Lung structural remodeling and pulmonary hypertension after myocardial infarction: complete reversal with irbesartan

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Abstract

**Objectives:** The severity of pulmonary hypertension associated with heart failure carries a poor prognosis. The lungs are very sensitive to the constrictive and proliferative effects of angiotensin-II and could represent a preferential target for this peptide. **Methods:** Rats with large myocardial infarcts or sham surgery received the angiotensin-II receptor antagonist irbesartan (40 mg/kg/day) or vehicle for 2 or 8 weeks (n = 5 to 8 for each group). Hemodynamic and morphometric measurements were obtained followed by immunohistochemistry, immunofluorescence analysis and electron microscopic characterization of lung sections. **Results:** The infarct groups developed progressive pulmonary hypertension and right ventricular hypertrophy with elevated left ventricular filling pressures (all P < 0.01). Despite similar infarct size, filling pressures were lower (P < 0.01) while pulmonary hypertension and right ventricular hypertrophy were completely normalized by irbesartan. Isolated lungs pressure–flow relationships were identical at 2 weeks. At 8 weeks it was steepest and shifted upward in the infarct group (P < 0.001), and completely normalized by irbesartan. Lung weight doubled after infarct with no evidence of pulmonary edema and was also normalized by irbesartan. Important lungs structural remodeling evidenced by collagen and reticulin deposition, thickening of the alveolar septa and proliferation of cells with ultrastructural characteristics of myofibroblasts (pericytes) were identified after infarct. **Conclusions:** After large myocardial infarct there is important pulmonary structural remodeling in which myofibroblasts (pericytes) proliferation may play an important role. This initially protective mechanism against high filling pressures could eventually contribute to the development of pulmonary hypertension and right ventricular hypertrophy. Future studies are needed to determine if angiotensin-II directly modulates pulmonary remodeling after myocardial infarct.

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**Keywords:** Angiotensin; Heart failure; Pulmonary circulation; Hypertension; Remodeling

1. Introduction

Paul Dudley White recognized as early as 1936 that the most common cause of right ventricular hypertrophy (RVH) was in fact left ventricular (LV) strain and failure [1]. Congestive heart failure (CHF) of all etiologies leads to impairment of left ventricular filling with subsequent congestion of the pulmonary venous circulation. Pulmonary hypertension is a frequent complication of CHF that is associated with reduced exercise capacity and carries a poor prognosis, especially when associated with right ventricular (RV) dysfunction [2–5].

Stimulation of the renin–angiotensin system is a hallmark of the neurohumoral activation found in CHF. The pulmonary vascular endothelium is the predominant site for the angiotensin-converting enzyme which hydrolyses angiotensin-I to angiotensin-II (Ang-II). The pulmonary circulation, which is very sensitive to the vasoconstrictive and proliferative effects of Ang-II [6,7], could thus be a preferential target for this potent peptide in CHF. This is supported by a recent study demonstrating that angiotensin-
sin-converting enzyme genotype modulates pulmonary function and exercise capacity in patients with CHF [8].

This study was designed to better define the time course and nature of pulmonary hypertension and structural remodeling after myocardial infarction (MI) and the potential effect of therapy with the angiotensin AT<sub>1</sub> receptor antagonist irbesartan.

2. Methods

The study protocol was approved by the animal ethics and research committee of the Montreal Heart Institute and conducted according to guidelines from the Canadian council for the care of laboratory animals.

2.1. Surgical procedures

MIs were induced in male Wistar rats (Charles River) weighing between 150 to 200 g as previously described in detail [9]. The Sham group was subjected to the same procedure except for the ligation of the coronary artery. To maximize the likelihood for the development of pulmonary hypertension, only the animals with large MIs were included in this study. Accordingly, the presence of an infarct was assessed by 12 leads electrocardiogram 48 h after surgery and only the rats with electrical evidence of an MI were kept into the study. Additionally, the presence of a large MI was verified at the time of sacrifice and defined as a scar/body weights ratio >0.030%. Rats with smaller infarct weight were then rejected from the study.

2.2. Experimental protocol

Rats were randomly assigned to received once daily gavage therapy with either irbesartan (40 mg/kg/day) or vehicle (soya oil) beginning 10 h after coronary ligation or sham surgery for a duration of either 2 or 8 weeks. This resulted in four 2-week groups; Sham+vehicle (Sham, n=5), Sham+irbesartan (Sham+Irb, n=5), MI+vehicle (MI, n=8) and MI+irbesartan (MI+Irb, n=6) and in four 8-week groups; Sham (n=7), Sham+Irb (n=6), MI (n=5) and MI+Irb (n=6).

2.3. In vivo hemodynamic measurements and isolated lungs pressure–flow relationships

Gavages were stopped 48 h before anesthesia with xylazine (10 mg/kg) and ketamine (50 mg/kg). The right jugular vein and carotid artery were then isolated, incised and polyethylene catheters (PE 50; 0.97 mm O.D., 0.58 mm I.D.) were advanced in the right and left ventricles (RV and LV). RV and LV pressures were measured and recorded using a polygraph (Gould TA 4000).

The trachea was then isolated, intubated and connected to a rodent ventilator (Harvard Apparatus) set at a constant rate of 60 cycles/min, a tidal volume of 1 ml and a positive end-expiratory pressure of 2 cm H<sub>2</sub>O. After a midline sternotomy the heart and lungs were exposed. The pulmonary artery was cannulated and initially perfused with Krebs solution supplemented with 100 U heparin at 2 ml/min. The Krebs composition was the following (mmol/l); NaCl 120, NaHCO<sub>3</sub> 25, KCl 4.7, KH<sub>2</sub>PO<sub>4</sub> 1.18, MgSO<sub>4</sub> 1.17, CaCl<sub>2</sub> 2.5 and glucose 5.5. This solution was oxygenated with 95% O<sub>2</sub>–5% CO<sub>2</sub> and the pH was maintain at 7.4. The lungs were then rapidly removed, placed in a water-jacketed chamber maintained at 37 °C and perfused with Krebs solution supplemented with 3% albumin at a flow of 5 ml/min. After a 10 min of equilibration, the pressure–flow relationship was determined by increasing the flow rate from 5 to 25 ml/min and simultaneously recording corresponding pulmonary perfusion pressures.

2.4. Morphometric measurements

The right lung and the heart were removed and dissected. RVH was assessed by the ratio of the RV/LV weights. Afterwards, the wet lung weight was immediately measured and the lung was put aside to dry. The lung weight was evaluated daily to determine dry lung weight, usually attained after 72 h. The presence of pulmonary edema was evaluated by measuring the ratio of dry/wet lung weights. The LV scar was dissected and weighed and its surface area determined by planimetry.

2.5. Light microscopy and immunohistochemistry

A barium–gelatin mixture (60 °C) was perfused in the left pulmonary artery at a pressure of 50 cm H<sub>2</sub>O for 2 min. This was followed by perfusion of the airways with formaline fixative solution (Sigma) at a pressure of 36 cm H<sub>2</sub>O for 2 min. The lung was immersed in toto in formaline for 24 to 48 h. Three transverse sections at three different levels were obtained and embedded with paraffin. Sections of 5 μm were cut for staining with hematoxylin phloxin safran (HPS), Masson’s trichrome for identification of collagen, Gomori staining for reticulin, Turnbull’s blue for identification of siderophages and for immunohistochemistry using the indirect immunoperoxidase method with specific antibodies for smooth muscle α-actin, desmin, factor VIII, leucocyte common antigen and CD68 (DACCO).

2.6. Immunofluorescence analyses

Lung transverse sections were obtained and embedded with paraffin. Paraffin from 10 μm thick sections was removed with xylene and these sections were rehydrated with graded alcohol to water. A boiling citrate buffer (0.01 M, pH 6.0) was then used for an antigen retrieval method and the sections were blocked with 2% normal donkey
serum (NDS) for 1 h. Doublelabeling with a rabbit anti-
desmin antibody (Abcam) and a mouse anti-α-smooth
muscle actin antibody (Sigma), respectively diluted 1:100
and 1:200 with 1% NDS, was performed. The antibodies
were applied and incubated for 1 h at room temperature
and then overnight at 4 °C. After lavage, the sections were
incubated for 1 h at room temperature with an anti-rabbit
(donkey) antibody conjugated with Cy5 and a anti-mouse
(donkey) conjugated with tetramethyl rhodamine iso-thio-
cyanate (TRITC) (Jackson Immunoresearch Inc.) diluted
1:300 with 1% NDS. After lavage the sections were
mounted and examined with a Zeiss Axiovert microscope
equipped with the LSM 510 confocal imaging system. To
determine nonspecific binding, control experiments with
secondary antibody without primary antibody were also
performed.

2.7. Electron microscopy

In order to evaluate the ultrastructural characteristics of
the lungs in heart failure, additional animals were evalu-
ated at 2 weeks ($n=5$) and 8 weeks ($n=5$) post-MI. The
lungs were isolated and fixed with 4% formaldehyde in a
phosphate-buffered saline (PBS) solution at a 50 cm H₂O
pressure for 10 min. Afterwards 1-mm small blocks were
made. Those blocks were fixed with osmic acid (2%), dehydrated with ethanol and embedded with epoxy. Repre-
sentative areas of 1 μm semi-thin sections stained with
toluidin blue were cut in ultrafine slices (400 Å) with an
ultratome NOVA (LKB), double stained with uranyl
cyanate (TRITC) (Jackson Immunoresearch Inc.) diluted
1:200 with 1% NDS, was performed. The antibodies
determine nonspecific binding, control experiments with
between groups for hemodynamic and morphologic param-
eters were compared by repeated-measures ANOVA. Statistical sig-
nificance was assumed when $P<0.05$.

3. Results

Except for early death within the first 24 h after MI,
there was no mortality in any of the eight groups studied.
Infarct size, evaluated from its weight and surface, was
similar in the MI groups compared to the MI+Irb groups
at both 2 and 8 weeks (Table 1). Infarct expansion
measured from the ratio of scar weight and surface was
also similar. No significant differences in non-infarcted LV
weight were seen between MI and MI+Irb groups (data
not shown).

3.1. Effects of irbesartan on systemic hemodynamics and
LV function

Heart rate was similar among all groups (Table 1). At
both 2 and 8 weeks, mean arterial pressure was reduced in
all groups compared to Sham (Table 1). MI induced an
increase in LV end-diastolic pressure (LVEDP) in the
2-week MI group (29.9±2.1 mmHg) as well as in the
8-week MI group (28.8±1.5 mmHg) compared to their
respective Sham groups (2 weeks, 6.3±1.7 mmHg; 8

Table 1

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<tr>
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<td>94±6†</td>
<td>97±6‡</td>
<td>98±3†</td>
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<td>CVP (mmHg)</td>
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<td>6.5±0.2†</td>
<td>4.8±0.3*</td>
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<td>LVEDP (mmHg)</td>
<td>6.3±1.7</td>
<td>9.4±2.2</td>
<td>29.9±2.1†</td>
<td>15.6±2.2†*</td>
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<td>LV(--)dP/dt (mmHg/s)</td>
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<td>6250±198‡</td>
<td>4464±495‡</td>
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<td>LV(--)dP/dt (mmHg/s)</td>
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<td>4438±207‡</td>
<td>2857±337†</td>
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<td>RV(--)dP/dt (mmHg/s)</td>
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<td>1638±75</td>
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<td>RV(--)dP/dt (mmHg/s)</td>
<td>1225±61</td>
<td>1275±47</td>
<td>1625±106†</td>
<td>1188±72*</td>
</tr>
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|                      | 2 weeks |            | 8 weeks |            |
|                      | Sham    | Sham+Irb  | MI      | MI+Irb     |
|                      | (n=7)   | (n=6)     | (n=5)   | (n=6)      |
|                      |         |           |         |            |
| Morphometric parameters |        |           |         |            |
| Body weight (g)      | 377±10  | 338±14‡   | 343±5.8‡| 312±8.1*   |
| Scar weight (g)      | N/A     | N/A       | 0.113±0.008| 0.115±0.007|
| Scar/body weight (%) | N/A     | N/A       | 0.033±0.002| 0.037±0.003|
| Scar surface (mm²)   | N/A     | N/A       | 121±8  | 124±7      |
| Scar weight/surface (g/mm²) | N/A | N/A | 0.085±0.004| 0.092±0.003|

HR: Heart rate; MAP: mean arterial pressure; CVP: central venous pressure; LVEDP: LV end-diastolic pressure.
‡P<0.05 versus Sham; †P<0.01 versus Sham; §P<0.05 versus MI; *P<0.01 versus MI.
weeks, 8.2±1.2 mmHg, *P<0.01). Irbesartan therapy in MI groups greatly reduced LVEDP to 15.6±2.2 mmHg after 2 weeks and to 10.4±1.5 mmHg after 8 weeks (*P<0.01, Table 1). Indices of LV contractility and relaxation [(+] and (−)[dP/dt)] were significantly reduced 2- and 8-week post-MI (Table 1).

3.2. Effects of irbesartan on pulmonary hemodynamics, RV function and lung pressure–flow relationships

The 2-week MI group developed severe pulmonary hypertension (PHT) with right ventricular systolic pressure (RVSP) of 50.1±3.5 mmHg compared with 30.3±0.6 mmHg in the Sham group (*P<0.01, Fig. 1a). PHT was even more pronounced in the 8-week MI group with a RVSP of 64.8±5.1 mmHg compared with 30.5±0.8 mmHg in the Sham group (*P<0.01). Complete reversal of PHT as shown by normalization of RVSP was seen in the MI+Irb groups with a decrease to 31.7±1.0 mmHg after 2 weeks and to 30.2±0.8 mmHg after 8 weeks (*P<0.01 compared to MI, Fig. 1a). After, respectively, 2 and 8 weeks RV end-diastolic pressure (RVEDP) was significantly increased to 9.0±0.6 and 9.3±1.1 mmHg in MI groups compared with 4.8±0.4 and 5.7±0.3 mmHg in their respective Sham groups (*P<0.01). Daily therapy with irbesartan after MI normalized RVEDP to 5.7±0.4 mmHg after 2 weeks and to 4.8±0.1 mmHg after 8 weeks (*P<0.01, Fig. 1b). RV (−) and (+)dP/dt was significantly increased in both 2 and 8 weeks MI groups compared to their Sham groups (*P<0.01). Therapy with irbesartan normalized these indices of relaxation and contractility either after 2 or 8 weeks (*P<0.01, Table 1). MI induced RVH in the 2-week group as shown by a RV/LV+Septum weights ratio of 34.1±2.4% compared with 26.0±1.0% in the Sham group (*P<0.01, Fig. 1c). RVH was even more pronounced after 8 weeks with a ratio of 50.3±2.7% compared with 24.5±1.1% in the Sham group (*P<0.01). Treatment with irbesartan for either 2 or 8 weeks completely normalized RVH with respective ratios of 26.1±2.0% and 25.6±1.0% (*P<0.01 versus MI, Fig. 1c).

After 2 weeks, pulmonary pressure–flow relationships were unaffected by MI or irbesartan therapy as shown by a near perfect superposition of all groups (Fig. 2). After 8 weeks however, the relationship was shifted upwards with a steeper slope in the MI group (*P<0.01 versus Sham). This was normalized by irbesartan therapy and became superposable to the sham groups (*P<0.01 versus MI, Fig. 2).

3.3. Effects of irbesartan on pulmonary structural remodeling

The wet lung/body weights ratio almost doubled to 0.21±0.02% 2 weeks after MI compared to 0.12±0.01% in the Sham group (*P<0.01, Fig. 3). This ratio was also greatly increased to 0.23±0.02% in the 8-week MI group compared to 0.09±0.01% in the 8-week Sham group (*P<0.01). Irbesartan therapy completely normalized this wet lung/body weights ratio to 0.12±0.01% after 2 weeks and to 0.09±0.01% after 8 weeks (*P<0.01 versus MI, Fig. 3). Similarly, the dry lung/body weights ratio approximately doubled to 0.040±0.004% in the 2-week MI group and to 0.043±0.002% in the 8-week MI group compared to their respective Sham groups (0.023±0.002 and 0.017±0.001%; *P<0.01). Again, treatment with the AT1 receptor antagonist completely reversed this increase after both 2 weeks (0.023±0.001%) and 8 weeks (0.017±0.001%) (*P<0.01, Fig. 3). The dry/wet lung weights ratio was also measured to determine the presence of pulmonary edema. This ratio was similar in all study groups except in the MI+Irb group after 8 weeks where
Fig. 2. Effect of irbesartan on lungs pressure–flow relationships after 2 and 8 weeks of treatment in MI and Sham rats. †$P<0.01$ versus Sham; *$P<0.01$ between MI and MI+Irb.

there was a slight but significant increase in the ratio compared to the MI group ($P<0.01$).

Microscopic examinations of the lungs from the Sham and MI+Irb groups did not reveal any abnormal findings (Fig. 4a and c). There was however important structural modifications in the MI groups characterized by an increase in alveolar septum thickness, as shown by HPS staining (Fig. 4b), but no evidence of pulmonary edema. In the MI groups, there was evidence of collagen (Fig. 5a), reticulin (Fig. 5b) and siderophages (Fig. 5c) deposition as shown by Masson’s trichrome, Gomori staining and Turnbull’s blue staining. There was also evidence of cellular proliferation in the interalveolar septa composed primarily of elongated cells with cytoplasmic projections reminiscent of pericytes. Immunostaining sections revealed that these cells positively stained for smooth muscle $\alpha$-actin (Fig. 5d) and desmin (Fig. 5e) but not for factor VIII, leucocyte common antigen or CD68 (data not shown). Immunohistochemistry was also performed on lungs sections from Sham groups (data not shown) and MI+Irb groups (Fig. 5f–j). Sham and MI+Irb groups did not reveal any abnormal findings.

Immunofluorescence analysis with doublelabeling for smooth muscle $\alpha$-actin and desmin was also performed. In MI rats, there was important staining for both smooth muscle $\alpha$-actin and desmin in the alveolar septa with evidence of colocalization (Fig. 6). There was no significant staining for smooth muscle $\alpha$-actin and desmin in the alveolar septum of Sham groups (data not shown). There was no non-specific binding in sections that were not treated with the primary antibody (data not shown).

An electron microscopic study was specifically performed to better characterize the nature of the cellular infiltration found with light microscopy. In MI rats there is thickening of septa with segmental enlargement of the alveolar basement membrane and evidence of deposition of
4. Discussion

We have demonstrated that rats with large MIs develop progressive PHT and RVH already apparent after 2 weeks. Our most striking finding is the presence of important pulmonary structural remodeling with approximate doubling of the lung weight also already present after 2 weeks. Immunohistochemistry and electron microscopic analysis of lung sections revealed the presence of myofibroblasts (pericytes) proliferation that may therefore play an important role in lung structural remodeling associated with CHF. The Ang-II receptor antagonist irbesartan did not prevent macroscopic LV remodeling in these large MIs but substantially reduced LV filling pressures and essentially abolished the impact of the MI on the pulmonary circulation and right ventricle.

4.1. Pulmonary structural remodeling after MI

An unexpected but dramatic finding of the present study is the presence of important pulmonary structural remodeling. This is evidenced by the approximate doubling of lung weight in the absence of detectable change in the ratio of dry/wet lung weight. We found no difference in that ratio in the MI groups thus suggesting the absence of significant edema formation in the lungs.

Other investigators however previously measured the presence of pulmonary edema in this model. In one study, there was no evidence of pulmonary edema after 4 weeks but minimal increase in the wet/dry lung weight after 8 weeks from $4.8 \pm 0.67$ to $5.5 \pm 0.04$ (mean±S.E., $P<0.05$) [10]. To compare with the present study, this is an equivalent decrease in the dry/wet lung weight ratio from 20.8 to 18.2%. Another study found that the equivalent dry/wet lung weight after 8 weeks decreased from 21.7 to 19.6% ($P<0.05$) [11]. Our study combined with these previous observations therefore demonstrate that there is no or minimal increase in the relative lung water content 8 weeks after coronary ligation in the rat.

This was confirmed by light microscopy with no evidence of interstitial edema but important collagen and reticulin deposition in the alveolar septa, the presence of siderophages and the proliferation of cells possessing contractile proteins. The identity of the latter was confirmed by immunohistochemistry, immunofluorescence and electron microscopic analysis. These cells are often referred to as lung myofibroblasts [12,13]. Some authors have however used pericytes as a general term that includes myofibroblasts, mesenchymal cells and hepatic stellate cells among others [14]. The diversity within pericytes between tissues and organs is well recognized with a distribution that reflects postarteriolar hydrostatic pressures [15]. In the bovine lung’s gas exchange capillaries they tend to be located near endothelial cells junctions [16].

Pericytes are ubiquitous cells with stellate shape, which
are more abundant on venous capillaries and post-capillary venules. Those cells possess extensive processes, which wrap around microvessels and even share the same basal membrane as adjacent endothelial cells [17]. Pericytes exhibit several characteristics of smooth muscle cells. Indeed, the presence of smooth muscle α-actin and myosin in pericytes has been shown in several studies implicating those cells in the contraction of the microvessels and the regulation of blood flow [18,19]. Pericytes have also been implicated in the regulation of capillary growth and consequently in vessel formation [20]. Furthermore, pericytes synthesize and secrete numerous vasoactive peptides, components of extracellular matrix [21–25] and express receptors for several vasoactive peptides and growth factors [26–29]. Those vasoactive peptides have been shown to regulate the proliferation and migration of
pericytes. In PHT induced by chronic hypoxia, pericytes can hypertrophy, proliferate and differentiate into cells with characteristics of mature smooth muscle cells [30].

Myofibroblasts (pericytes) proliferation could therefore contribute to the development of PHT by two different mechanisms: (1) by actively increasing vascular tone either by contracting themselves or through secreting vasoactive peptides and (2) by structural remodeling of the lung parenchyma including blood vessels.

4.2. PHT and RVH after MI

Rats with large MI developed progressive severe PHT and RVH as shown by marked increases in the right ventricular systolic and diastolic pressures and in the RV/LV+Septum weight ratio. We also evaluated isolated lungs vascular resistive properties by performing pressure–flow relationships. Surprisingly, despite the presence of PHT and RVH after 2 weeks, the pressure–flow relation
was unaffected after MI at that time point. This suggests that PHT after 2 weeks is mainly due to an active increase in pulmonary vascular tone and that the structural remodeling we observed at 2 weeks does not contribute to PHT. The pressure–flow relationship was however shifted upward 8 weeks after MI, demonstrating a marked increase in pulmonary vascular resistance. Although we did not evaluate pulmonary vascular morphometry in this study, we have previously shown an increase in medial wall thickness of small resistance pulmonary arteries (50 to 200 \( \mu m \)) 4 weeks after MI [9]. Thus we could speculate that the upward shift seen in pressure–flow relationship at 8-week post-MI could be due to increase medial wall thickness of the pulmonary arteries not present after 2 weeks.

4.3. Effects of irbesartan after MI

Rats with large MI receiving irbesartan had significant improvement of LV function as shown by a decrease in LV filling pressures. Measurements of scar surface and scar weight/scar surface ratio were similar in both treated and non-treated groups suggesting no effects of irbesartan on the remodeling and the expansion of the scar following MI. In the present study however we cannot firmly conclude on the effect of irbesartan on scar remodeling since only rats with large infarcts were included in order to maximize the development of PHT and RVH.

The effects of irbesartan therapy could be a direct consequence of AT\(_1\) receptor antagonism or indirect effects as a result of the improvement in LV filling pressures. The reversal of PHT could primarily be due to a decrease in active vasomotor tone since the pulmonary circulation have been shown to be very sensitive to the vasoconstrictive effects of Ang-II [6,7]. Similarly, the normalization of RVH could be due to decrease AT\(_1\) receptor dependent hypertrophic effects in cardiomyocytes. Ang-II receptors are present on retinal pericytes where their stimulation induces migration [31] and production of growth factors [32] which can be inhibited by AT\(_1\) receptor antagonists. Thus, a direct effect of Ang-II on pericytes could contribute to pulmonary structural remodeling. Finally, reduction of LV filling pressures secondary to the systemic and myocardial effects of irbesartan could indirectly improve pulmonary pressures, RVH and
lungs structural remodeling. Since myofibroblasts (pericytes) are particularly abundant in vascular beds were venous pressures are increased, this may represent an important stimulus to their proliferation and phenotypic modification.

4.4. Basic and clinical relevance of this study

The rat MI model is the most frequently used model of CHF and its usefulness in the development of drugs for the therapy of CHF has been validated. In this model, an increase in total lung weight is generally regarded as a marker of pulmonary edema. Our results emphasize the importance of reporting total as well as measuring both wet and dry lung weights in order to differentiate edema from structural remodeling. Our findings are relevant to human CHF since Kapanci et al. [12] previously demonstrated thickening of alveolar septa with proliferation of myofibroblasts in 17 patients with postcapillary PHT, including 10 patients with CHF. These changes were however absent in 20 patients with precapillary PHT. These authors proposed that the mechanical stretch due to capillary congestion might be responsible for the generation of these contractile cells. Proliferation of pulmonary myofibroblasts (pericytes) could possibly help to prevent pulmonary edema following the increase of LV filling pressures. Chronically however, their proliferation could become maladaptive and contribute to the development of PHT, reduced lung diffusing capacity and poorer exercise tolerance.

5. Conclusions

Rats with large MIs develop progressive PHT and RVH with important pulmonary structural remodeling characterized by myofibroblasts (pericytes) proliferation. These changes are completely reversed by therapy with the Ang-II receptor antagonist irbesartan. This initially protective mechanism against high filling pressures could eventually contribute to the development of PHT and RVH and reduced lung diffusing capacity. Future studies are needed to determine if Ang-II directly modulates pulmonary remodeling after MI.

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