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Excitation-contraction coupling and relaxation alteration in right ventricular remodelling caused by pulmonary arterial hypertension

Abbreviated title: Pulmonary arterial hypertension-related right ventricular remodelling

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Summary

Pulmonary arterial hypertension is a progressive and lethal cardiopulmonary disease. The rise in right ventricular afterload leads to right ventricular hypertrophy and failure. Right ventricular failure is the most important prognostic factor for morbidity and mortality in pulmonary arterial hypertension or pulmonary hypertension caused by left heart diseases. Surprisingly, the right ventricle is not targeted by pulmonary arterial hypertension-specific therapies. The current profound lack of basic understanding of pulmonary arterial hypertension-related right ventricular remodelling can explain, at least in part, this paradox. The physiology and haemodynamic function of the right ventricle in the normal state differ considerably from those of the left ventricle, and the known mechanisms of left ventricular dysfunction cannot be generalized to right ventricular dysfunction. Ion channel activities and calcium homeostasis tightly regulate cardiac function, and their dysfunction contributes to the pathogenesis of cardiac diseases. This review focuses on the ion channels (potassium, calcium) and intracellular calcium handling remodelling involved in right ventricular hypertrophy and dysfunction caused by pulmonary arterial hypertension.

KEYWORDS

Potassium channel;

Calcium channel;

Calcium handling;

Excitation-contraction coupling;

Right ventricular dysfunction;

Pulmonary arterial hypertension

Abbreviations: AP, action potential; Ca^{2+} , calcium; $[\text{Ca}^{2+}]_i$, intracellular Ca^{2+} ; CH, chronic hypoxia; CTEPH, chronic thromboembolic pulmonary hypertension; ECC, excitation/contraction coupling; I_{CaL} , L-type Ca^{2+} current; I_{CaT} , T-type Ca^{2+} current; I_{K1} , inwardly rectifying K^+ current; I_{KCNK3} , KCNK3/TASK-1 current; $\text{IP}_3\text{R2}$, inositol trisphosphate receptor subtype 2; I_{Sus} , sustained outward K^+ current; I_{to} , transient outward K^+ current; K^+ , potassium; KCNK3/TASK-1, TWIK-related acid-sensitive K^+ channel; Kir , inward-rectifier K^+ channel; Kv , voltage-gated K^+ channel; LV, left ventricular; MCT, monocrotaline; mPAP, mean pulmonary arterial pressure; mRNA, messenger ribonucleic acid; NCX, sodium-calcium

exchanger; PAB, pulmonary arterial banding; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RV, right ventricle/ventricular; RVF, right ventricular failure; RVH, right ventricular hypertrophy; RyR2, ryanodine receptor 2; SERCA, sarco/endoplasmic reticulum Ca²⁺-adenosine triphosphatase; SOCE, store-operated Ca²⁺ entry; SR, sarcoplasmic reticulum; STIM, stromal interaction molecule; STIM1L, long stromal interaction molecule; SU/Hx, Sugen 5416/hypoxia; TAPSE, tricuspid annular plane systolic excursion; TRPC, transient receptor potential canonical.

Background

Pulmonary hypertension (PH) is a group of diseases defined by an elevation of mean pulmonary arterial pressure (mPAP) to ≥ 20 mmHg at rest compared with 14 mmHg in normal subjects, measured by right heart catheterization [1]. Depending on the pathophysiological mechanisms, clinical features, haemodynamic characteristics and therapeutic management, PH is classified into five groups. PH group 1 comprises pulmonary arterial hypertension (PAH); in addition to the increased mPAP ≥ 20 mmHg, the 6th PH World Symposium included pulmonary vascular resistance ≥ 3 Wood Units in the definition of all forms of PAH (including idiopathic PAH, heritable PAH, drug or toxin-induced PAH and PAH associated with other pathologies, as well as pulmonary veno-occlusive disease) [1]. PH group 2 comprises PH caused by left heart diseases. PH group 3 comprises PH caused by lung diseases and/or hypoxia. PH group 4 comprises PH caused by pulmonary artery obstruction. PH group 5 comprises PH with unclear and/or multifactorial mechanisms [1].

These different pulmonary vascular diseases chronically increase right ventricular (RV) afterload, inducing right heart remodelling to adapt to this pressure overload (RV adaptive remodelling) and to maintain normal cardiac output and ventriculoarterial coupling [2]. However, over time, and despite optimal medical management, RV remodelling will rapidly progress from an adaptive to a maladaptive phenotype and, finally, to end-stage failure. The symptoms of right heart failure are largely caused by systemic venous congestion and/or reduced cardiac output. Clinical symptoms include dyspnoea, fatigue, reduced exercise capacity and right upper abdominal discomfort or pain, as well as lung congestion [3]. There are no specific biomarkers for RV failure (RVF), but increased brain natriuretic peptide and troponins reflect stress, injury and the severity of the disease [4].

It is recognized worldwide that RV function is the main prognostic factor in patients with PH [3, 5]. However, the shift in RV remodelling during the development of the disease is not well elucidated. Many factors may be involved in this process, such as ion channels, neurohormonal activation, myocardial metabolism, myocardial perfusion, genetic factors, inflammation and extracellular matrix changes [6]. Despite the crucial role of RV function, which determines the fate of patients with PH, the right ventricle (RV) is not targeted by specific therapies. The current lack of understanding regarding RV remodelling in PH can explain this paradox. As the two ventricles have many differences, including different embryological origins, extrapolating our knowledge of left ventricular (LV) hypertrophy could

be easy and helpful, but is incorrect. The PH research field has just begun to decipher the mechanisms responsible for adaptive and maladaptive RV remodelling.

As we know, RV hypertrophy (RVH) and RVF are caused, in part, by remodelling of ion channels and intracellular calcium [Ca^{2+}]; handling abnormalities, combined with structural remodelling (e.g. fibrosis, reduced vessel number and RV perfusion). The ion channel composition of each cardiac cell contributes to the formation of the cardiac action potential (AP) that is important for propagation of excitation. In the present review, we report on the altered excitation/contraction coupling (ECC) and relaxation associated with potassium (K^+) channel and calcium (Ca^{2+}) handling protein remodelling. We focus on the potential pathogenic role of ion channel deregulation in the onset and progression of RV dysfunction associated with PAH.

Clinical aspects of RV remodelling

RV function assessment plays a central role in the choice between double-lung and heart-lung transplantation, and also in the timing of listing of patients with PH. Indeed, because of the lack of clear comprehension of RV remodelling pathophysiology, it is challenging to determine precisely the best timing for listing of patients with PH. Consequently, a large number of patients with PH are transplanted at the time of RVF, requiring RV support as a bridge to transplantation, with challenging postoperative care [7]. A better understanding of adaptive-to-maladaptive RVH transition and RVF pathophysiology, and the development of RV-targeted therapeutic targets, would help to determine the ideal time for the transplantation. Moreover, optimizing RV recovery before transplantation and under support may improve the clinical result of double-lung transplantation in patients with a failing heart.

RV plasticity is an additional major characteristic of the RV compartment, as it has been demonstrated that RV function can recover after double-lung transplantation, independent of the severity of RV dysfunction [8, 9]. However, the choice between heart-lung transplantation versus double-lung transplantation is debatable, as RV recovery may take several weeks and, thus, may be a matter of concern during the early postoperative care in case of pretransplant failing RV [10]. Reverse RV remodelling occurs once the RV afterload is corrected. Major improvement has been demonstrated within the first month, but it has been shown that RV function continues to improve 2 years after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension (CTEPH; PH group 4) [11]. Similarly to RV adaptive remodelling, the pathophysiology of RV “reverse”

remodelling is not fully understood, although it is assumed that it is a reversal of all adaptive processes set up in the early phase of the disease. The methodology of phenotypic assessment of the RV has been widely covered recently [12, 13]. Cardiac magnetic resonance imaging is considered as the clinical gold standard for structural evaluation of the RV, enabling measurement of RV volumes, mass and ejection fraction, but with some limitations such as long scanning times, scanner noise and claustrophobia. Echocardiography remains the clinical cornerstone for RV phenotyping, allowing estimation of RV function by measuring RV fractional area change, strain, S' wave, tricuspid annular plane systolic excursion (TAPSE), end-systolic remodelling (RV dimensions, RV end-systolic remodelling index) and haemodynamics [14].

Animal models for studying RV remodelling

Most animal models of RV remodelling are developed to study PAH pathophysiology. However, these models do not perfectly reproduce PAH, and are broadly considered as PH animal models ([Table 1](#)).

Monocrotaline (MCT)-induced PH model (rat)

MCT is a pyrrolizidine alkaloid extracted from the plant *Crotalaria spectabilis*. A single dose of MCT (40–100 mg/kg, subcutaneously) causes PH in rats within 3–4 weeks, and leads to death as a result of RVF. The MCT rat model sums up many features of human PAH, such as early endothelial dysfunction, pulmonary vascular remodelling and metabolic abnormalities in the pulmonary vasculature. As a consequence of pulmonary vasculature remodelling, the RV is progressively hypertrophied with septum derivation until RVF [15]. RV remodelling and dysfunction in MCT-exposed rats are regularly associated with reduction of exercise capacity, and sometimes with lung congestion [16-18]. RV dysfunction is characterized by a 35–40% reduction in RV fractional area change and decreased TAPSE (two RV systolic function variables) [19-21].

MCT exposure induces a different level of RV dysfunction severity, which depends on the degree of the pulmonary artery stenosis, but always leads to RVF. The severity of RV dysfunction is also dependent on the strain of the rats, the dose of MCT and the weight/age of the exposed rats. MCT also induces RV inflammation, fibrosis and capillary rarefaction [22-24], and may have an additional direct effect on the RV, which should be considered by scientists.

The chronic hypoxia (CH) model (mouse or rat)

Rodents are exposed to 10% oxygen for 3–4 weeks in normobaric or hypobaric hypoxia to induce pulmonary arterial medial hypertrophy, elevated mPAP and RVH without RVF. CH rats are characterized by a temporal increase in RV end-diastolic diameter, whereas TAPSE [25] and RV function [26] are unchanged. PH, pulmonary vascular remodelling and increased RV end-diastolic diameter reverse when the animals return to normoxia [15, 25]. RVH induced by CH is also associated with activation of the local renin-angiotensin system [27-29]. In CH rats, RV function is preserved; however, activation of the hypoxia-activated gene was observed 3 weeks after hypoxia exposure, which could explain irreversible RV structural alterations [30, 31].

The Sugen 5416/hypoxia (SU/Hx) model (rat)

After a single subcutaneous dose of vascular endothelial growth factor receptor blocker, Sugen 5416 (20 mg/kg) rats are additionally exposed to hypoxia (10% oxygen) for 3 weeks. Thereafter, the rats return to normoxia for an additional 5–11 weeks. SU/Hx animals develop plexiform lesions that mimic the histology observed in human PAH. Similarly to MCT and CH models, RVH and RV dysfunction in the SU/Hx model is caused by pulmonary vascular remodelling. SU/Hx may also induce direct RV lesions, which remain underexplored [32].

However, SU/Hx exposition does not lead to RVF as observed in the MCT-PH model [33], and constitutes for several research groups a model of adaptive RV remodelling in response to pressure overload related to pulmonary vascular disease. Indeed, it has been recently demonstrated using cardiac magnetic resonance imaging that 5 weeks after SU/Hx exposure, rats develop RVH and RV dilation with a reduced RV ejection fraction. However, after 8 weeks, despite high RV systolic pressure, the RVH and RV dysfunction are improved, suggesting adaptive remodelling of the RV in SU/Hx rats [34]. de Raaf et al. demonstrated that SU/Hx rats develop an increase in RV end-diastolic diameter and a decrease in TAPSE during the hypoxia period, which partially recover 2 weeks later [25]. In line with these observations, SU/Hx rats showed no reduction in exercise capacity compared with control rats [35].

Pulmonary arterial banding (PAB) (rat, dog, cat and rabbit)

Under anaesthesia, the pulmonary artery is dissected free from the ascending aorta; then, a small needle is placed in parallel to the main pulmonary artery, and ligated with a silk suture. The withdrawal of the needle induces a stable pulmonary artery stenosis; 3–4 weeks after the surgery, PAB animals develop RVH and have decreased RV performance [15, 36]. The immediate and constant mechanical overload induces RVH, which is independent of the renin-angiotensin system or other circulating factors, unlike CH, SU/Hx or MCT models [37-40]. The banding of the pulmonary artery induces no toxic side effects; however, the severity of the RV remodelling may depend on the degree of pulmonary artery constriction. Mild constriction leads to a chronic compensated state with no symptoms of RVF [41-44]. However, stronger pulmonary artery constriction leads to clinical symptoms of RVF, including loss of RV contractility, decreased exercise capacity, poor peripheral circulation, dyspnoea, ascites, pleural/pericardial effusions and, ultimately, death [42, 45, 46].

Large animal model of RV remodelling and reverse remodelling

One large animal model of CTEPH has been used to study RV remodelling and RV reverse remodelling [47, 48]. The model consists of ligation of the left pulmonary artery, followed by weekly embolization of the contralateral pulmonary artery with non-resorbable glue. After 5 weeks, animals develop adaptive or maladaptive RV remodelling, depending on the severity of the disease [49].

This large animal model enables repeated non-invasive and invasive measurements (cardiac echography, cardiac magnetic resonance imaging, right heart catheterization and RV biopsies) to follow changes in pulmonary haemodynamics and RV function [50, 51]. This model replicates the pathophysiology of CTEPH (PH group 4), and is really useful to help our understanding of RV remodelling over a wide range of disease severities, depending on the number of right lower lobe embolizations. This porcine CTEPH model is also characterized by remodelling of small pulmonary arteries/arterioles, septal veins and preseptal venules [52], contributing to RV remodelling.

Finally, two other large animal models may be of value in the near future for PH-induced RV remodelling studies, using other means to increase RV afterload. The first is an overflow model [53], mimicking volume overload situation, and the second is microsphere embolization plus L-NAME

injection [54], replicating PH and microvascular disease. These models, in addition to the first piglet model, may help to shed light on RV remodelling mechanisms and improve patient care.

Relevance of models for studying RV remodelling

To study the mechanisms of RV remodelling, these animal models have been developed to mimic the spectrum of patients with RVF. The MCT model is used most frequently to study PH and RVF.

However, MCT animals die from undetermined causes, which could be RVF or other organ dysfunction, including lung or liver toxicity [55]. MCT administration has been associated with RV myocardium neutrophil and leucocyte accumulation during the early stages of disease, which could affect RV function [56, 57].

Compared with the MCT model, the SU/Hx model presents a higher degree of pulmonary hypertension, but both models develop a similar degree of RV dysfunction, evaluated by the increased RV internal diameter and the decreased TAPSE [55]. Regarding CH rats, which were developed to mimic PH group 3, RV dysfunction is not developed compared with MCT or SU/Hx rats. These three models are all models of PH-induced RV remodelling as a consequence of pulmonary vascular disease, which should limit their use to specifically studying the pathobiology of RV remodelling and dysfunction.

PAB models avoid these limitations, because of the pulmonary vascular disease, and have no systemic or toxic effects. However, the difficulties in generating PAB models means they are studied less frequently than the others, despite being more relevant to the study of RVF. Moreover, and as shown by Bogaard et al., this mechanical RV overload (PAB) is not sufficient to totally explain right heart failure [32].

ECC and relaxation remodelling in hypertrophied RV myocytes

Ion channels are important regulators in many heart functions, such as electrophysiological processes, ECC, regulation of contractile protein activity, energy metabolism and transcriptional regulation. For example, the cardiac AP, which is controlled by different and well-orchestrated ionic currents and transporters, provides the basis for conduction throughout the heart, and for ECC, which is essential for normal heart function. Consequently, perturbation of its homeostasis leads to life-threatening

diseases, including hypertrophic cardiac remodelling, cardiac arrhythmias and cell death [58]. Multiple ion channels are remodelled during the development of left heart failure, and remodelling of these ion channels is less studied in RV dysfunction.

When a heart develops hypertrophy and, subsequently, heart failure, profound changes occur at the macroscopic and molecular levels. At the molecular level, left-sided diseases are commonly associated with reduced contractility as a result of altered ECC function [59].

Compared with left heart failure, RVH and RVF are rarely studied. The impact of chronic PH on RV Ca^{2+} handling proteins is unclear, and appears to differ from that predicted in the failing left ventricle. The limited research into RV Ca^{2+} remodelling warrants further investigation, to clarify and heighten our understanding of the role of Ca^{2+} signalling in PH-related RV remodelling.

Changes in AP duration in hypertrophied RV myocytes

In ventricles, the initial depolarization step is mediated by the fast sodium current I_{Na^+} , followed by a brief repolarization carried by the transient outward K^+ current (I_{to}). The plateau phase is caused by Ca^{2+} influx through the L-type Ca^{2+} current (I_{CaL}), and the sustained outward K^+ current (I_{sus}) constitutes the repolarization phase. The return to the resting membrane potential (-80 to -90 mV) is mainly provided by the inwardly rectifying K^+ current (I_{K1}).

In the MCT-PH model, prolonged action potentials at early, mild and late repolarization have been described in the myocytes from adaptive and maladaptive RVH and RVF [23, 60-63].

Outward K^+ currents

RVF in MCT rats leads to QT prolongation as a result of the downregulation of repolarizing voltage-gated K^+ channels (Kvs) (including Kv1.2 , Kv1.5 and Kv4.1) in the RV myocyte [64].

In the MCT-PH model, maladaptive RVH is associated with prolongation of the QT interval and AP duration, and reduction of expression of Kv1.2 , Kv1.5 , Kv4.2 , Kv4.3 , inward-rectifier K^+ channel ($\text{Kir}2.1$, Kv7.1 , Kv11.1 and Kir3.1) [63, 65-67]. We also found, in MCT rats, significant prolongation of AP duration in isolated adult RV cardiomyocytes from adaptive and maladaptive RVH [63].

Interestingly, in adaptive or maladaptive RVH with RVF induced by PAB, Kv1.5 messenger ribonucleic

acid (mRNA) expression is increased, and is correlated with prolongation of PQ, QRS and QT intervals [68].

We also demonstrated recently that this deregulation of outward K^+ channels is associated with a severe reduction of I_{to} and I_{sus} [63] in RV myocytes isolated from adaptive and maladaptive RVH in MCT rats. In addition, I_{K1} current is reduced, in association with a reduction of *Kir2.1* at the mRNA level (coding for I_{K1} channel) in RV cardiomyocytes from MCT rats with maladaptive RVH [63]. All these alterations to I_{to} , I_{sus} and I_{K1} contribute to abnormal AP repolarization during RVH.

Temple et al. found that expression of KCNK3 or TASK-1 (TWIK-related acid-sensitive K^+ channel) is also decreased in RV tissue from MCT rats with RVF [66]. Later, we revealed that KCNK3/TASK-1 current (I_{KCNK3}) is severely reduced in RV cardiomyocytes during the development of adaptive or maladaptive RVH in several rat models of PH (MCT rats, CH rats and SU/Hx rats) and PAB rats. Of note, in RV cardiomyocytes isolated from MCT rats, I_{KCNK3} is progressively reduced during the development of RV dysfunction, and this reduction of I_{KCNK3} precedes RV remodelling and dysfunction. *KCNK3* mRNA expression is also reduced in human RV tissue from patients with PAH compared with patients without PAH [63]. Moreover, in vivo chronic inhibition of KCNK3/TASK1 in control rats with the selective KCNK3/TASK1 inhibitor (A293) induces moderate RV fibrosis, RV inflammation and subsequent loss of RV performance, as assessed by echocardiography [63]. We also demonstrated that AP is significantly prolonged in RV cardiomyocytes from *Kcnk3*-mutated rats compared with wild-type rats, indicating that KCNK3 function contributes to AP repolarization [69]. These results, and the fact that loss of function mutations in the *KCNK3* gene [70-72] have been previously identified in patients with PAH, suggest that KCNK3/TASK-1 loss of function could also predispose to RV alterations [73].

***I*_{CaL} current and T-type Ca^{2+} current (*I*_{CaT})**

Using the MCT rat model, Lee et al. speculated that the AP duration prolongation in adaptive RVH may be caused by an increase in I_{CaL} density, whereas the AP duration prolongation in maladaptive RVH may be ascribed to a reduction in I_{to} density [74]. Re-expression of T-type Ca^{2+} channels, such as the CaV3.1 and 3.2 isoforms, correlated with increased I_{CaT} current in maladaptive hypertrophied and failing RV myocytes from MCT rats, whereas I_{CaL} density was unchanged [61, 62, 75-77].

However, T-tubule disruption in cardiomyocytes from MCT rats would produce a less effective I_{CaL} ,

reducing the gain of ECC. In accordance with this, another study showed that MCT-induced RVF is associated with a significant reduction in CaV1.2 channel expression because of the loss of the T-tubule network [61, 77].

The changes in AP duration and K⁺ and Ca²⁺ channel expression and activity in different PH animal models are summarized in [Table 2](#).

Changes in [Ca²⁺]_i transients in hypertrophied RV myocytes

Early studies using aequorin bioluminescence have shown that MCT rats with adaptive RVH display prolongation of [Ca²⁺]_i transients as a result of a decreased rate of Ca²⁺ sequestration correlated with similar prolonged isovolumic contraction [78, 79]. By contrast, increased [Ca²⁺]_i transients have been found in adaptive RVH from MCT rat hearts, suggesting enhanced Ca²⁺ mobilization and sequestration during contraction/relaxation cycles, with an increase in density and number of the sarcoplasmic reticulum (SR) [80, 81]. In adaptive RVH induced by PAB in rabbits, the amplitude of [Ca²⁺]_i transients is higher, but the [Ca²⁺]_i transient decline is longer compared with control rabbits, without changes in force of relaxation [82].

In maladaptive RVH, we found an increase in the amplitude of [Ca²⁺]_i transients associated with an increased SR-Ca²⁺ load and faster Ca²⁺ reuptake, leading to improved cell contraction, in RV myocytes from MCT rats [23]. In maladaptive RVH from PAB rabbits, the electrical frequency-dependent rise in the amplitude of [Ca²⁺]_i transients was lower in PAB rabbits compared with sham rabbits, whereas the rise in diastolic Ca²⁺ with frequency was not different between groups. No difference in [Ca²⁺]_i transient decline was observed [83].

In severe maladaptive RVH with congestive heart failure, RV myocytes from MCT rats have drastic T-tubule loss and smaller and slower [Ca²⁺]_i transients, with a decreased network density of SR and altered SR-Ca²⁺ release, which is consistent with data from experimental models of LV failure [77, 80, 81, 84]. By contrast, higher peaks of [Ca²⁺]_i transients, with greater SR-Ca²⁺ load and cell shortening, have also been reported in failing myocytes from MCT rats [75, 85], but decline at high stimulation frequencies.

RV cardiomyocytes from the porcine model reproducing repaired tetralogy of Fallot, which detected early impairment of overloaded RV function and cardiac reserve, displayed prolonged [Ca²⁺]_i transients and attenuated inotropic responses to isoproterenol [86].

Sarco/endoplasmic reticulum Ca²⁺-adenosine triphosphatase (SERCA) and phospholamban expression/activities in hypertrophied RV myocytes

In a porcine model of moderate PH with adaptive RVH and preserved RV contractility, protein expression levels of SERCA2a and phospholamban remained unaffected [87]. Larsen et al. demonstrated no changes in phospholamban or SERCA2a, but significant downregulation of phosphorylated phospholamban at Ser16 in adaptive RVH from CH mice [88]. In RV tissue from dehydro-MCT-exposed dogs, which induces mild PH and RVH, no changes in SERCA and phospholamban levels were observed [89]. Although we found no changes in SERCA2a and phospholamban protein abundance in maladaptive RVH from MCT rats, we showed an increase in phospholamban phosphorylation by protein kinase A at Ser16, which could account for the higher SR-Ca²⁺ content [23].

In mild PAB rabbits with adaptive RVH, SERCA and phospholamban expression levels were lower, while phospholamban phosphorylation (Ser16 and Thr17) was unchanged [83]. In mild PAB dogs with adaptive RVH, there was no change in SERCA or phospholamban, but the phosphorylation of phospholamban at Ser16 was reduced. By contrast, in severe PAB dogs with significant RVH but preserved RV function, SERCA levels and phospholamban phosphorylation at Ser16 fell in the RV [89]. SERCA2a expression and phosphorylated phospholamban at Ser16 and Thr17 levels were significantly reduced in RV tissue from PAB cats with RVF, which is consistent with reduced SR-Ca²⁺ load and impaired contractile reserve [90].

In severe MCT rats with RVF, SERCA2a and phospholamban expression were decreased, suggesting reduced Ca²⁺ handling by the SR [60, 77, 80, 81, 85, 91-93]. This was associated with increased relaxation time and decreased contractile reserve after treatment with isoproterenol [92].

Ryanodine receptor (RyR2) expression/activity in hypertrophied RV myocytes

Higher SR-Ca²⁺ release fraction and higher SR-Ca²⁺ leak in failing RV cardiomyocytes from MCT rats have been reported, suggesting higher RyR2 activity [23, 75, 85].

For Xie et al. [77], the altered SR-Ca²⁺ release in MCT rats with RVF was not caused by changes in RyR2 expression, while Kogler et al. observed a significant reduction in RyR2 level [92].

RyR2 phosphorylation at Ser2809 is significantly reduced in PAB cats with RVF [90], so SR-Ca²⁺ leak does not seem to correlate with the phosphorylation state at Ser2809.

Miura et al. demonstrated in MCT rats with RVF that the higher diastolic [Ca²⁺]_i may be caused by faster and larger Ca²⁺ waves, because of increased Ca²⁺ sensitivity of the RyR2 [93]. In addition, in MCT rats, we and others have shown an enhanced Ca²⁺ spark frequency and Ca²⁺ spark mass [23, 75, 85], and a shift to wider and longer Ca²⁺ sparks in hypertrophied or failing RV myocytes. These modifications are not caused by changes in RyR2 expression or protein kinase A-mediated phosphorylation (Ser2808) or by calcium/calmodulin-dependent protein kinase II-mediated phosphorylation (Ser2814), but result from a robust disorganization of the RyR2 network, with impaired RyR clusters in RV cardiomyocytes from MCT rats, suggesting an altered junctional SR structure. Moreover, the T-tubule network is lost and disorganized [23, 77]; this could lead to the emergence of non-junctional RyRs, and produce Ca²⁺ sparks whose diffusion is not restricted in the space by the adjacent T-tubules, thus accounting for the wider and longer Ca²⁺ sparks that we observed.

This indicates a combination of increased diastolic Ca²⁺ leak and disruption of organization of the T-tubular system in RV hypertrophy-altered ECC before the development of RVF.

In this way, in MCT-rats with RVF, it has been demonstrated that the clustering pattern of RyR2 is broadly similar in control and MCT RV cells, although solitary punctua are more abundant. Clusters near the surface appear smaller and contain visibly fewer RyRs. Thus, smaller RyR clusters coupled with a higher abundance of solitary RyRs are observed in RVs from MCT rats, with greater variability in the RyR-RyR distances. All these data are in agreement with the fact that the calcium-induced calcium release is not conserved, as recruitment of their neighbouring RyRs was neither cumulative nor complete [94].

Sodium-calcium exchanger (NCX) expression/activity in hypertrophied RV myocytes

Few studies have reported on NCX expression and activity in the context of RVH and RVF. In mild PAB rabbits with maladaptive RVH, NCX1 protein expression is increased [83]. In rats with MCT-

induced RVF or PAB cats, NCX1 mRNA/protein levels are not differentially expressed [90, 92] or decreased [77].

Ca²⁺ handling protein expression in RVs from patients with PAH

RV diastolic function is impaired in patients with PAH. Rain et al. investigated the altered expression levels that contribute to cellular diastolic dysfunction in patients with PAH. SERCA2a expression and phospholamban phosphorylation state, except at the calcium/calmodulin-dependent protein kinase II-dependent phosphorylation site (Thr17), were significantly lower in PAH cardiomyocytes, suggesting an altered cellular relaxation pattern caused by reduced diastolic Ca²⁺ clearance and increased residual diastolic Ca²⁺. RyR2 and NCX1 expression were not modified in right cardiomyocytes from patients with PAH. Rain et al. also observed a decrease in cardiac troponin I phosphorylation compared with donor samples, suggesting higher myofilament Ca²⁺ sensitivity. An increase in sarcomere Ca²⁺ sensitivity can lead to incomplete actin-myosin detachment, despite low Ca²⁺ levels, impairing the relaxation phase [95]. Only expression level was quantified in this study – functional relevance needs to be investigated in the future.

With regard to these controversial data, perturbations in intracellular Ca²⁺ homeostasis appear to be dependent on the degree of RV pressure overload and the model used to mimic the RV effects of PH.

Transient receptor potential canonical (TRPC) and Ca²⁺ release-activated Ca²⁺ channel protein (Orai) channels as emergent Ca²⁺ actors in hypertrophied RV myocytes

The functional role of TRPC/Orai1/stromal interaction molecule 1 (STIM1) proteins in cardiac cells is still unclear. We and others have suggested that TRPC/Orai1/STIM1-mediated store-operated Ca²⁺ entry (SOCE) plays a role in the regulating cardiac diastolic Ca²⁺ homeostasis [96-98]. In the context of cardiac diseases, in vitro and in vivo data clearly demonstrate that TRPC/STIM/Orai-dependent Ca²⁺ entry is instrumental for pathological LV hypertrophy development [96]. However, the contribution of TRPC, Orai and STIM proteins to RVH and RVF caused by PH remains unknown.

Benoist et al. were the first to highlight a possible contribution by these molecules in the RV. Acute or chronic stretch can also trigger arrhythmias, possibly via the activation of mechanosensitive cationic channels, such as TRPC channels. However, the authors showed that the failing RV are unresponsive to stretch-induced disruption to rhythm, which could be attributable to decreased TRPC1 and TREK-1 expression at the mRNA level, while the TRPC6 mRNA level is increased [60].

Using MCT rats with maladaptive RVH, we found that the glycosylated form of Orai1, TRPC1/TRPC4 expression and the long STIM1 (STIM1L)/STIM1 ratio were increased in hypertrophied RV cardiomyocytes. This was correlated with an increased Ca^{2+} current elicited by STIM1L and TRPCs/Orai1, which contributes to the enhanced SR- Ca^{2+} content and to the RV-specific cellular Ca^{2+} cycling remodelling in experimental maladaptive RVH, highlighting the roles of these molecules in RVH in the context of PH [23].

Previously, it has been described that the inositol trisphosphate receptor subtype 2 (IP₃R2) may inhibit the progression of PAH by promoting apoptosis and inhibiting SOCE via the STIM-Orai pathway in pulmonary arterial smooth muscle cells [99]. In LV cardiomyocytes, Ca^{2+} mobilized from the SR via IP₃R2 contributes to decreased resting membrane potentials, prolonged AP and the occurrence of early afterdepolarizations [100]. Interestingly, we found that the IP₃R2 isoform was strongly increased in RV compartments from MCT rats [23]. Further investigation is required to determine whether IP₃R2 in association with SOCE could contribute to Ca^{2+} homeostasis remodelling in RV cardiomyocytes from PH rats.

The changes in actors involved in ECC and relaxation, and in the expression and activity of TRPC/Orai/STIM channels in different PH animal models are summarized in [Table 3](#).

Therapeutic relevance: Targeting the Ca^{2+} signalling pathway

As RV dysfunction is the consequence of pulmonary artery obstruction, treatment of patients with PAH especially targets pulmonary vascular remodelling and, currently, there is no specific therapy to prevent or treat RV dysfunction. The drugs in used were designed to correct the imbalance of vasoactive factors in PAH. The four main drugs are: voltage-gated Ca^{2+} channel blockers (nifedipine, diltiazem); endothelin-1 receptor antagonists (bosentan, ambrisentan and macitentan); phosphodiesterase 5 inhibitors (sildenafil and tadalafil) or guanylate cyclase stimulators (riociguat);

and those affecting the prostacyclin pathway – prostacyclin analogues (epoprostenol and treprostinil) or prostacyclin receptor agonist (selexipag) [101].

As a result of the absence of specific therapy to prevent or treat RV dysfunction in PAH, identification of new therapeutic options is necessary. Strategies to improve RV function and delay RV dysfunction may be beneficial for improving the survival and functional state of patients with severe RVF.

Ca²⁺ antagonists

Currently, one ion channel therapy used in PAH is the L-type Ca²⁺ channel antagonist (nifedipine, diltiazem, amlodipine). Inhibition of L-type Ca²⁺ influx reduces excessive pulmonary arterial vasoconstriction; however, these molecules also dilate non-pulmonary arteries. Moreover, L-type Ca²⁺ channel blockers are only effective in a small subgroup of idiopathic PAH; the responders are defined by a fall of 10–40 mmHg in mPAP during inhalation of nitric oxide [102].

In both CH and MCT rats, Ca²⁺ channel antagonist therapy has beneficial effects on pulmonary vascular remodelling because of the vasodilator properties, but also protects the endothelial cells from injury. Daily treatment with nifedipine prevents the development of PH in MCT rats by reducing RV systolic pressure and RVH, demonstrating a pulmonary and/or cardiac effect of nifedipine [103].

A novel *N*-acylhydrazone derivative LASSBio-1289 promotes vasorelaxation in the rat aorta by inhibiting the L-type Ca²⁺ channel. The daily treatment of MCT rats with LASSBio-1289 for 2 weeks ameliorates MCT-induced elevation of RV systolic pressure, RVH and RV contractility and relaxation. Consequently, treatment with LASSBio-1289 normalizes MCT-induced haemodynamic abnormalities, RVH and dysfunction by reducing pulmonary vascular resistance. These data highlight the reversibility of RV remodelling and dysfunction [104].

The Ca²⁺ sensitizer levosimendan that is used in left heart failure has also been suggested for the management of PH and RHF. Levosimendan displays positive inotropic effects by increasing the affinity of myocardial troponin C for Ca²⁺. In several animal models of pressure overload-induced RVF, acute administration of levosimendan improves RV contractility and function. In addition, in MCT rats, acute administration of levosimendan improves RV contractility, RV lusitropy and RV stroke volume [105]. Long-term treatment with levosimendan in SU/Hx rats improves both RV haemodynamics and RV remodelling [106]. However, the molecular and cellular mechanisms of action

have not been elucidated. Similar results have been reported in patients with PAH, but further clinical studies are obviously required to confirm the efficacy and safety of levosimendan in PAH [107].

Molina et al. demonstrated that adenovirus-mediated SERCA gene transfer enhanced RV Ca^{2+} handling and improved contractility in an aortic constriction model of biventricular failure, probably as a result of decreased phenotypic severity of LV dysfunction [108]. Hadri et al. demonstrated a decrease in SERCA2a expression in the RVs from MCT rats with RVF; they also demonstrated that SERCA2a gene transfer restores SERCA expression in RV compartments, and has beneficial effects on RV haemodynamics [91]. The AAV1-SERCA2a gene transfer limits pulmonary vascular remodelling and the elevation of RV systolic pressure, and prevents RV remodelling. It is plausible that future therapeutic interventions may combine directly pulmonary vascular and RV transduction in established PAH with RVF.

Phosphodiesterase antagonists

The drug trapidil (*N,N*-diethyl-5-methyl-[1,24]-triazol-[1,5]-pyrimidine-7-amine) is a triazolpyrimidine used widely in clinics in patients with cardiac disease, notably because of its vasodilatory activity by inhibition of phosphodiesterases. Trapidil improved RV remodelling in MCT rats, which may indicate its cardiac functional benefits; this was associated with a higher phosphorylated phospholamban ratio in the RVs of MCT rats, and increased RyR2 and SERCA2a expression, which could contribute to greater contractility and relaxation at this stage of this disease, and more Ca^{2+} being available for the next contraction. However, in this study, they were still at the RV compensated stage. It will be interesting to analyse the beneficial effect of trapidil in RVF. Further studies are needed to investigate the effects of trapidil during longer periods of PAH, and its ability to protect the RV during progression of the disease [109].

Sildenafil, a phosphodiesterase 5 inhibitor, is approved for the treatment of PAH, to relax pulmonary arteries. Xie et al. demonstrated that sildenafil prevents the development of PAH, as well as RVH and RVF, by preserving normal T-tubule ultrastructures, Ca^{2+} transient properties and expression of key Ca^{2+} handling proteins. When given at a delayed stage, with established RVH and RVF, sildenafil reverses MCT-induced PH, but not RVH, and partially restores RV contractile function, T-tubule ultrastructures, Ca^{2+} transients and Ca^{2+} handling proteins [77]. A recent article provided evidence that phosphodiesterase 5 is increased in hypertrophied human RV myocardium, suggesting

a direct effect of phosphodiesterase 5 inhibition on RV myocyte function in RV disease [110]. However, two groups provided evidence that sildenafil does not prevent RVH in a pre-established RVH model induced by PAB [111]. Therefore, it is still under debate whether sildenafil exerts its therapeutic effects via its action on the pulmonary vasculature and/or via a direct effect on RV remodelling. What is clear is that early intervention with sildenafil prevents PH, preserves RV structure and function and prevents pathological remodelling of the RV – a finding with important translational implications.

Interestingly, it has been demonstrated that the antihypertrophic effects of sildenafil in left hearts are dependent on TRPC1/3/6 expression and activity [112]. These data raised the possibility that sildenafil might regulate the expression and activity of TRPCs in the RV, and via its action on TRPC channels could constitute a potential therapeutic option for RVH and dysfunction in the context of PH.

Beta-adrenergic receptor antagonists

Beta-adrenoceptor blockers were once considered paradoxical, but quickly revolutionized the treatment of LV failure by delaying ventricular remodelling and reducing mortality. However, beta-blockers are currently not recommended in PAH because of possible negative inotropic effects [113]. Bisoprolol, a cardioselective beta-blocker, delays the progression of the disease. Bisoprolol treatment improves cardiac function by improving RV contractility and filling and ventriculoarterial coupling, and is well tolerated in MCT rats [114].

Chronic treatment with another beta-1 selective blocker (metoprolol) delays the onset of RVF signs in MCT rats by reducing hypertrophy, improving RV function and attenuating repolarization remodelling *in vivo*. Metoprolol also improves the Ca²⁺ handling and contractility of isolated RV cardiomyocytes from MCT rats; this is associated with preservation of T-tubule morphology, homogenous Ca²⁺ release and decreased susceptibility to spontaneous diastolic Ca²⁺ release. Decreased SERCA2a protein is also partially restored by metoprolol treatment [85].

Therefore, a cardioselective beta-blocker may be a valid and promising therapy to delay the progression of RVF in the context of PAH.

Conclusions and perspectives

RVF is the most common cause of death in patients with PAH, as the RV rapidly switches from adaptive to maladaptive RH in contrast to the left ventricle. Although stopping or slowing down the progression of the right disease appears necessary to avoid double transplantation, there is no treatment that specifically addresses RV dysfunction. RVF in general is a complex and heterogeneous disease in which various remodelling processes, including changes in ion channel composition and function, occur.

As summarized in this review, ion channels and Ca²⁺ protein actors are important contributors to RV remodelling (Fig. 1). However, most studies related to ion channels and RV dysfunction are performed using small animal models of RV dysfunction caused by pulmonary vessel remodelling, such as MCT rats. Further basic research and clinical studies are needed to decipher ion channel remodelling in a large animal model of RV remodelling or PAB animals, to study the cellular and molecular mechanisms involved in RV dysfunction where pulmonary vascular remodelling is not reversible. Further investigations will be required to apply these findings to a clinical setting. Finally, one of the main differences between RV and LV dysfunction is the existence of reversible RV remodelling, which needs to be investigated more thoroughly at the cellular and molecular levels. In conclusion, understanding of ion channel composition and remodelling in RV pathophysiology needs detailed investigation to provide a basis for novel therapeutic options for improving the care of patients with PH.

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Disclosure of interest

M. H. Trial investigator, consultant and member of scientific boards for the companies **Actelion**, **Bayer**, **GSK**, **Novartis** and **Pfizer**.

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Figure legend

Figure 1. Ion channel remodelling in maladaptive right ventricular hypertrophy and failure; see description of each channel in the text. Ca²⁺: calcium; CaV: L-type Ca²⁺ channel or T-type Ca²⁺ channel; K⁺: potassium; KCNK3/TASK-1: TWIK-related acid sensitive K⁺ channel; Kir: inward-rectifier K⁺ channel; Kv: voltage-gated K⁺ channel; Na⁺: sodium; Orai: Ca²⁺ release-activated Ca²⁺ channel protein; P: phosphoryl; PLB: phospholamban; RyR: ryanodine receptor; SERCA: sarco/endoplasmic reticulum Ca²⁺-adenosine triphosphatase; SR: sarcoplasmic reticulum; STIM1L: long stromal interaction molecule 1; TRPC: transient receptor potential canonical.

Table 1 Summary of experimental animal models used to study right ventricular remodelling.

Model	RV remodelling						Pulmonary disease
	Adaptive RV hypertrophy	Maladaptive RV hypertrophy	Reduced RV systolic function	Reduced exercise capacity	Lung congestion	RV failure	
MCT rat	Yes	Yes	Depending on the stage	Depending on the stage	Depending on the stage	Depending on the stage	Yes
CH rat/mouse	Yes	No	No	No	No	No	Yes
SU/Hx rat	Yes	Yes	Yes (reversible)	No	No	No	Yes
PAB rat/dog/cat	Yes	Yes	Depending on the banding	Depending on the banding	Depending on the banding	Depending on the banding	No
CTEPH pig	Yes	Yes	Yes	?	Yes	Yes	Yes

CH: chronic hypoxia; CTPH: chronic thromboembolic pulmonary hypertension; MCT: monocrotaline; PAB: pulmonary arterial banding; RV: right ventricular; SU/Hx: Sugen 5416/hypoxia.

Table 2 Changes in messenger ribonucleic acid, protein and function of calcium and potassium channels in adaptive or maladaptive right ventricular hypertrophy and failure reported in different animal models of pulmonary hypertension.

Channel/protein	Permeability	mRNA	Protein	Function	Human	Animal model	Cardiac phenotype	References
				AP prolongation		MCT	Adaptive and maladaptive RVH and RHF	[23, 60-63]
Kv1.2	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT	Adaptive and maladaptive RVH and RHF	[61, 63-65, 67, 68]
Kv1.5	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT; PAB rat	Adaptive and maladaptive RVH and RHF	[64]
Kv4.1	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT	Adaptive and maladaptive RVH and RHF	[61, 63-65, 67]
Kv4.2	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT	Adaptive and maladaptive RVH and RHF	[61, 63-65, 67]
Kv4.3	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT	Adaptive and maladaptive RVH and RHF	[61, 63-65, 67]
Kv7.1	K ⁺	↓		↓ outward K ⁺ current (<i>I_{to}</i> and <i>I_{SUS}</i>)		MCT	Adaptive and maladaptive RVH and RHF	[61, 63-65, 67]
Kv11.1	K ⁺	↓		↓ outward K ⁺ current		MCT	Adaptive and maladaptive RVH	[61, 63-65, 67]

			(I_{to} and I_{sus})			and RHF
Kir2.1	K ⁺	↓	↓ I_{K1} current		MCT	Adaptive and maladaptive RVH and RHF [61, 63-65, 67]
Kir3.1	K ⁺	↓			MCT	Adaptive and maladaptive RVH and RHF [61, 63-65, 67]
TREK-1	K ⁺	↓			MCT	RVF [60]
KCNK3/TASK-1	K ⁺		↓	Loss of function mutations in patients with PAH		[70-72]
	K ⁺	↓		RV from iPAH		RVF [63]
	K ⁺	↓	↓	↓	MCT	Adaptive and maladaptive RVH [63, 66]
	K ⁺		↓		CH rat	Adaptive RVH [63]
	K ⁺		↓		SU/Hx rat	Adaptive RVH [63]
	K ⁺	↓			PAB rat	Adaptive RVH [63]
CaV1.2	Ca ²⁺		↑ I_{CaL}		MCT	Adaptive RVH [74]
	Ca ²⁺		↓		MCT	RVF [77]
	Ca ²⁺	↓	= I_{CaL}		MCT	RVF [61, 75]
CaV3.1 and CaV3.2	Ca ²⁺	↑	↑ I_{CaT}		MCT	RVF [61, 62, 79]

↑: increase; ↓ decrease; =: stable expression or function; AP: action potential; Ca²⁺: calcium; CaV: L-type or T-type Ca²⁺ channel; CH: chronic hypoxia; I_{CaL} : L-type Ca²⁺ current; I_{CaT} : T-type Ca²⁺ current; I_{K1} : inwardly rectifying K⁺ current; iPAH: idiopathic PAH; I_{sus} : sustained outward K⁺ current; I_{to} : transient outward K⁺ current; MCT: monocrotaline; mRNA:

messenger ribonucleic acid; K⁺: potassium; KCNK3/TASK-1: TWIK-related acid-sensitive K⁺ channel; Kir: inward-rectifier K⁺ channel; Kv: voltage-gated K⁺ channel; PAB: pulmonary arterial banding; PAH: pulmonary arterial hypertension; RV: right ventricular; RVF: right ventricular failure; RVH: right ventricular hypertrophy; SU/Hx: Sugen 5416/hypoxia.

Table 3 Changes in messenger ribonucleic acid, protein and function of calcium actors involved in excitation/contraction coupling and relaxation in adaptive or maladaptive right ventricular hypertrophy and failure reported in different animal models of pulmonary hypertension.

Channel/protein	Permeability	mRNA	Protein	Function	Human	Animal model	Cardiac phenotype	References
[Ca ²⁺] _i transients amplitude	Ca ²⁺			↑		MCT; PAB rabbit	Adaptive RVH	[23, 80-82]
	Ca ²⁺			↑		MCT	Maladaptive RVH	[23]
	Ca ²⁺			↓		PAB rabbit	Maladaptive RVH	[83]
	Ca ²⁺			↑		MCT	RVF	[75, 85]
	Ca ²⁺			↓		MCT	RVF	[77, 80, 81, 84]
[Ca ²⁺] _i transients decay time	Ca ²⁺			↑		MCT; PAB rabbit	Adaptive RVH	[78, 79, 82]
	Ca ²⁺			↑		MCT	RVF	[77, 80, 81, 84]
	Ca ²⁺			↓		MCT	Maladaptive RVH	[23]
	Ca ²⁺			=		PAB rabbit	Maladaptive RVH	[83]
SERCA2a	Ca ²⁺		↓		RV from patients with PAH		RVF	[95]
	Ca ²⁺		=			Embolized porcine	Adaptive RVH	[87]
	Ca ²⁺		=			CH mouse	Adaptive RVH	[88]
	Ca ²⁺		↓ or =			PAB dog	Adaptive RVH	[89]
	Ca ²⁺		↓			PAB rabbit	Adaptive RVH	[83]
	Ca ²⁺		=			MCT	Maladaptive RVH	[23]
	Ca ²⁺	↓	↓			MCT	RVF	[60, 77, 92, 93]

	Ca ²⁺	↓		PAB cat	RVF	[90]
PLB		=		Embolized porcine	Adaptive RVH	[87]
		=		CH mouse	Adaptive RVH	[88]
		=		PAB dog	Adaptive RVH	[89]
		↓		PAB rabbit	Adaptive RVH	[83]
		=			Maladaptive RVH	[77]
		=		MCT	Maladaptive RVH	[23]
		↓		MCT	RVF	[60, 92]
PLB Ser16		↓	RV from patients with PAH		RVF	[95]
		↓		CH mouse	Adaptive RVH	[88]
		↓		PAB dog	Adaptive RVH	[89]
		=		PAB rabbit	Adaptive RVH	[83]
		=		PAB rabbit	Adaptive RVH	[83]
		↓		MVT	Maladaptive RVH	[23]
		↓		PAB cat	RVF	[90]
PBL Thr17		=	RV from patients with PAH		RVF	[95]
		↓		MCT	RVF	[60]
		=		PAB rabbit	Adaptive RVH	[83]
		=		MCT	Maladaptive RVH	[23]

			↓		PAB cat	RVF	[90]
RyR2	Ca ²⁺	=		RV from patients with PAH		RVF	[95]
	Ca ²⁺		↑		MCT	RVF	[23, 75, 85]
	Ca ²⁺	=			MCT	RVF	[23, 77]
	Ca ²⁺		↓		MCT	RVF	[92]
RyR2 Ser2814	Ca ²⁺	=			MCT	Maladaptive RVH	[23]
RyR2 Ser2808	Ca ²⁺	=			MCT	Maladaptive RVH	[23]
RyR2 Ser2809	Ca ²⁺		↓		PAB cat	RVF	[90]
NCX	Na ⁺ , Ca ²⁺	=		RV from patients with PAH		RVF	[95]
	Na ⁺ , Ca ²⁺		↑		PAB rabbit	Maladaptive RVH	[83]
	Na ⁺ , Ca ²⁺	=			PAB cat	RVF	[90]
	Na ⁺ , Ca ²⁺	=	↓ or =		MCT	RVF	[77, 92]
STIM1			↓		MCT	Maladaptive RVH	[23]
STIM1L			Induction		MCT	Maladaptive RVH	[23]
STIM2		=			MCT	Maladaptive RVH	[23]
Orai1	Ca ²⁺		↑		MCT	Maladaptive RVH	[23]
Orai3	Ca ²⁺	=			MCT	Maladaptive RVH	[23]
SOCE	Ca ²⁺ , Na ⁺			↑	MCT	Maladaptive RVH	[23]
TRPC1	Ca ²⁺ , Na ⁺		↓		MCT	RVF	[60]

	Ca ²⁺ , Na ⁺	↑		MCT	Maladaptive RVH	[23]
TRPC3	Ca ²⁺ , Na ⁺	=		MCT	Maladaptive RVH	[23]
TRPC4	Ca ²⁺ , Na ⁺	↑		MCT	Maladaptive RVH	[23]
TRPC5	Ca ²⁺ , Na ⁺	↓		MCT	Maladaptive RVH	[23]
TRPC6	Ca ²⁺ , Na ⁺	↑		MCT	RVF	[60]
	Ca ²⁺ , Na ⁺	=		MCT	Maladaptive RVH	[23]
IP ₃ R2	Ca ²⁺	↑		MCT	Maladaptive RVH	[23]

↑: increase; ↓ decrease; =: stable expression or function; Ca²⁺: calcium; [Ca²⁺]_i: intracellular calcium; CH: chronic hypoxia; IP₃R₂: inositol trisphosphate receptor subtype 2;

MCT: monocrotaline; mRNA: messenger ribonucleic acid; Na⁺: sodium; NCX: sodium-calcium exchanger; Orai: Ca²⁺ release-activated Ca²⁺ channel protein; PAB: pulmonary arterial banding; PAH: pulmonary arterial hypertension; RV: right ventricle; RVF: right ventricular failure; RVH: right ventricular hypertrophy; RyR2: ryanodine receptor 2;

SERCA: sarco/endoplasmic reticulum Ca²⁺-adenosine triphosphatase; SOCE: store-operated Ca²⁺ entry; STIM1: stromal interaction molecule 1; STIM1L: long stromal interaction molecule 1; STIM2: stromal interaction molecule 2; TRPC: transient receptor potential canonical.

Figure 1

⇝ Decreased channel activity
 ⇝ Increased channel activity
 ⇝ Unchanged channel activity



