficulties have precluded accurate assessment of RV oxygen supply. Further, other groups have argued that reliance on carbohydrate metabolism

predisposes the hypertrophied myocardium to contractile dysfunction, and maintaining the inherent metabolic profile of fatty acid fuel preference may be a more beneficial approach [89].

5.2. Mitochondrial dysfunction in right heart failure

Similar to the LV, mitochondrial dysfunction is also implicated in RHF, albeit with less literature supporting the mechanistic link, and more conflicting reports depending on the model. MCT and SuHx models of RHF tend to demonstrate more severe mitochondrial dysfunction and depression of mitochondrial biogenesis. Decreased PGC-1 α expression and a net loss of mitochondrial protein and oxidative capacity have been reported in SuHx rats, alongside abnormal mitochondrial shape and size by electron microscopy [90]. On the other hand, changes in mitochondrial function in chronic hypoxia models have been particularly discordant and warrant further discussion. Chronic hypoxia decreased ATP synthesis and measurements of mitochondrial number in a rat model of chronic hypoxia in both ventricles, however, the effect was slightly delayed in the right compared to LV [91]. Data from our lab in the neonatal calf model of PH-induced RV dysfunction also demonstrated similar changes to mitochondrial function in both ventricles, with no additional impact of pressure overload on the RV [92]. In these models of PH and RV dysfunction, the hypoxic stimulus is administered systemically using a hypobaric chamber. Thus, the LV experiences similar degrees of hypoxia as the RV, yet does not show signs of contractile or relaxation deficits until much later in disease progression. It's possible that interventricular differences in oxygen supply and demand explain the similar findings in both ventricles, and support the need for better mechanistic understanding of the similarities and differences in oxygen delivery and metabolism in the RV exposed to pathological load.

Mitochondrial dynamics are not well-described in the failing right heart. However, in a study by Marsboom et al., administration of the Drp1 inhibitor Mdivi-1 regressed PH in rodents by arresting proliferation of pulmonary artery smooth muscle cells, resulting in improved exercise capacity and RV function. Therefore, while not described in the RV, modulation of mitochondrial dynamics may be therapeutically viable for right heart failure [93]. Even less has been described on the role of mitophagy in the setting of right heart failure. However, one group has attempted to elucidate the impact of autophagy on remodeling following PAB. p62 and LC3 II/I were both increased in the hypertrophied RV [94]. These data support similar findings in MCT-induced RV dysfunction, with increased autophagy signaling and autophagosome formation by EM [95]. Expression of these markers temporally increased post MCT injection, which the authors suggest indicates a causal role for autophagy during the progression from hypertrophy to failure. Future work is needed to elucidate the changes that occur with mitochondrial dynamics and mitophagy in the failing right heart, and future investigations should test myocyte-specific deletion of Mfn1, Mfn2, and Drp1 in experimental RV failure.

Our understanding of mitochondrial abnormalities in human RV failure is equally as understudied. Although availability of human samples is methodologically limiting, the use of pediatric congenital heart explants has shed some light on changes which underlie human RHF. One study of RV samples obtained from 31 pediatric patients undergoing cardiac surgery for congenital heart disease classified patients based on compensated RV function or failure based on echocardiography, right heart catheterization and MRI. Citrate synthase activity was maintained

during hypertrophy, but decreased at failure, while mtDNA content progressively decreased with worsening clinical disease [96]. In addition, adult RV samples of various etiologies demonstrate increased mitochondrial membrane potential which positively correlates with the degree of hypertrophy [97]. A complete understanding of mitochondrial function in human right heart failure is limited by methodological constraints of assessing comprehensive ETC function.

5.3. Non-energy producing mitochondrial mechanisms of right heart failure

Studies of non-energy producing roles of mitochondria are in their infancy in the RV. However, some evidence supports a causative role of ROS, as increased lipid peroxidation is observed in the RV 6 weeks following MCT injection [98]. NADPH oxidase is significant source of ROS in LV hypertrophy, and its expression increases during MCT-induced RV hypertrophy alongside decreased SOD1 and SOD2 expression [99]. Increased expression of pro-apoptotic proteins Bax and capase-3 have also been noted in the RV after PAB, with concomitant increased RV myocyte cell death [100]. Together, the limited investigations of the metabolic and non-metabolic roles of mitochondria in right heart failure highlight the need for additional work to elucidate similarly and differentially regulated pathways in left and right HF.

6. Therapeutic intervention

To date, no RV-directed therapies exist. Right-sided heart failure is typically treated with the goal of improving LV function or lowering pulmonary pressures. Extrapolation of LV pathophysiology and pharmacology to the failing RV has not yet proven fruitful, and in some cases, has accelerated disease progression [101]. Interestingly, lowering of pulmonary pressures (either by pharmaceutical approaches or by lung transplant) does not consistently improve RV function [102], suggesting a cardiac-specific irreversible effect of long-term pressure overload, or contribution of circulating systemic factors. Whatever the reason for insufficient return of RV function despite reduction in afterload, we and others believe that identification of new, or repurposing of old therapies requires an RV-centric approach.

6.1. Metabolic therapeutic interventions

Enhancing glucose oxidation at the expense of FAO as emerged as a therapeutic strategy in RV dysfunction, based on the reciprocal relationship between these two energy sources. In large part, enhancing glucose oxidation has gained attention as a strategy because of the higher ATP production per oxygen molecule provided by carbohydrate compared to lipid sources. Partial inhibitors of FAO are approved for a few human cardiovascular indications including refractory ischemia [103]. These drugs (trimetazidine) have also been experimentally tested in RV dysfunction [86]. Rats with PAB-induced RV dysfunction treated with partial FAO inhibitors had elevated RV glucose oxidation alongside increased exercise capacity and cardiac output. The beneficial effect of this drug has also been demonstrated in MCT-induced RV dysfunction, where trimetazidine enhanced cardiac mitochondrial function and increased oxygen consumption while reducing ROS formation [104].

The metabolic switch that occurs in the hypertrophied RV is suggested to be mediated in part through PDK4 [81]. Dichloroacetate (DCA), a small molecule inhibitor of pyruvate dehydrogenase, improves glucose oxidation and has reported improvements in RV stroke volume, cardiac output, and exercise capacity [81, 105]. It is also associated with restoration of RV mitochondrial function and mitochondrial-dependent apoptosis [106]. Though a Phase I clinical trial has been completed in subjects with advanced PH (Clinical Trial Identifier NCT01083524), study results have not been published, and the therapeutic potential of DCA in human RV failure remains unknown. As discussed above, the therapeutic strategy of FAO and improved glucose oxidation lacks consensus [89], and in part is predicated on the balance between ATP production and oxygen availability. While continued efforts to test metabolic mediators in RHF are warranted, a mechanistic understanding of energy production, relative RV ischemia, and the molecular regulators of these processes are necessary for development of targeted metabolic therapy.

6.2. Mitochondrial therapeutic interventions

The causal role of ROS in cardiac dysfunction led to the early belief that antioxidants would attenuate cardiovascular disease. In experimental models, treatments with antioxidants have somewhat inconsistently tended to improve cardiac function [107]. However, clinical trials have largely failed to show benefit of antioxidants in treatment of chronic disease [108]. In light of these disappointing results, many groups have taken fundamentally different approaches to improving redox status. Induction of endogenous antioxidants by a phytochemical supplement preserved RV function and prevented RV fibrosis and capillary loss [109], suggesting activation of cytoprotective transcription factors may more robustly attenuate oxidant stress than traditional vitamin supplements. Other groups use mitochondrially-directed peptides to scavenge free radicals. One such peptide, SS31, accumulates more than 1000-fold in mitochondria [110]. This peptide prevented LV hypertrophy, fibrosis, and diastolic dysfunction [111], and reduced mitochondrial oxidant damage [112]. To date, however, targeted mitochondrial peptides have not been tested in models of RV failure.

Interventions which boost mitochondrial function and/or biogenesis have large therapeutic potential in many types of cardiovascular disease, including RV failure. Phytochemical compounds which elicit mitochondrial biogenic properties have received attention lately, such as resveratrol. Resveratrol, the primary polyphenol in red wine, stimulates mitochondrial content, ATP production, and FAO, while inhibiting mitochondrial ROS production in several tissue types and disease contexts [113, 114]. In addition, it is currently in testing as a therapy for chronic obstructive pulmonary disorder (NCT02245932) and non-ischemic heart failure (NCT01914081). Identification of other plant-based or pharmaceutical approaches which stimulate the synthesis of new mitochondria to increase energy production while decreasing oxidant damage may have profound impact on the failing right heart.

6.3. Exercise as right heart therapy

Exercise-induced cardiac hypertrophy has been known to be cardioprotective for decades [115], though the exact mechanisms underlying physiological hypertrophy have remained somewhat

elusive. RV-specific adaptations to exercise, however, have lagged, in large part due to clinical concerns. Even in healthy individuals with normal pulmonary vascular function, the hemodynamic load on the RV increases with a relatively greater proportion during exercise than LV hemodynamic load. This disproportionate increase in load is accentuated in patients with PH. Exercise-induced increases in pulmonary artery pressures may exceed RV contractile reserve, resulting in attenuated cardiac output and exercise intolerance. Thus only recently have clinical and pre-clinical studies begun looking at the cardioprotective role of exercise specifically on the RV.

The primary goal of most of the recent studies of exercise in PH patients was to evaluate safety of low-level exercise training and changes in systolic pulmonary artery pressure. A recent meta-analysis assessing safety outcomes in low intensity aerobic exercise in the form of walking, cycling, and light resistance training found improvement of non-invasive measurements of cardiac performance and exercise capacity, as well as improvement of PH functional class and quality of life [116]. Preclinical studies in rodents with MCT-induced PH also support the benefit of aerobic exercise training. Several animal studies show improvement of mean pulmonary arterial pressure, measured by right heart catheterization following 3–5 weeks of exercise training consisting of 30–60 min of 50–60% maximal aerobic capacity [117]. Subsequent work to investigate the timing of exercise for therapeutic benefit in experimental PH induced by MCT found that exercise initiated early, before MCT injection, was markedly more successful at improving disease outcomes such as survival, diastolic RV function, cardiac output and exercise tolerance, although some benefit was also observed in the cohort who began exercise training 2 weeks after MCT injection [118].

Though exercise stimulates a multitude of cardioprotective mechanisms, endurance exercise is a well-known stimulator of mitochondrial biogenesis, first reported by measuring mitochondrial mass in the myocardium in 1967 [119]. Subsequent mechanistic studies have shown lower mPTP opening rates and apoptosis resistance in endurance trained animals [120], decreased mitochondrial ROS production in exercise trained rats [121], and increased oxidative capacity and mitochondrial volume [122], and increased mitochondrial biogenesis [123]. To our knowledge, no groups have investigated these mechanisms in RV failure and exercise, and virtually nothing is known about the molecular adaptations within the RV that occur in response to exercise therapy.

7. Conclusions and future investigations

Understanding of RV metabolism and mitochondrial function has lagged that of the left heart, and arguably even less is known about how RV mitochondria adapt to pathological stress. What little is known about the role of mitochondrial function and metabolism in the dysfunctional or failing RV (summarized in **Table 2**) has largely been extrapolated from studies of LV dysfunction, and there is a large need for more mechanistic studies of the failing RV to more successfully target therapies. In addition to a need for both pre-clinical and clinical investigations of the right heart, a reductionist approach may be needed to make significant strides in RV therapy. The heart (and the RV) is comprised of multiple different cell types. Due to the fact that cardiac myocytes are the work horses of the heart, heart failure studies have historically been myocyte-centric. However, emerging data from our group and others suggests that

Mitochondrial phenotype	Regulators/assessment	LV failure	RV failure
Content: % of cell occupied by mitochondria	mt/nDNA, EM, citrate synthase activity	↓ [68, 71, 77]	↓ [98, 99, 104]
Function: electron transport chain activity	Complex I-V activity respiration (Ouroboros, Seahorse)	↓ [68–75]	NC [98–100, 112]
Fusion: elongation of mitochondrial network	Mfn1, Mfn2, OPA1 mitochondrial volume	↓ [21, 68]	NC [99, 100]
Fission: fragmentation of mitochondrial network	Fis1, Drp1 mitochondrial size	↑ [21, 79]	↑ [99–101]
Biogenesis: turnover and synthesis of new mitochondria	PGC-1 α , NRF1, TFAM mitochondrial protein synthesis	↓ [76, 77]	NC [98, 104]
Mitophagy: removal of damaged mitochondria	LC3 II/I, Pink/Parkin, EM	NC [28, 80, 81]	NC [102, 103]
Apoptosis	Pro: Bax, caspase 3 Anti: Bcl-2	↑ [34, 69, 70, 84]	↑ [34, 108, 114]
ROS and oxidant damage	Protein, lipid, DNA oxidation, ROS production (O ₂ ^{•-} , H ₂ O ₂)	↑ [68–70, 74, 82]	↑ [106, 107]
Antioxidant defenses	Antioxidant enzyme expression (SOD2, catalase) and non-enzymatic antioxidants	↓ [68]	↓ [43, 106, 117]

Legend: Mitochondrial alterations in left and right heart failure. Assessment of mitochondrial content, function, dynamics, biogenesis, quality control, and non-energy production roles of mitochondria and changes in HF are summarized. Arrows indicate directional change with heart failure. NC: no consensus.

Table 2. Mitochondrial changes in left and right HF.

other cell types within the heart and within the dysfunctional RV may be causally involved in disease progression. Specifically, the cardiac fibroblast is emerging as a vital cell type in regulating cardiac function and pathophysiology [124]. Not only do these cells primarily regulate the extracellular matrix (and thus fibrosis, electrical remodeling, and inflammation), but it is becoming increasingly apparent that they communicate with other cell types such as myocytes to regulate cardiac function. Virtually nothing is known about RV fibroblast mitochondrial metabolism or biology, or how these cell types respond to cardiac stress. In conclusion, the RV is not a thinner, lower pressure LV. Significant physiological and pathophysiological differences separate the two ventricles, and RV-centric approaches are necessary for the identification, repurposing, or development of therapies for RHF.

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