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Emerging role of angiogenesis in adaptive and maladaptive right ventricular remodeling in pulmonary hypertension

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Abstract

Right ventricular (RV) function is the primary prognostic factor for both morbidity and mortality in pulmonary hypertension (PH). RV hypertrophy is initially an adaptive physiological response to increased overload; however, with persistent and/or progressive afterload increase, this response frequently transitions to more pathological maladaptive remodeling. The mechanisms and disease processes underlying this transition are mostly unknown. Angiogenesis has recently emerged as a major modifier of RV adaptation in the setting of pressure overload. A novel paradigm has emerged that suggests that angiogenesis and angiogenic signaling are required for RV adaptation to afterload increases and that

, we summarize our current understanding of the concepts of maladaptive and adaptive RV remodeling, discuss the current literature on angiogenesis in the adapted and failing RV, and identify potential therapeutic approaches targeting angiogenesis in RV failure.

INTRODUCTION

Pulmonary hypertension (PH) is a chronic and progressive disease of the lung vasculature and right heart that is characterized by pulmonary artery (PA) vasoconstriction and remodeling, resulting in increased afterload on the right ventricle (RV) (68, 160, 175, 176). Many common cardiopulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, sleep disordered breathing, and left heart disease (systolic or diastolic dysfunction as well as valvular heart disease) are complicated by PH and/or RV failure (68, 98, 99, 137, 166). Approximately 70 million patients with these conditions in the US

alone are estimated to have PH (27, 71, 95, 102, 103, 128). These patients either have overt RV dysfunction or are at a major risk for developing this condition. In addition, 3.8% of patients with pulmonary embolism develop chronic thromboembolic PH and are therefore at major risk for developing RV failure (121). Last, pulmonary arterial hypertension (PAH), one of the most aggressive types of PH and a condition that arises spontaneously, hereditarily or as a complication of such frequent entities as liver cirrhosis, HIV infection, congenital heart disease, and drug and toxin use, commonly leads to profound and refractory RV failure (148).

Abnormal angiogenic processes in the lung have been recognized as a critical player in PH etiology (123, 184). More recently, the vasculature of the RV has emerged as a critical modulator of RV adaptation to the increased afterload in PH. The objective of this review is to highlight the role of angiogenesis in RV failure. In particular, we *1*) briefly introduce the concepts of adaptive and maladaptive remodeling in the RV, *2*) discuss our current understanding of angiogenesis in the adapted and failing RV, and *3*) identify potential therapeutic approaches targeting angiogenesis in RV failure.

THE CRITICAL ROLE OF RV FUNCTION IN PATIENTS WITH PH

The RV initially compensates for the PH-induced increase in afterload through hypertrophy and increased contractile function (125, 176). However, as PH continues to worsen, the RV's compensatory mechanisms fail, leading to RV failure and death (175, 176). Consequentially, in many different types of PH, deteriorating RV function is one of the strongest predictors of mortality (11, 35, 54, 70, 130, 169). RV-directed therapies would strengthen the ability of the RV to adapt to the increased afterload, would inhibit maladaptive responses, and would be predicted to improve the functional capacity, quality of life, and longevity of patients with PH (133, 175). However, despite the critical importance of RV function to outcomes in PH, no RV-directed therapies exist. For example, in PAH, current therapies predominantly focus on the pulmonary artery (PA) vasoconstriction component of the disease, indicating a significant treatment gap (17, 45, 90, 152). Furthermore, in PH due to chronic left heart or lung disease, pulmonary vasodilators have been used to decrease RV afterload; however, their use is associated with worse outcomes, such as fluid retention, worsening ventilation-perfusion mismatch, and even death (137, 166). Last, therapies developed for the failing left ventricle (LV) cannot be extrapolated to the RV due to their embryological and anatomic differences (51). This indicates a critical need to develop better therapeutic strategies for patients with PH-induced RV failure.

THE CONCEPT OF ADAPTIVE VS. MALADAPTIVE RV REMODELING

To understand the role of the macro- and microvasculature in the failing RV, it is important to understand how the RV responds to increases in afterload. The specific mechanisms of RV failure development have been elegantly discussed in detail elsewhere (133, 174, 175) and are beyond the scope of this review. Briefly, as RV afterload increases during the development of PH, the RV exhibits compensatory mechanisms that include structural changes, neurohormonal activation, and increased contractility (133, 175) (Fig. 1). On a cellular level, these changes are accompanied by increased angiogenesis, changes in mitochondrial function and substrate utilization, increased production of reactive oxygen species, changes in myosin isoform expression, and altered sarcomere organization (133). These mechanisms allow for a state of adaptive (or compensated) RV hypertrophy (RVH), characterized by a cardiac output that is still sufficient to meet the metabolic demands of the body (175, 176). However, once the RV's compensatory mechanisms are exhausted, the RV will transition from adaptive to maladaptive (or decompensated) RVH, and RV failure with decreased cardiac output and decreased oxygen delivery develops (175, 176) (Fig. 1). At cellular and molecular levels, maladaptive RVH purportedly is characterized by marked inflammation, oxidative stress, metabolic dysfunction, and impaired calcium handling, with an end result of cell death and profound fibrosis (12, 174, 175). There currently is an unmet need in PH to prevent, delay, or reverse the

transition from adaptive to maladaptive RVH (133, 174–176). Impaired angiogenesis may be one of the key processes leading to RV decompensation, and modulating angiogenic signaling may be a novel approach to maintain, prolong, or even reestablish adaptive RVH (14, 124). In the remainder of this review, we will *1*) provide a brief overview of angiogenesis, *2*) identify potential novel modulators of angiogenic signaling in the RV, and *3*) discuss the pros and cons of angiogenic signaling as a target in RV failure.

OVERVIEW OF ANGIOGENESIS

To better understand the regulation of angiogenesis in the RV, it is important to understand key concepts of this process. Angiogenesis initiates and directs the proper formation of new, functional blood vessels from existing vessels. It is important to note that angiogenesis is distinct from vasculogenesis; the latter is the de novo formation of vessels through recruitment of circulating hemangioblasts or endothelial progenitor cells (reviewed in Refs. 24, 53, 118, 129). In adult systems, angiogenesis is thought to be the driving mechanism for vessel repair and regeneration. Angiogenesis occurs through two processes: *1*) intussusceptive microvascular growth, where new vessels are formed through the splitting of preexisting vessels or *2*) sprouting angiogenesis, which consists of endothelial cell (EC) migration, proliferation and tube formation (53). Of these two angiogenic processes, sprouting angiogenesis is the best characterized. Sprouting angiogenesis primarily utilizes two distinct vascular EC phenotypes: tip cells and stalk cells. The tip cell extends, or “sprouts” filopodia and migrates toward a hypoxic or ischemic area. Tip cells induce the migration of the stalk cells into the newly forming vessel branch. Stalk cells are highly proliferative and primarily form the new vessel and lumen. During vessel maturation, excess vessels are pruned in a process known as vessel regression (9, 24, 141). Each vascular endothelial cell (EC) is intrinsically capable of becoming a tip or stalk cell, or to remain as a quiescent EC, or phalanx cell, in the stable vessel (9). Individual ECs actively rotate between each phenotype through rapid induction and repression of a distinct transcriptome (41, 150). This active shuffling between phenotypes involves rapid integration of extracellular pro- and antiangiogenic chemotactic cues from surrounding tissues as well as neighboring vascular ECs (9). The vascular endothelial growth factor (VEGF) family is important for the induction of both cell phenotypes. Not only does VEGF drive tip cell phenotype and migration, it also regulates stalk cell proliferation (10). The ratio of tip cells to stalk cells is crucial for proper formation of new vessels and is tightly regulated by integration of several pathways, including ephrin, notch, bone morphogenetic protein (BMP), Wnt, and VEGF signaling (24, 74). These mechanisms are discussed in greater detail elsewhere (8–10, 24, 112).

When the dynamic regulation of angiogenesis is disrupted or hijacked, it can become a contributing factor to pathogenic processes (24). For example, multiple cancers exploit angiogenic pathways to supply oxygen and nutrients to tumors, driving their growth and fueling inflammatory responses (23, 63, 104). In addition, angiogenesis is relevant to many noncancerous conditions. For example, impaired and/or inappropriate angiogenesis has been linked to multiple cardiovascular diseases such as peripheral vascular disease (33), coronary artery disease (171), and diabetic retinopathy (2, 36).

POTENTIAL RELATIONSHIP BETWEEN THE CARDIAC VASCULATURE AND THE TRANSITION FROM ADAPTIVE TO MALADAPTIVE RVH

Macrovascular Dysfunction in PH

Increased RV afterload results in increased RV wall tension, a process associated with compromised coronary perfusion. This was shown by van Wolferen et al., (170) who demonstrated in patients with PAH that perfusion of the right coronary artery (RCA) was markedly decreased in diastole, whereas this was maintained in control patients. Moreover, increases in RV systolic pressure correlated inversely with decreases in systolic-to-diastolic flow ratio in the RCA. A recent study by Melonche et al. (101)

demonstrated that coronary artery remodeling in human and experimental models of PAH was associated with increased RV DNA damage, inflammation, and bromodomain protein-4 (BRD4) overexpression. These data suggest that coronary artery remodeling and flow impairment contribute to a decrease in RV perfusion and clinically relevant mascrovascular impairment in PAH. This phenomenon is likely exacerbated by increased myocardial oxygen demand as a result of increased RV workload.

Microvascular Dysfunction in PH

In addition to RV macrovascular impairment, evidence exists that microvascular alterations occur in the RV as well. Increased RV afterload leads to increased cardiac workload and cardiomyocyte hypertrophy (175, 176). We know from studies of the LV that adequate angiogenesis is critical to maintaining substrate delivery to the hypertrophied myocardium (112, 178). In addition, the endothelium serves as a paracrine "machine" that regulates the function of the surrounding myocardium (108, 175). Capillary dropout and microvascular ischemia therefore have long been postulated to be critical contributors to RV failure development (174). Indeed, analysis of two-dimensional sections in PH models associated with RV failure demonstrates reduced RV vascular density, and this has been identified as a critical mediator of the transition from adaptive to maladaptive RVH (14, 43, 117, 122, 124). Collectively, these studies (summarized in Tables 1 and 2) suggest that the RV microvasculature in PH is dysfunctional and rarefied, rendering it unable to meet the increased substrate demand of the hypertrophied myocardium, thus resulting in clinically relevant RV ischemia (59). A similar paradigm has been proposed in LV failure (112, 147, 178). However, a recent analysis of human RV tissue by a stereological approach noted an increase in total vascular length in PH RVs vs. controls (61). It should be noted, however, that clinical background information about the donor patients was limited. These studies demonstrate that, while there undoubtedly has been progress in the field, controversies exist, and the mechanisms responsible for RV vascular rarefaction and microvascular ischemia remain incompletely understood. The following section reviews the currently known mechanisms and modifiers of angiogenesis in adaptive and maladaptive RV remodeling in more detail.

MECHANISMS AND MODIFIERS OF MICROVASCULAR FUNCTION IN ADAPTIVE AND MALADAPTIVE RV REMODELING

Here, we describe our current understanding of angiogenesis in adaptive and maladaptive RV remodeling. As in the LV, it has been speculated (though not definitively shown) that RV adaptive responses are induced or mediated through increased angiogenesis and that transition to maladaptive remodeling is characterized in part by loss of capillaries. We review the pertinent literature in more detail in the following sections. A summary is outlined in Tables 1 and 2.

Modulators of Microvascular Function of Relevance to the RV

This section discusses molecular mechanisms and pathways that are of interest to the study of angiogenesis in the RV (Fig. 2). We focus on mediators and pathways that either have been identified in the RV already or play a major role in the LV. For comprehensive reviews of the molecular mechanisms driving angiogenesis in health and disease in general, we refer the reader to Refs. 9, 24, 139, 173.

Hypoxia-Inducible Factors

Hypoxia-inducible factors (HIFs) are major regulators of angiogenesis, vasculogenesis, and EC homeostasis (139). Under homeostatic conditions, quiescent ECs express oxygen sensors prolyl hydroxylase domain proteins 1–3 (PHD1–3), which regulate the expression of HIF-1α and HIF-2α (139). Under hypoxic or ischemic conditions, these sensors become inactive, resulting in the stabilization and accumulation of HIF-1α and HIF-2α. The accumulation of HIFs rapidly regulates the transcriptional

expression of a large number of target genes. One purpose of the HIF transcriptome is to stimulate sprouting angiogenesis in an effort to repair or prevent injury by increasing oxygen supply to ischemic or hypoxic tissues (97).

Although the role of HIF-1α and HIF-2α in stimulating angiogenic responses is complex and tightly regulated, in general, HIF-1α promotes vessel sprouting, while HIF-2α mediates vascular homeostasis (50). HIFs are necessary for proper vascular and cardiac development, as demonstrated in mice homozygous for a germline *Hif1α*-null allele, which is embryonically lethal due to cardiac and vascular defects (85, 132). Furthermore, mice heterozygous for this allele demonstrate impaired vascular development and decreased revascularization of injured or ischemic tissues (22). Cardiomyocyte-specific deletion of *Hif1α* in mice results in decreased capillary density (69), whereas transgenic mice overexpressing *Hif1α* in the heart have increased capillary density after myocardial infarction (78), demonstrating the importance of HIF-1α in the response to cardiovascular injury. Similarly, homozygous *Hif2α* germline null mutations are embryonically lethal and are associated with defects in vascular formation (34, 120, 159). Given the prominent role of HIFs in cardiac development and maintenance of cardiac homeostasis, it is not surprising that several studies have implicated regulators of HIF signaling in heart failure development (107, 134, 183).

In the pulmonary vasculature of PH models, HIF-1α plays a complex role but has been implicated in pathogenic angiogenesis and smooth muscle cell proliferation (reviewed in Refs. 140, 146, 162, 172). Similarly, HIF-2α in ECs has been implicated as a driver of pulmonary vascular remodeling (37, 76, 87). Although studies of HIFs in the LV and pulmonary vasculature have greatly increased our understanding of their roles in these compartments, the role of HIFs in the RV remains largely unexplored, leading to several questions, including (but not limited to) the following. *1*) Are HIFs necessary and sufficient to promote angiogenesis in the RV? *2*) Is activation of HIFs sufficient to delay the transition to maladaptive remodeling? *3*) What is the effect of acute vs. chronic HIF signaling in the RV? While hypoxia-induced angiogenesis suggests a HIF-1α-mediated response in the RV (14, 84, 117, 151, 164), studies directly manipulating the HIF signaling pathway have only begun. Given this pathway's role in promoting angiogenesis in other ischemic tissues, including the LV and the pulmonary vasculature, it is likely that, at least acutely (84), HIFs are promoting angiogenesis in the RV. However, one should note that HIF-1α also affects RV metabolism (14, 122, 151), thereby regulating RV adaptive and maladaptive responses independently of angiogenesis and demonstrating that this pathway plays a role in regulating RV function that is complex and multifaceted.

VEGF

Members of the VEGF family, comprising three main receptors (VEGFR1, VEGFR2, and VEGFR3) and five ligands (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PIGF), are major regulators of EC function, playing diverse and largely nonredundant roles in vascular homeostasis (23, 48, 173).

VEGF-A is the major ligand associated with stimulating angiogenesis during homeostasis and disease through interaction with its receptor, VEGFR2 (Flk1), leading to the induction of pro-survival and proangiogenic signaling (155, 187). VEGF-B binds primarily to VEGFR1 and prevents angiotensin II–induced cardiac diastolic dysfunction (142) and facilitates fatty acid transport in vascular ECs (62). VEGF-C, which signals through VEGFR2 and VEGFR3, activates endothelial tip cells and is necessary for embryogenesis (165) and is also a key regulator in adult lymphangiogenesis (20). VEGF receptors are critical for VEGF signaling. Germline deletion of *Vegfr2* in mouse models is embryonically lethal due to lack of vascular bed formation (143). Interestingly, VEGFR1 (Flt-1) and VEGFR2 exhibit an antagonistic relationship, with VEGFR1 functioning as a decoy receptor to prevent activation of VEGFR2 (49). Along those lines, germline deletion of *Flt1* is embryonically lethal due to excessive proliferation of angioblasts (49). Furthermore, a soluble, alternatively spliced variant of VEGFR1, s-Flt1, can repress VEGF signaling

by sequestering VEGF, thus demonstrating another mechanism by which the activity of VEGFR2 can be tightly controlled (77).

Interestingly, VEGF-A plasma levels are elevated in patients with severe angioobliterative PAH (44, 116, 138). Plexiform lesions and pulmonary ECs from the lungs of PAH patients also strongly express VEGF-A and VEGFR2 (66, 156). However, whether VEGF-A is necessary for driving pulmonary vascular remodeling has not been elucidated. Like HIF-1α, the role of VEGF signaling in PAH is complex, and contradictory effects have been described (173). These differences are likely due to context- and time-dependent effects. For example, while VEGF signaling in general is thought to be a major contributor to PAH development (31, 156, 161), VEGFR2 blockade with Su5416 is used to induce experimental PH in rodents (32, 110, 156).

In the RV, VEGF-A has frequently, but not always, been reported as upregulated in animal models with adaptive RV remodeling (14, 43, 117, 124, 151) and decreased in animal models with RV failure (14, 15, 122), paralleling the decrease in capillarization shown in RV failure (14, 15, 43, 122, 151). In the rat Su546/hypoxia (SuHx) model of PH, treatment with the adrenergic receptor blocker carvedilol was associated with increased RV VEGF-A expression and RV capillarization (15). Recently, in the same model, it was shown that the antioxidant defense system, heme oxygenase-1, upregulated VEGF-A and increased RV capillarization (14). However, a direct causative link between decreased VEGF expression and capillary rarefaction has not yet been established. On the other hand, it was shown in RVs from patients with decompensated RV function that VEGF-A and VEGFR2 were not decreased compared with compensated RVs (124). Instead, it was shown that the capillary rarefaction observed in the decompensated RVs was due to upregulation of Sprouty-related EVH1 domain-containing protein-1 (SPRED-1), an inhibitor of the VEGF downstream target phospho-ERK1/2 (p42/44 MAPK) (124). This resulted in impaired angiogenic activity in cardiac ECs isolated from decompensated human RVs, which could be chemically and biologically rescued by inhibiting SPRED-1 (124). Together, these observations link VEGF signaling to angiogenesis in the RV. However, further study defining the role of VEGF signaling in adaptive and maladaptive remodeling in the RV is still needed. Furthermore, the role of other VEGF family members (e.g., VEGF-B), has not yet been studied in the RV.

Apelin and Elabela/Toddler

Apelin is a secreted peptide expressed in the vasculature and heart that exerts its effects via the G protein-coupled apelin receptor (APLNR) (6, 79–82, 91). Apelin and APLNR play a critical role in cardiac development (79, 86), angiogenesis (94, 182), pro-survival signaling (4), nitric oxide-dependent vasodilation (186), and inotropic signaling (153). Important for angiogenesis, apelin is expressed in tip and stalk cells, while APLNR is expressed only in stalk cells (94). APLNR is purported to play a role in vasculogenesis and is strongly expressed in circulating endothelial progenitor cells (157). Both hypoxia and VEGF-A induce the expression of APLNR in vascular ECs (94, 145), suggesting significant cross-talk between hypoxia, VEGF signaling, and apelin signaling.

Several lines of evidence suggest a role for apelin in PAH (reviewed in Refs. 6, 80) and cardiovascular disease (reviewed in Refs. 38, 72, 73). For example, apelin-null mice exhibit worsening PH (26), and plasma apelin levels are decreased in PAH patients (26, 55). Furthermore, treatment with APLNR ligand attenuates PH in multiple animal models (4, 46, 47). Finally, hypoxic mice infused with apelin exhibit increased cardiac output (4). Together, these data make a strong case for targeting this pathway therapeutically in cardiopulmonary diseases.

Despite the reported protective effects of apelin in PH, very little is known about its effects in the RV. It was reported in two experimental models of PH of adaptive RV remodeling [chronic hypoxia and pulmonary artery banding (PAB) without RV failure] that RV apelin mRNA and protein expression is

increased (43). On the other hand, in models of maladaptive RV remodeling (SuHx, PAB with copper-depleted diet), apelin protein was decreased (43). Our group has recently shown that apelin mRNA is decreased in RVs from male and female SuHx-PH rats and that this decrease was more pronounced in male animals (52). These effects were linked to the female sex steroid 17β-estradiol (E_2), as ovariectomy (OVX) decreased the level of apelin in female RVs to the same level found in male RVs, whereas E_2 repletion in OVX females restored apelin levels (52). Interestingly, the increase in apelin abundance in intact females and E_2-replete OVX females was associated with an increase in RV capillary density (unpublished data), suggesting that E_2 and apelin have proangiogenic effects in the RV. Combined, these data suggest a role for apelin in modifying angiogenic responses in the RV. However, the specific mechanisms of apelin-mediated signaling responses in RV vascular homeostasis and adaptive as well as maladaptive remodeling are unknown. This is currently under investigation in our laboratory.

In addition to apelin, Elabela/Toddler is an endogenous ligand of APLNR and is strongly expressed in the pulmonary and cardiac vasculature. For a more in-depth overview of this signaling pathway, we refer the reader to several excellent reviews (28, 29, 180). Recently, exogenous treatment with Elabela/Toddler and apelin were shown to have significant beneficial effects on the pulmonary vasculature and RV function in a monocrotaline rat model of PH, reducing RV systolic pressure, RVH, and pulmonary vascular remodeling (181). PAH patients also exhibited decreased Elabela/Toddler expression in the pulmonary vasculature, LV, and coronary arteries (181). However, as with apelin, the effects of Elabela/Toddler signaling on the RV vasculature remain unknown. Taken together, these data make a compelling case for apelin/APLNR and Elabela/Toddler/APLNR pathways as clinically promising targets in both the pulmonary vasculature and RV in PH.

MicroRNAs

Evidence suggesting the epigenetic control of angiogenesis has been accumulating, particularly through noncoding microRNAs (miRNAs), which induce messenger RNA degradation or block translation (21). Since they target multiple genes rapidly, miRNAs are well positioned to regulate complex processes such as angiogenesis (30, 67, 92, 177). ECs express several miRNAs that are induced by hypoxia or VEGF during adaptive remodeling or acute ischemia (111, 135). Most of those stimulate angiogenesis by repressing angiostatic pathways and stimulating proangiogenic cascades (111). For example, expression of miR-126 is induced by the mechanosensitive transcription factor KLF2A and integrates the mechanosensory stimulus of blood flow (109). Furthermore, this miRNA was shown to play a major role in the transition from adaptive RV remodeling to maladaptive remodeling in PAH (124). Likewise, in monocrotaline PH rats with RV failure, downregulation of miR-208 lead to upregulation and activation of the complex mediator of transcription 13/nuclear receptor corepressor 1 axis and subsequently the inhibition of its target MEF2C (119). Although this mechanism was demonstrated in RV cardiomyocytes, MEF2C is also expressed in ECs, and the targeted deletion of *Mef2c* in mice is embryonically lethal due to cardiovascular defects and severe vascular abnormalities, making this axis potentially relevant for the RV vasculature (93, 96). Building on the idea that miRNAs are epigenetic regulators of angiogenesis, studies profiling miRNA expression patterns during progressive RV failure identified four RV-specific miRNAs that were upregulated in RV failure: miR-34a, −28, −93, and −148a (126, 127). These miRNAs were associated with DNA repair impediment, oxidant damage, and downregulation of proangiogenic regulatory networks (127, 154). In summary, several miRNAs seem to offer significant pro- or antiangiogenic potential and could rapidly affect adaptive and maladaptive signaling networks in the RV (19, 158). More work is needed to understand the role of miRNAs in RV angiogenesis, adaptive remodeling and failure.

Structural and Molecular Studies of Microvascular Function in Adaptive RVH

Although early studies did not always specifically assess RV function, they provided important information

about angiogenic responses in the RV during adaptive remodeling (studies investigating angiogenesis in adaptive RVH are summarized in Table 1). For example, in a chronic rat hypoxia model of PH (10% FI_{O_2}), VEGF mRNA expression was potently induced within 12 h after hypoxia exposure in both the RV and LV (117). After prolonged exposure to hypoxia, VEGF mRNA remained elevated in the RV, but not in the LV, peaking at 30 days. This was associated with an increased number of capillaries per RV myocyte in rats exposed to 30 days of hypoxia (117). In another rat model of chronic hypoxia (simulated altitude of 3,500 m for 4 wk), there was an increase of capillary density and decrease of muscle fiber density and fiber-to-capillary ratio in RVs but not in LVs (163). Similarly, our group previously demonstrated increased capillary-to-myocyte ratio in RVs from chronically hypoxic rats (88). Another early study assessed the gene expression profile in chronically hypoxic mouse RVs (12% FI_{O_2} for 4 wk). To directly test the role of HIF-1α in this model, Bohuslavova et al. (16) analyzed a panel of eleven hypoxia-responsive candidate genes, six of which were HIF-1α target genes. Of those six HIF-1α target genes, two are known regulators of angiogenesis: *Vegfa* and *Flt1*. In *Hif1a* partially deficient hypoxic male mice, the authors found that *Vegfa* mRNA was the only significantly decreased HIF1-α target gene in the RV (16). This suggests that VEGF is highly dependent on HIF-α mediated induction under chronic hypoxic conditions in the RV. And finally, a study using the rat monocrotaline model of PH (60 mg/kg for 3 wk) demonstrated an increase in RV capillary proliferation relative to muscle fibers (83). Together, these data lead to the observation that early RV adaptive responses are characterized by increased capillarization driven by early hypoxic responses. Whether these responses are driven primarily by VEGF-A and HIF-1α, or if there are also HIF-independent mechanisms at play, is currently not known.

More recent studies revealed that when following the monocrotaline rat model over time (60 mg/kg for 2–6 wk), compensated RVs exhibit increased HIF-1α activity [demonstrated by increased nuclear localization and upregulation of the target protein glucose transporter 1 (Glut1)] as well as increased expression of the proangiogenic regulators VEGF-A and stromal cell-derived factor 1 (SDF1) (151). This was associated with increased RV capillarization, with lectin fluorescence and von Willebrand factor expression peaking at 3 wk after monocrotaline injection. Another study used a stereological analysis approach to determine capillarization in an adaptive mouse model of PH (10% FI_{O_2} for 3 wk) (84). This study found correlations in RV angiogenesis, RVH, and RV function (assessed by echocardiography and pressure-volume loop measurement). In fact, within 7 days of hypoxia exposure, RV-specific increases in capillary length, surface area, and volume were detected and found to be accompanied by increased RV EC proliferation. Interestingly, whereas continued exposure to hypoxia led to a further increase in hypertrophy, this did not lead to an additional increase in angiogenesis. Finally, while *Vegf-a* and *Vegf-b* mRNA were not significantly changed, VEGF-A protein was significantly increased after 3 wk of hypoxia. To better understand the transcriptome that might be mediating RV adaptive responses, Drake et al. (43) performed gene expression microarray analyses in two models of RV adaptive remodeling (chronic hypoxia and PAB). Signaling networks upregulated in adaptive RV remodeling were associated with growth and cellular maintenance, angiogenesis, and energy metabolism. Of particular interest, apelin mRNA and protein were significantly increased in both models, whereas VEGF and insulin-like growth factor 1 (IGF-1) mRNA were significantly increased in at least one model of compensated RVH. Finally, in a PAB model of compensated RVH (6 wk of banding), RV function (evaluated by echocardiography) was preserved, accompanied by a trend for increased *Vegf-a* mRNA and by significantly upregulated HIF-1α protein and activity (evaluated by nuclear localization) (14). However, neither capillary volume nor density was significantly affected.

However, there are also studies in which RV adaptive remodeling was not associated with increased vascular density or proangiogenic signaling. For example, in a model of stable PH (40 mg/kg monocrotaline; defined as preserved cardiac output assessed by echocardiography), RV remodeling was characterized by decreased capillarization (131). Additionally, in a rat PAB study (PAB for 4 wk, defined as

adaptive remodeling by less severe ischemia, and preserved TAPSE), whereas there was a trend for increased VEGF-A, there was a significant decrease RV microvasculature (measured by CD31 staining) and blood flow compared with controls (122).

One published study evaluated vascularization and EC function in human RVs and isolated human RV ECs. That study demonstrated that human ECs isolated from compensated human RVs displayed increased angiogenic potential compared with control human RVs (124). Furthermore, it was shown that antagomir-mediated downregulation of miR-126 decreased angiogenesis and tube formation in compensated human RV ECs.

Taken together, these data indicate an increase in vascularization and proangiogenesis signaling in several models of adaptive RVH. Data are most consistent and most convincing for chronic hypoxia models, whereas data for monocrotaline or PAB models are somewhat more mixed. This may either indicate that hypoxia is a particularly potent angiogenesis stimulator in the RV, or reflect inconsistencies in models and/or experimental approaches [e.g., tightness of band and duration of banding in the PAB model or differences in the metabolization of monocrotaline between rat strains (58, 115)]. Finally, data from human RV tissue and isolated RV ECs suggest that angiogenesis and EC function are maintained in cases of adaptive RV remodeling.

Structural and Molecular Studies of Microvascular Function in Maladaptive RVH

Studies in models of maladaptive RVH generally demonstrate impairments in angiogenesis and microvascular function (summarized in Table 2). However, discrepancies between studies exist. For example, one study using a monocrotaline model of RV failure (60 mg/kg) found RV VEGF mRNA expression decreased by 50% in the RV after 30 days; however, the number of capillaries per RV myocyte was unchanged (117). Conversely, other studies found that monocrotaline (60 mg/kg with a 4-wk experimental period) decreased RV capillary density vs. controls (131), decreased VEGF-A abundance, and RV capillarization compared with controls or PAB rats (122), and reduced coronary blood flow compared with control rats (122). In another study, Sutendra et al. (151) investigated the mechanism of adaptive and maladaptive RV remodeling using the monocrotaline model (60 mg/kg and duration of 5–6 wk). Those authors defined decompensated (maladaptive) remodeling as the point at which RV systolic pressure and cardiac output started decreasing. Interestingly, decompensated RVs were characterized by an inhibition of HIF-1α, activation of p53, and a decrease in angiogenic proteins (VEGF-A, SDF-1) and angiogenesis (evaluated by lectin stain), compared with compensated RVs but, importantly, not controls.

Despite this progress in defining maladaptive RV remodeling, studies have only begun to assess the mechanisms that might be driving the transition from adaptive to maladaptive remodeling. For instance, the previously mentioned study by Potus et al., (124) using a monocrotaline model (60 mg/kg), monitored the development of PH weekly by echocardiography. Between 3 and 4 wk, RV size and RV end-diastolic pressure increased, while TAPSE, stroke volume, and cardiac output significantly decreased. This stage was defined as decompensated RVH. It was observed that in decompensated RVs miR-126 was downregulated, associated with increased expression of SPRED-1, an inhibitor of the VEGF target ERK1/2. The authors concluded that upregulation of SPRED-1 in decompensated RVs inhibits VEGF signaling (despite an increase in VEGF protein), thus inhibiting angiogenesis. Interestingly, treatment with a miR-126 mimic increased angiogenesis in vitro and increased vascular density in vivo.

A study using different rat models of RV failure [SuHx (Su5416 injection followed by 4 wk of 10% O_2 and 2 wk of 21% O_2) or PAB with dietary copper depletion to inhibit HIF-1α] noted capillary rarefaction, associated with decreased mRNA of the angiogenic factors VEGF-A, IGF-1, apelin, and angiopoietin-1 compared with adaptive models (chronic hypoxia and PAB). Interestingly, apelin and IGF-1 protein expression, but not VEGF-A or angiopoietin-1, were decreased compared with animals with adaptive RV

remodeling (43). This study defined decompensation by reduced cardiac output, echo measurements of decreased RV function (e.g., TAPSE), septal shift, presence of pericardial effusion, as well as loss of capillaries and presence of RV fibrosis. Similarly, our group found capillary numbers were decreased in the SuHx rat model vs. controls (Fig. 3). Subsequent studies found that SuHx-RVs exhibited decreased capillary density as well as VEGF-A mRNA and protein, whereas HIF-1α stabilization and nuclear accumulation remained intact, suggesting an uncoupling of VEGF-A and HIF-1α (14). This study also found that the RV vasculature was morphologically heterogeneous, with vessels being narrow and pruned in some areas and dilated and irregularly shaped in other areas. Interestingly, stimulation of heme oxygenase-1 with dietary supplementation with protandim prevented capillary loss, recoupled VEFG-A and HIF-1α, and preserved RV function. Finally, in another study, upregulation of VEGF-A and reduction in capillary rarefaction were achieved in SuHx rats after treatment with the β-adrenergic receptor antagonist carvedilol, accompanied by improved RV function (15).

Studies using human RV tissues are rare (boldface text in Tables 1 and 2). Initial studies in human PAH RVs demonstrated that the myocardial tissue of 10 PAH patients exhibited decreased capillary density compared with RV tissue from patients with myocardial infarction (131). Another study reported RV myocyte hypertrophy and capillary rarefaction in patients with scleroderma-associated PAH (122). Potus et al. studied RV free wall tissues from humans with normal RVs, compensated RVH, and PAH patients with decompensated RV failure and found that patients with decompensated RV failure exhibited decreased capillary density, functionally impaired ECs (defined as inability to form networks in vitro), and decreased miR-126 expression compared with controls and compensated RVs (124). Although these studies suggest a decrease in vascular density in human RV failure, a recent study utilizing stereological approaches in human RV tissue from PAH patients ($n = 4$), found that RV volume and length were actually increased in PAH vs. control ($n = 3$) tissue (61). These findings are important, as they are the first to use unbiased stereological approaches in human RV; however, it should be noted that clinical parameters from these patients were not reported, ischemia tissue was not detected in the RVs, and the sample size was limited, making it challenging to determine whether these RVs were decompensated at the time of patient death.

Taken together, the majority of these studies demonstrate that vascular density decreased and angiogenesis is impaired in maladaptive RVH. The current body of evidence suggests that proangiogenic mediators such as VEGF or miR-126 are either decreased or insufficiently increased, or are inhibited in the setting of maladaptive RVH. However, we have only started to identify the drivers of these processes. Furthermore, not all studies demonstrate these findings. Differences in techniques (e.g., two-dimensional analysis vs. unbiased stereology), control groups, animal models used (see Table 3 for an overview), animal strains, disease stage, and RV region (e.g., apex vs. outflow tract) may explain such discrepancies in results. Clearly, further study of the role of angiogenesis in adaptive and maladaptive RV remodeling while paying meticulous attention to these factors is needed.

POTENTIAL ROLE OF PROANGIOGENIC THERAPEUTIC INTERVENTIONS FOR THE FAILING RV

Although the role of angiogenesis in adaptive vs. maladaptive remodeling of the RV is not yet fully understood, preliminary evidence exists that regulation of angiogenesis may be a potential therapeutic intervention to attenuate RV failure. Treatment strategies shown to be associated with increased RV vascularization and/or increased proangiogenic mediator expression include carvedilol (associated with increased VEGF-A protein and RV vascularization) (15), the soy phytoestrogen genistein (associated with increased RV vascularization) (100), steroid dehydroepiandrosterone (DHEA; associated with prevention of capillary rarefaction) (5), exercise training (associated with increased RV capillarization in a model of stable PH but not progressive PH) (64), protandim (associated with prevention of capillary loss through regulation of heme oxygenase-1) (14) or prostacyclin therapy (associated with an increase in capillary-to-

cardiomyocyte ratio in a rat model of flow-associated PH) (168). However, since these strategies were pursued in PH models where they also attenuated pulmonary vascular remodeling, it is unclear whether the beneficial effects on the RV vasculature were due to a direct effect on the RV or merely a consequence of RV afterload reduction.

As mentioned above, treatment with miR-126 mimic restored RV vascularization and RV function in a rat monocrotaline model of PH (124). Since these effects occurred without any significant changes in the pulmonary vasculature, and since miR-126 enhances the angiogenic potential of ECs isolated from human decompensated RVs, it is likely that miR-126 exerts direct protective effects on the RV vasculature.

A variety of proangiogenic interventions have been shown to be beneficial in LV failure (reviewed in Refs. 112, 178). However, it is unknown whether such strategies would also be beneficial in the failing RV. It remains to be determined whether proangiogenic strategies are able to delay the progression from adaptive to maladaptive RVH. Another important question is how therapeutic approaches aimed at enhancing angiogenesis in the RV would affect the pulmonary vasculature in PAH. This is an important point, since dysregulated and possibly exaggerated angiogenesis has been linked to PAH pathogenesis (39, 167, 173).

KNOWLEDGE GAPS AND PATHWAYS FORWARD

Despite recent progress, several knowledge gaps remain. A summary of the current knowledge gaps in RV angiogenesis is provided in Table 4. Most of our knowledge regarding cardiomyocyte hypertrophy, remodeling, and angiogenesis comes from models of LV failure (112). We currently do not yet know if angiogenesis is necessary or sufficient for myocyte hypertrophy in the RV, as it is in the LV (112). Expanding on this, we currently do not know for sure if decreased angiogenesis is contributing to maladaptive remodeling. Recent studies have begun to link impaired angiogenesis to RV decompensation (14, 43, 124), but a clear causal relationship has yet to be established. To address this knowledge gap, we propose a move from studies using loss of RV capillaries as a descriptive characteristic of RV failure to mechanistic studies with the goal of altering angiogenesis to determine its role in the progression to RV failure.

A better characterization of the molecular regulators of RV angiogenesis is needed. Studies have only begun to identify such mechanisms, and further mechanistic studies are needed to identify upstream regulators and downstream targets responsible for regulating beneficial and detrimental angiogenic processes in the RV in health and disease. Mechanistic studies, including both unbiased screens for angiogenic and angiostatic mediators and hypothesis-driven assessment of specific regulatory candidates during multiple stages of RV remodeling will advance the field. Identification of plasma or imaging biomarkers reflecting angiogenic signaling in the RV would be of great value.

A particular problem in the field is that the RV functional stage is not fully characterized in many studies and that the terms “adaptive” and “maladaptive” are used differently by different investigators, making comparisons between studies challenging. A uniform definition of adaptive and maladaptive RVH is needed. This inconsistency is further confounded by differences in animal models and animal strains (Table 3). A “best” animal model of RV failure probably does not exist. Rather, the model used should be a function of the experimental question asked. For example, SuHx-PH shares features of human PAH and RV failure, but interventions aimed at modulating angiogenesis in the RV may also affect the pulmonary vasculature (and thus RV afterload). PAB avoids this problem, but the RV remodeling in this model is not always maladaptive. Therefore, whenever possible, results should be corroborated in more than one animal model. Finally, thorough RV phenotyping in preclinical (via echo and pressure-volume loop assessment) and clinical (via serial echos or MRI throughout the patient’s disease progression as well as right heart catheterization) studies would be a step forward.

Building on the challenge of incomplete RV phenotyping, another important knowledge gap is the absence of RV vascular assessment in preclinical and clinical interventions targeting the pulmonary vasculature. This is important, since RV function and RV vascular health may be negatively affected by interventions targeting the pulmonary vasculature in PAH. An example is the use of use of histone deacetylase (HDAC) inhibitors in PAH. Several HDAC inhibitors have been shown to be beneficial for the pulmonary vasculature in models of PAH (18, 25, 185). On the other hand, the HDAC inhibitors trichostatin A and valproic acid exerted negative effects on the RV vasculature (13). Specifically, in a 4-wk PAB rat model, animals treated with either agent for 2 wk exhibited decreased RV capillarization as well as decreased VEGF-A and angiopoietin-1 expression (13). Other studies of HDAC inhibition in experimental PH did not evaluate RV capillarization (18, 25, 40, 185). Careful evaluation of any potential cardiotoxic effects of HDAC inhibitors is therefore warranted before use in human PH patients. However, it should be noted that effects of HDAC inhibitors are highly class specific and that results from one class cannot be extrapolated to other classes or more selective HDAC inhibitors. Similarly, endothelin-1 blockade in PAH may be associated with negative effects on RV inotropic signaling (106). Future studies will need to evaluate whether and how the pulmonary vasculature can be safely targeted in PAH without negatively affecting the RV vasculature (and vice versa). Experts have suggested that RV function should be closely monitored in clinical trials of PAH drugs (7).

One important point of consideration is that RV angiogenesis has been evaluated in multiple animal models of PH using traditional two-dimensional approaches to quantify capillary counts. This approach can lead to underestimation of effective capillary length and surface area and unintentional sampling bias and has led to inconsistent findings (75, 105). On the other hand, data reporting capillary rarefaction in the failing RV obtained from several laboratories are consistent and are in line with data reporting vascular rarefaction in LV hypertrophy. Further studies are needed to define the “best” way of assessing RV vascularization in tissues. Such studies should be accompanied by the development of noninvasive imaging markers of RV vascularization (e.g., via CT, MRI, or PET) that could be used in animal studies as well as clinical studies.

Last, studies employing human RV tissue are rare. More investigations using clinically well-characterized human RV tissues, in particular from patients with adaptive remodeling, are clearly needed and would advance the field. Additionally, the development of new technologies such as the “heart on a chip” (to study RV EC-cardiomyocyte interactions) and cardiomyocytes or ECs differentiated from human PH-induced pluripotent stem cells (to screen drugs and determine cytotoxicity) may help overcome limitations of RV tissue rarity and allow for greater molecular and biochemical characterization of the cell types comprising the RV.

CONCLUSION

RV failure is a major determinant of morbidity and mortality in various types of PH. An important clinical need exists to identify the mechanisms that lead to RV failure development in PH and that facilitate the transition from adaptive to maladaptive RV remodeling. Angiogenesis has emerged as a clinically relevant modulator of RV failure development. The current body of evidence suggests that impaired angiogenesis and vascular rarefaction are major drivers of RV decompensation. However, we are only beginning to understand the underlying mechanisms leading to EC dysfunction and vascular rarefaction in the failing RV. Further studies are needed to identify regulators and downstream targets of angiogenic modulators in the RV. Ultimately, such investigations may lead to the development of novel therapeutic approaches that maintain or restore vascular health in the pressure-overloaded RV, thus enhancing RV function and improving patient outcomes.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

A.L.F., S.B., V.A.d.J.P., and T.L. conceived and designed research; A.L.F. interpreted results of experiments; A.L.F. prepared figures; A.L.F., S.B., V.A.d.J.P., and T.L. drafted manuscript; A.L.F., S.B., V.A.d.J.P., and T.L. edited and revised manuscript; A.L.F., S.B., V.A.d.J.P., and T.L. approved final version of manuscript.

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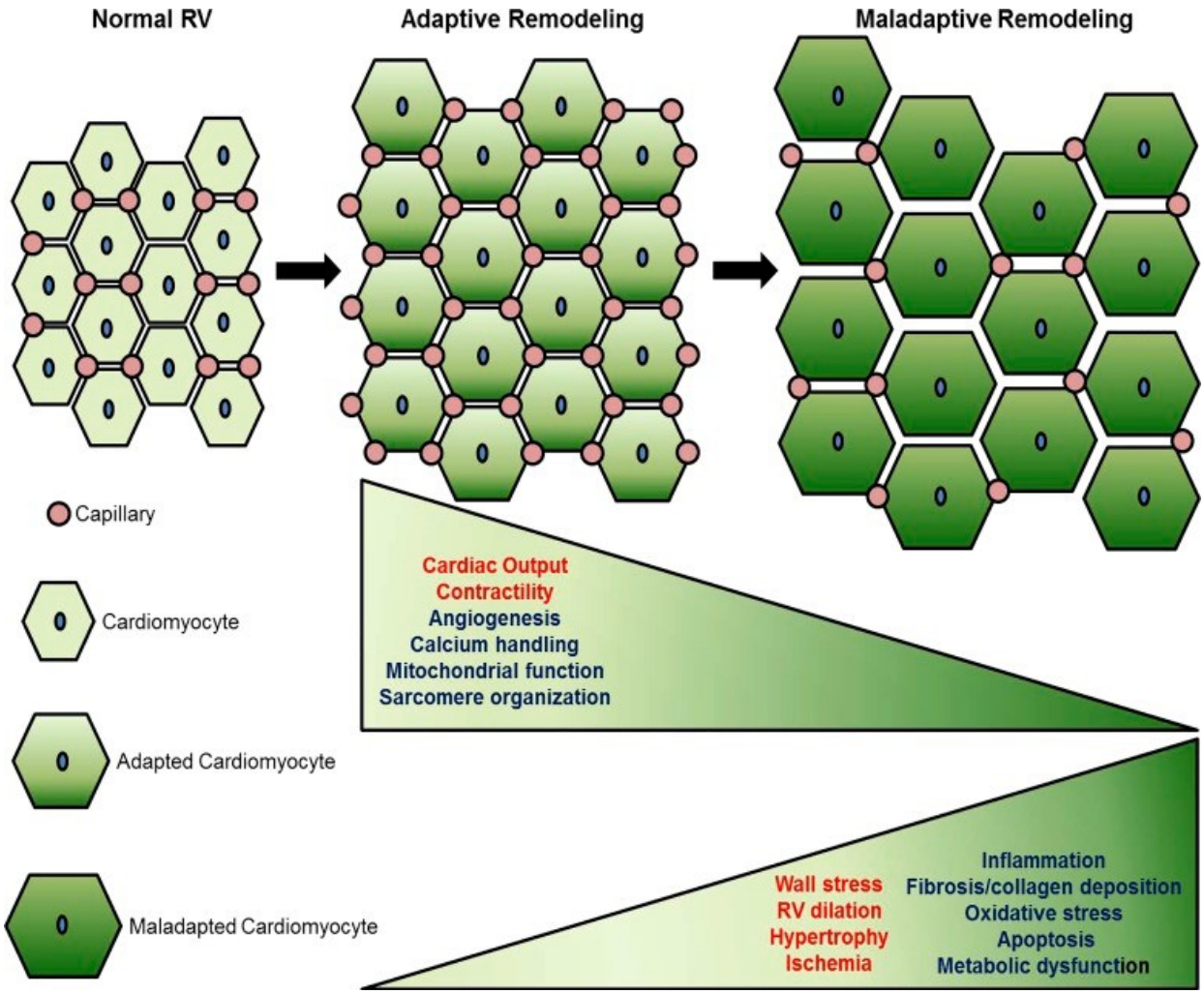
Figures and Tables

Fig. 1.



Right ventricle (RV) vasculature during transition from adaptive to maladaptive RV remodeling**.** Current evidence associates RV adaptive remodeling (characterized by maintained RV contractile function) with increased proangiogenic signaling and capillary density, whereas the transition to maladaptive remodeling (characterized by decreased RV contractile function) is marked by RV endothelial cell dysfunction and capillary rarefaction. In addition to capillary rarefaction, the transition from adaptive to maladaptive RV remodeling is characterized by decreased calcium handling, mitochondrial function, and sarcomere organization and increased hypertrophy, ischemia, inflammation, fibrosis, oxidative stress, apoptosis, and metabolic dysfunction. The exact contribution of each of these molecular processes is currently unknown and remains to be determined. Functionally, this process is characterized by worsening cardiac output and increasing RV dilation with increasing wall stress. Functional/structural changes shown in red font; biochemical/molecular changes shown in blue font.

Table 1.

Studies evaluating the RV vasculature in adaptive RV hypertrophy

Reference	Adaptive Model(s)	How Was Adaptive Remodeling Defined?	RV Function Measured by	Main Results
Partovian et al. (117)	Rats: Hx (10% FI_{O_2}, 1–30 days)	DNE	RVSP, RVH, RV function by right heart catheterization	↑VEGF mRNA at 12 hrs, peaking at 30 days, ↑capillary to myocyte ratio
Turek et al. (163)	Rats: Hx (simulated elevation at 3,500 m, 4 wk)	DNE	RVH	↑Capillary density
Lahm et al. (88)	Rats: Hx (10% FI_{O_2}, 3 wk)	DNE	RVSP, RVH RV function by echocardiograph, right heart catheterization, exercise capacity	↑Capillary to myocyte ratio
Bohuslavovia et al. (16)	*Hif1α*$^{+/-}$ mice: Hx (12% FI_{O_2}, 4 wk)	DNE	RVSP, RVH, RV function by right heart catheterization	↓VEGF
Kobayashi et al. (83)	Rats: MCT (60 mg/kg, 3 wk)	DNE	DNE	↑RV capillarization relative to muscle fibers
Sutendra et al. (151)	Rats: MCT (60 mg/kg, 3–4 wk)	RVH, maintained cardiac output and RVSP	RVSP, RVH, RV function by echocardiography, right heart catheterization	↑HIF1 nuclear localization/activity ↑VEGF-A, ↑SDF1↑RV capillarization
Kolb et al. (84)	Mice: Hx (10% FI_{O_2}, 7 days-3 wk)	RVH, preserved RV function (ie contractility, PA-RV coupling)	RVH RV function and hemodynamics by pressure-volume loops	Stereological assessment ↑RV length, ↑volume, and ↑surface area at 7 days ↑RV EC proliferation ↑VEGFA protein at 3 wk
Drake et al. (43)	Rats: Hx (10% FI_{O_2}, 6 wk) Rats: PAB (6 wk)	Preserved cardiac output, TAPSE, preservation/increase of capillaries, absence of fibrosis	DNE	Microarray analysis revealed pathways associated with cell maturation, angiogenesis, and energy metabolism. ↑Apelin mRNA and protein in Hx, PAB ↑VEGF mRNA in Hx ↑IGF1 mRNA in Hx, PAB

Reference	Adaptive Model(s)	How Was Adaptive Remodeling Defined?	RV Function Measured by	Main Results
Bogaard et al. (14)	Rats: PAB (6 wk)	RVH, preserved cardiac output, TAPSE	RVSP, RVH, RV function by echocardiography, pressure-volume loops, thermodilution	↑HIF-1 nuclear accumulation
Ruiter et al. (131)	Rats: MCT (40 mg/kg, 6 wk)	Preserved cardiac output	RVSP, RVH, RV function by right heart catheterization, endurance testing and echocardiography	↓Capillarization
Piao et al. (122)	Rats: PAB (4 wk)	RVH, preserved function (TAPSE), less severe ischemia	RVSP, RVH RV function by echocardiography, right heart catheterization thermodilution, Langendorff	↓RV microvasculature
Potus et al. (124)	Rats: MCT (60 mg/kg, 2–3 wk)	Rats: RVH, ↑RVSP, slight ↓TAPSE, preserved stroke volume, cardiac output, and RV end-diastolic pressure	Rats: RVSP, RVH, RV function by pressure-volume loops, echocardiograph, endurance testing	Trend for ↑capillary density vs controls
	ECs isolated from Human compensated RVs	Humans: RVH, absence of LV hypertrophy, preserved TAPSE	Humans: Echocardiography	↑Tube formation/angiogenic potential mediated through mIR-126
Handoko et al. (64)	Rats: MCT (40 mg/kg, 6 wk-last 4 wk exercise training)	Preserved cardiac output	RVSP, RVH, RV function by right heart catheterization, endurance testing and echocardiography	Exercise training ↑capillarization
Bogaard et al. (13)	Rats: PAB (4 wk + 2 wk TSA or VPA)	RVH, ↑RVSP, preserved cardiac output, TAPSE	RVSP, RVH, RV function by echocardiography, pressure-volume loops	HDAC inhibition ↓RV capillarization, ↓VEGF, ↓Ang1

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Studies using human tissue are in boldface. Ang1, angiopoietin-1; DNE, did not evaluate adaptive vs. malaptive remodeling; ↑, increase; ↓, decrease; EC, endothelial cell; HIF1, hypoxia-inducible factor 1; *Hif1α*$^{+/-}$, Hif1α heterozygous knockout mouse; Hx, Chronic hypoxia; IGF-1, insulin-like growth factor 1; MCT, monocrotaline; PAB, pulmonary artery banding; PABCu^{2+}, pulmonary artery banding + copper-depleted diet; RVH, right ventricular hypertrophy; RVSP, right ventricular systolic pressure; SDF1, stromal derived factor 1; SuHx, Sugen5416 + hypoxia; TAPSE, tricuspid annular plane systolic excursion; TSA, trichostatin A; VEGF, vascular endothelial growth factor; VPA, valproic acid.

Table 2.

Studies evaluating RV vasculature in maladaptive RV hypertrophy

Reference	Maladaptive Model(s)	How Was Maladaptive Remodeling Defined?	RV Parameters Evaluated	Main Results
Partovian et al. (117)	Rats: MCT (60 mg/kg, 1–30 days)	DNE	RVSP, RVH, RV function by right heart catheterization	↓RV VEGF mRNA
Ruiter et al. (131)	Rats: MCT (60 mg/kg, 4 wk) **Human PAH RVs**	↓cardiac output, ↓body weight	RVSP, RVH, RV function by right heart catheterization, endurance testing and echocardiography	↓RV capillary density
Piao et al. (122)	Rats: MCT (60 mg/kg, 4 wk) **Human PAH and Scleroderma-PAH RVs**	RVH, more severe ischemia, autonomic remodeling, ↓TAPSE, ↓RV dysfunction compared with PAB	RVSP, RVH RV function by echocardiography, right heart catheterization thermodilution, exercise capacity Contractile function by Langendorff	↓VEGFA ↓RV capillarization ↓Coronary blood flow ↓Capillarization in human scleroderma-PAH RVs
Sutendra et al. (151)	Rats: MCT (60 mg/kg, 5–6 wk)	↓RVSP and ↓cardiac output but ↑mean pulmonary artery pressure, continued RV remodeling, development of ascites, weight loss, fluid retention	RVH, RVSP, RV function by right heart catheterization, echocardiograph	Inhibition of HIF1 Activation of p53 ↓VEGFA, ↓SDF1 ↓RV angiogenesis compared with compensated RVs
Potus et al. (124)	Rats: MCT (60 mg/kg, 3–4 wk) **Human decompensated RVs and RV ECs**	Rats-↑RV size, ↑RV end-diastolic pressure increased, ↓TAPSE, ↓stroke volume, and ↓cardiac output Humans-↓TAPSE, RV dilation	Rats-RVSP, RVH, RV function by pressure-volume loops, echocardiograph, endurance testing Humans-Echocardiography, right heart catheterization	↓mIR-126 ↓SPRED1 ↓ RV angiogenesis ↓Capillary density Functionally impaired ECs
Drake et al. (43)	Rats: SuHx Rats: PABCu^{2+} (6 wk)	↓cardiac output, ↓TAPSE, paradoxical movement of interventricular septum, pericardial fluid, ↓capillaries, ↑fibrosis	DNE	↓Apelin protein ↓VEGF-A, IGF1, apelin and Ang1 mRNA
Bogaard et al. (14)	Rats: SuHx	RVH, pericardial fluid, paradox movement of septum, RV dilation,	RVSP, RVH, RV function by echocardiography, pressure-volume loops,	↓Capillary density ↓VEGFA mRNA and protein

Reference	Maladaptive Model(s)	How Was Maladaptive Remodeling Defined?	RV Parameters Evaluated	Main Results
		↓TAPSE, ↓cardiac output	thermodilution	Uncoupling of HIF1 and VEGF
Bogaard et al. (15)	Rats: SuHx + Carvedilol	RVH, pericardial fluid, paradox movement of septum, RV dilation, ↓TAPSE, ↓cardiac output	RVSP, RVH, RV function by echocardiography, exercise endurance, hemodynamic assessment	Carvedilol treated rats had ↑capillary density
Graham et al. (61)	**Human PH RVs**	DNE	DNE	Stereological assessment of human revealed RVs had ↑capillary length and volume
Matori et al. (100)	Rats: MCT (60 mg/kg 30 days +Genistein last 10days)	↓RV ejection fraction	RVSP, RVH, RV function by right heart catheterization, echocardiograph	↓ RV capillarization in MCT rats, Genistein treatment ↑capillarization
Alzoubi et al. (5)	Rats: SuHx + 5 wk DHEA	↓TAPSE ↓Cardiac Index	RVSP, RVH, RV function by right heart catheterization, echocardiograph	↓RV capillarization in SuHx rats, treatment with DHEA ↑ RV capillarization
Handoko et al. (64)	Rats: MCT (60 mg/kg, last 4 wk exercise training as able)	↓cardiac output, ↓body weight	RVSP, RVH, RV function by right heart catheterization, endurance testing and echocardiography	Exercise training ↓capillarization
van Albada (168)	Rats: aortocaval shunt + MCT (60 mg/kg + iloprost or aspirin for 30 days)	DNE	Mean pulmonary artery pressure, RVSP, RVH, RV function by right heart catheterization and echocardiograph	MCT ↓capillary to cardiomyocyte ratio Prostacyclin treatment ↑ capillary to cardiomyocyte ratio

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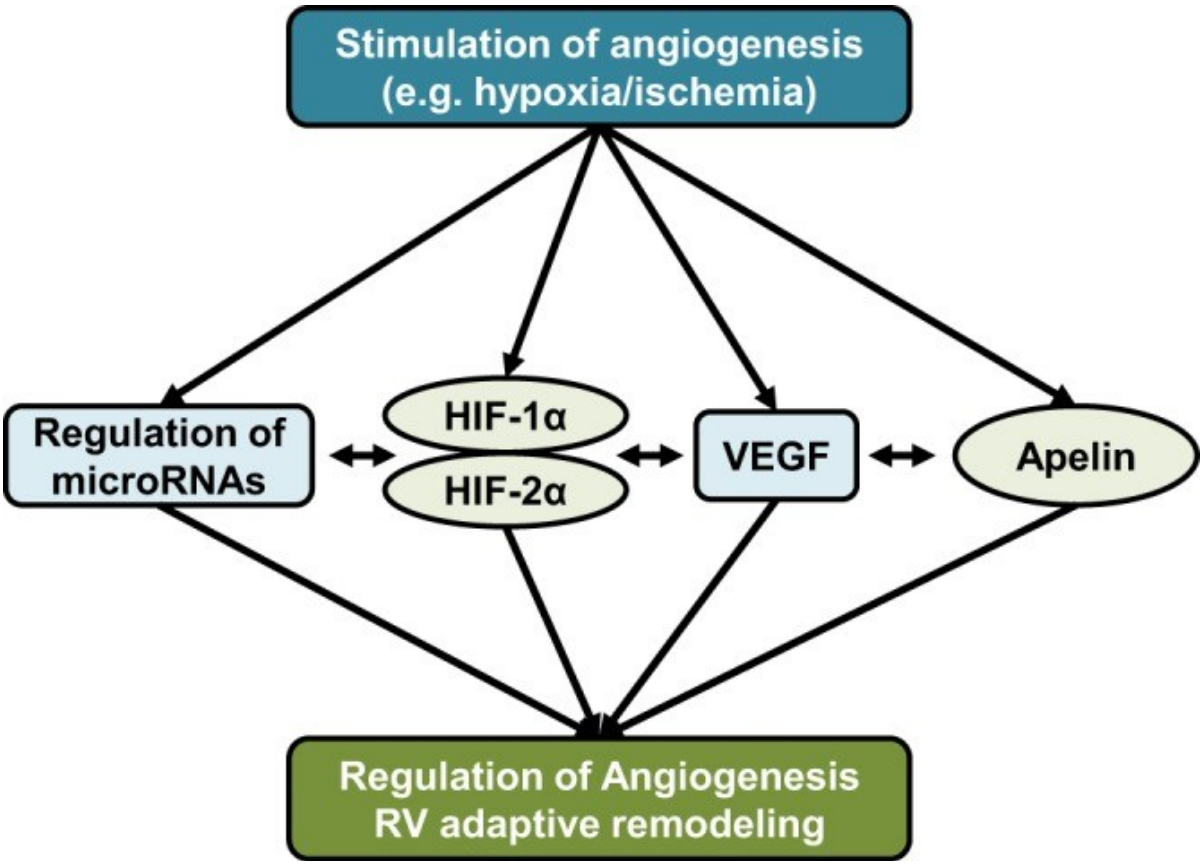
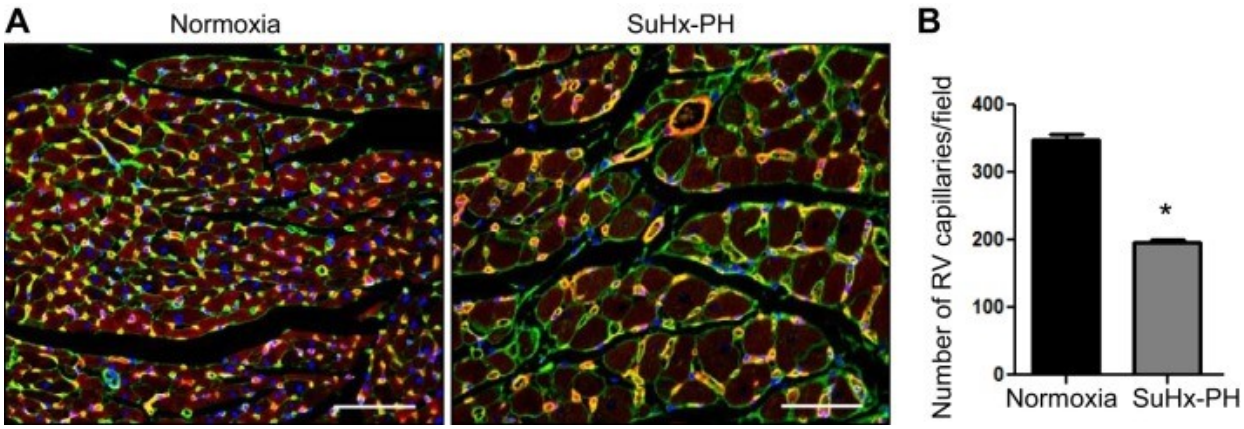
Studies using human tissue are in boldface. Ang1, angiopoietin-1; DNE, did not evaluate adaptive vs. malaptive remodeling; ↑, increase; ↓, decrease; DHEA, dehydroepiandrosterone; EC, endothelial cell; HIF1, hypoxia-inducible factor 1; *Hif1α*$^{+/-}$, *Hif1α* heterozygous knockout mouse; Hx, chronic hypoxia; IGF1, insulin-like growth factor 1; MCT, monocrotaline; PAB, pulmonary artery banding; PABCu2+, pulmonary artery banding + copper depleted diet; RVH, right ventricular hypertrophy; RVSP, right ventricular systolic pressure; SDF1, stromal derived factor 1; SuHx, Sugen5416 + hypoxia; TAPSE, tricuspid annular plane systolic excursion; TSA, trichostatin A; VEGF, vascular endothelial growth factor; VPA, valproic acid.

Fig. 2.



Simplified schematic of currently known pathways regulating angiogenesis in the right ventricle (RV). Proangiogenic factors such as hypoxia or ischemia increase activation and/or abundance of proangiogenic mediators such as hypoxia-inducible factors, VEGF, apelin, and micro-RNAs. Significant cross-talk exists between angiogenic pathways. For example, hypoxia-inducible factors (HIFs) are master regulators that regulate the expression of other regulators to induce angiogenesis during adaptive remodeling of the RV. However, vascular endothelial growth factor (VEGF), apelin, and micro-RNAs are likely also activated independently of HIFs. Decreased or insufficient upregulation of proangiogenic pathways, as well as defects in their downstream signaling pathways are purported to contribute to maladaptive RV remodeling and decompensation.

Fig. 3.



RV vascular rarefaction in Sugen5416 + Hypoxia- pulmonary hypertension (SuHx-PH) rats. *A*: immunofluorescence overlay of WGA (wheat germ agglutinin, green, cardiomyocytes), Lectin Griffonia simplicifolia (red, endothelial cells) and DAPI (blue, nuclei) stains in female normoxic control or SuHx-PH rats. *B*: capillaries were quantified from 4 fields per animal; $n = 4$ animals /group. Images were taken at ×20 magnification; scale bars, 50 μm. Data are expressed as means ± SE $*P < 0.05$ vs. normoxic control. Note that this analysis used traditional 2-D analysis similar to previous studies in the field.

Table 3.

Commonly used animal models to assess RV hypertrophy and failure

	Hypoxia	PA Banding	Monocrotaline	Sugen/Hypoxia
Method used	Exposure to FI_{O_2} 10% (or ½ atmosphere) for 3–5 wks	Suture or clip around main PA	Subcutaneous injection of alkaloid monocrotaline (40–60 mg/kg, 2–6 wk)	Subcutaneous injection of VEGFR2 antagonist Su5416 + hypoxia (2–4 wks) + room air (≥2 wks)
Type of RV remodeling	Adaptive	Adaptive or maladaptive (depending on tightness of band and duration of banding)	In general, maladaptive (may be adaptive in early stages)	Maladaptive
Cardiac output	Maintained or slightly decreased	Maintained or decreased (dependent on tightness of band and duration of banding)	Decreased	Decreased
Effect of model on RV ECs	Strong induction of EC proliferation and chronic hypoxia responses	Increased shear-stress signaling responses due to changes in RV load	Strong EC toxin, initial injection likely induces robust EC apoptosis	VEGFR2 inhibition, likely preventing initial pro-angiogenic response to hypoxia
RV vascular effects	Capillary proliferation	Capillary volume and density maintained or slightly decreased	Vascular inflammation, decreased capillary density	Decreased capillary volume and density
Pulmonary vascular effects	Yes	No	Yes	Yes
Strains used	Rats, Mice	Rats	Rats	Rats
Factors affecting disease phenotype	Sex, age, animal strain, degree and duration of hypoxia	Sex, age, animal strain, tightness and duration of banding	Sex, age, animal strain, MCT dose and duration of model	Sex, age, animal strain, Su5416 vendor, duration of model
Human condition modeled	Chronic hypoxia, high altitude, some aspects of chronic lung disease	RV afterload increase without pulmonary vascular injury (e.g., pulmonary stenosis)	Inflammatory PAH with RV dysfunction	PAH resulting from EC injury

Animal models of RV hypertrophy and failure from References (1, 3, 14, 15, 42, 56–58, 60, 65, 89, 113, 114, 136, 144, 149, 156, 179). MCT, monocrotaline; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RV, right ventricle; RVSP, right ventricular systolic pressure; VEGFR2, vascular endothelial growth factor receptor 2; PH development is more pronounced in younger animals.

Table 4.

Key knowledge gaps in the assessment of angiogenesis in the RV

What are the molecular regulators of RV angiogenesis (proangiogenic and angiostatic)?
Is angiogenesis necessary and sufficient to induce RV cardiomyocyte hypertrophy?
Does decreased angiogenesis contribute to maladaptive remodeling in the RV?
How should we define adaptive remodeling in the RV?
How should we define maladaptive remodeling in the RV?
What methodological approach should we use to measure RV function vs failure?
What is the most accurate methodological approach to quantifying RV vascularization?
Are we introducing unintentional sampling bias into our traditional approaches to capillary density?
Does the use of different RV endothelial cell markers (CD31, von Willebrand factor, or lectin) between researchers introduce bias to our quantification of capillaries?
How do interventions targeting the pulmonary vasculature affect the vasculature of the RV? How do interventions targeting the RV vasculature affect the pulmonary vasculature? Can these compartments be targeted separately?
How can we maximize results from the study of RV angiogenesis in vitro? What can we learn from studies of RV cardiomyocyte-endothelial cell interactions on a chip or from iPSC-cardiomyocytes from PH patients?
How can we maximize the collection of human RV tissue from well phenotyped patients and controls?
How can we best monitor RV vascular function in clinical studies?

RV, right ventricle.