Capillary filtration is reduced in lungs adapted to chronic heart failure: morphological and haemodynamic correlates

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Abstract

**Objective:** To determine pulmonary capillary filtration in experimental chronic heart failure and to investigate some morphological and haemodynamic mechanisms that could account for reduced filtration in lungs adapted to chronic heart failure. **Methods:** We studied pulmonary capillary filtration, vascular resistances and morphology in lungs from guinea-pigs adapted to chronic heart failure. Heart failure was induced by banding of the ascending aorta (n=66) or sham control operation (n=78) in guinea-pigs which were studied at 150±8 days post-operation. **Results:** Reduced cardiac output, increased systemic vascular resistance and LV end diastolic pressure and increased LV and RV weight:body weight ratio (all P<0.05) indicated chronic heart failure at 5 months following aortic banding in guinea-pigs. Lung weight was increased (61%, P<0.05) in heart failure compared with controls, but lung water content was reduced (5.5%, P<0.05), a reversal of the pattern seen acutely. Studies in isolated perfused lungs demonstrated a reduced capillary filtration coefficient (0.018±0.003 vs. 0.003±0.002 ml min⁻¹ mmHg⁻¹ g⁻¹, P<0.001), increased arterial (61%) and venous resistance (50%) in heart failure lungs, P<0.05. Wall thickness:lumen ratio was increased in small (<250 μm) pulmonary arterioles (0.15±0.02 vs. 0.08±0.01) and venules (0.06±0.005 vs. 0.04±0.002) in heart failure, P<0.01. Alveolar septal volume fractions (35.2±5.1 vs. 23.1±2.7) and septal:air-space volume ratios (60.5±13.6 vs. 31.9±5.3) were also increased in heart failure, P<0.05. **Conclusions:** Pulmonary adaptation to chronic heart failure is associated with vascular and alveolar remodelling that contributes to increased vascular resistance and reduced capillary filtration. These changes are likely to be important in mediating resistance to pulmonary oedema in chronic heart failure.

Keywords: Heart failure; Remodeling; Capillaries; Pulmonary circulation; Haemodynamics

1. Introduction

Congestive heart failure is associated with chronic exposure of the pulmonary vasculature to increased pressures and this increase in pulmonary capillary pressure carries the risk of pulmonary oedema. In clinical practice it is generally recognised that patients with longstanding heart failure are less prone to pulmonary oedema for given levels of pulmonary venous pressure. Thus, acute elevation of pulmonary venous pressure in patients with acute myocardial infarction frequently results in overt pulmonary oedema [1] while patients with chronic rheumatic mitral valve disease may tolerate even higher levels of pulmonary venous pressure without oedema [2]. Several mechanisms may contribute to the ability to resist the development of pulmonary oedema in lungs exposed to chronic left sided heart failure. Thickening of the pulmonary capillary basement membrane in heart failure [3] could act to limit permeability of proteins and water and thereby resist oedema formation. Clinical studies using double isotope scintigraphy as an indirect measure of pulmonary microvascular permeability suggest that this is reduced in patients with severe chronic heart failure [4]. Direct measurements of pulmonary capillary filtration coefficient...
in isolated perfused lungs obtained from dogs exposed to rapid ventricular pacing to induce heart failure were unchanged following 4 or 7 weeks of pacing [5,6]. In control lungs exposed to repeated increases in pulmonary venous pressure, capillary filtration coefficient was increased but was unchanged in lungs from paced animals [6]. Studies in chronic heart failure are not available and therefore it is unclear whether pulmonary capillary filtration declines progressively with advancing heart failure, ultimately leading to a reduced filtration coefficient and resistance to alveolar oedema formation.

Pulmonary vascular resistance is increased in heart failure and vascular capacitance is reduced [5,6]. These changes reflect vascular remodelling, which is known to occur in left ventricular dysfunction [7], pulmonary hypertension [8] and hypoxia [9]. Increased pulmonary vasoconstrictor responsiveness may also contribute to elevated pulmonary vascular resistance [5,7]. Thus increased resting pulmonary vascular resistance and/or enhanced pulmonary responses may ‘protect’ the pulmonary capillary bed in heart failure. At present it is unclear whether these changes are progressive with advancing heart failure and their relative importance in pulmonary adaptation to chronic heart failure is unknown.

In the present experiments we used a model of chronic heart failure in guinea-pigs. Isolated perfused lungs were studied up to 5 months following aortic banding to test whether capillary filtration coefficient is reduced and to examine some potential mechanisms involved. Our results demonstrated reduced lung water content in lungs adapted to chronic in contrast to acute heart failure. Capillary filtration coefficient was reduced in lungs adapted to chronic heart failure, while arterial and venous resistances were increased. Changes in pulmonary vascular and alveolar morphology suggest that lung remodelling in response to chronic heart failure contributes to these physiological adaptations resulting in resistance to oedema formation in heart failure.

2. Methods

2.1. Induction of chronic heart failure

Heart failure was induced by banding of the ascending aorta in male Dunkin–Hartley guinea-pigs (600–800 g), as previously described [10] using a modification of the method described by Ling and deBold [11]. Experiments were carried out at 150±8 days postoperation in order to study effects of chronic heart failure.

All animal work and surgery was performed in accordance with United Kingdom legislation (the Animals (Scientific Procedures) Act 1986.) The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

2.2. Haemodynamic assessment

Animals (sham n = 16, banded n = 16) were anaesthetised with a bolus intraperitoneal dose (60 mg/kg) of pentobarbitone (Animal Care, York, UK). ECGs, left atrial (LA), right ventricular (RV) and left ventricular (LV) pressures and aortic flow were measured as described previously [10]. Subsequently, organs were removed, weighed and dried at 70°C for 72 h to obtain the dry weight and calculate water content.

2.3. Isolated perfused lungs

Following anaesthesia, the trachea was cannulated and the animal ventilated with room air at 70 strokes/min and a tidal volume of 6 ml (using a small animal respirator, model no. 7025, Ugo Basile, Comerio, Italy) producing an end expiratory pressure of 1–1.5 mmHg. A thoracotomy was performed and 1500 I.U. of heparin (CP Pharmaceuticals, Wrexham, UK) were injected into the RV. The pulmonary artery was cannulated and pulmonary venous drainage achieved with a cannula inserted into the left atrium via the left ventricle. The lungs were gently flushed with heparinised Krebs–Henseleit solution and were immediately mounted and perfused with modified Krebs–Henseleit solution (pH 7.4, 37°C) containing (mmol/l): 118.0 NaCl, 4.7 KCl, 1.2 MgSO4, 1.1 KH2PO4, 24 NaHCO3, 2.5 CaCl2, 9 glucose, 2 pyruvate and 0.25% bovine serum albumin (BSA) saturated with 95% O2–5% CO2 using a peristaltic pump to maintain perfusion pressure at 13.4±1.1 mmHg. All chemicals were of analytic grade and were obtained from Merck (Lutterworth, UK).

By changing the mode of lung perfusion from a pump to a variable height reservoir, perfusion could be switched between constant flow and constant pressure perfusion without interruption. Pulmonary flow and arterial (Pao2), venous (P(ve)) and airway pressures (P(aw)) were monitored continuously using pressure transducers (Druck PDCR 75, Welwyn Garden City, UK). Lungs were suspended from an isometric transducer (EXP FSG-01/50, Experimetria, Budapest, Hungary) and change in lung weight was monitored as a measure of oedema formation. Lungs were allowed to equilibrate isogravimetrically for 30 min before commencing experiments. When the experiments were completed, the lungs were dried for 72 h at 70°C and dry weight noted. This preparation was used for the following experimental protocols.

2.4. Alteration of venous outflow pressure

Lungs from sham (n = 13) and banded (n = 11) animals were equilibrated under constant flow (10 ml/min) perfusion, the outflow reservoir was raised to increase venous pressure by 5 mmHg for 1 min and all parameters were recorded. The procedure was repeated with venous outflow
pressures of 10, 15 and 20 mmHg allowing the preparation to return to baseline between pressure challenges.

2.5. Determination of albumin-bound Evans blue dye accumulation

Evans blue dye solution was prepared by dissolving Evans blue dye (Sigma–Aldrich, Gillingham, UK) in a 10% (w/v) BSA (Sigma–Aldrich) and saline solution. The mixture was dialyzed overnight in Visking tubing (22/32, Medicell, London, UK) against an excess of distilled water. Lungs from sham (n=13) and banded (n=8) animals were set up under constant flow (10 ml/min) perfusion. Evans blue solution was infused through a side branch into the pulmonary artery at 0.2 ml/min, to give a final perfusate concentration of 0.196 mg/ml for 5 min. After 2 min venous outflow pressure was raised to 20 mmHg for 1 min, then returned to 0 mmHg and dye infusion continued for another 2 min. Lungs were perfused with Krebs–Henseleit solution for a further 3 min before being removed from the perfusion system. The lungs were gently blotted, weighed, dried at 70°C for 72 h and digested in formamide solution (Sigma–Aldrich) at 40°C for 48 h. After centrifugation at 2000 rpm for 30 min the supernatant was collected and read at 622 nm in a spectrophotometer (Ultracap 2000, Pharmacia Biotech, Vienna, Austria). The distribution volume in lung tissue was calculated by reference to the concentration of dye in the fluid perfusing the lung using the following equation:

\[
\text{Fluid accumulation} = (C_v \times V_t)/C
\]

where \(C\) is the Evans blue dye concentration (0.196 mg/ml), \(V_t\) is the volume of lung digestion solution (25 ml) and \(C_v\) is the concentration of Evans blue dye in the lung digestion solution.

2.6. Morphology

After equilibration at constant flow perfusion lungs from sham (n=6) and banded (n=6) animals were perfusion fixed with 10% formal saline at 10 ml/min for 5 min. Tissue cubes (0.5 cm³) were immersion fixed for 24 h, dehydrated and wax embedded. Tissue sections (5 µm) were cut and stained with haematoxylin and eosin following standard histology protocols [12]. Morphometric analysis of the sections was carried out using an image analysis system (Seescan Solitaire Plus, Cambridge, UK). Diameters of arterioles and venules were measured as the mean of radially arranged diameters every 2° around the central point of each vessel and wall thickness calculated from directly measured wall area and perimeter to minimise the error resulting from measuring obliquely sectioned structures. Alveolar septal and alveolar air space volume fractions were measured in six randomly assigned, standard sized (area=1.937×10⁵ µm²) frames for each section. Mean septal volume was expressed as a fraction of tissue volume and of alveolar airspace volume. For electron microscopic examination lungs were perfused with half strength Karnovsky’s fixation buffer and rinsed in phosphate buffer. Small 1-mm³ cubes of fixed tissue were washed, postfixed in osmium mixture, dehydrated in graded alcohol solutions and propylene oxide and infiltrated with Araldite for 12 h and then embedded in fresh Araldite. Sections were cut on a Reichert Ultracut E ultramicrotome and stained with toluidine blue aqueous solution. Thin sections (50–70 nm) were contrasted with uranyl acetate and lead citrate and examined using a Zeiss electron microscope.

2.7. Determination of segmental vascular resistance

Lungs from sham (n=14) and banded (n=10) animals were equilibrated at constant pressure perfusion for 30 min and pulmonary segmental vascular resistances were measured using two solenoid pinch-valves (P/N 075P, Bio-Chem, Boonton, NJ, USA) to interrupt abruptly pulmonary arterial and venous flows simultaneously or independently for a defined time [13,14]. Pulmonary arterial pressure (distal to the occlusion) and venous pressure (proximal to the venous occlusion) were recorded during arterial, venous and double 2 s occlusions. The inflection points between the rapid and slow components of the pressure–time curves following arterial and venous occlusion, \(P_{ao}\) and \(P_{vo}\), respectively, were taken as the pressure drop across these proximal arteries and veins when flow is present [15]. During double occlusion, arterial and venous pressures equilibrate at approximately equal values, the mean of which is taken as an estimate of microvascular pressure (\(P_{wm}\)). Total pulmonary vascular resistances \(R_v\) were estimated from the preocclusion arteriovenous pressure drop related to flow \(Q\), \(R_v = (P_{ao} - P_{vo})/Q\). Arterial resistance was calculated from the pressure drop across the proximal arteries \((P_a - P_{ao})/\text{flow}\) [15]. Similarly, the venous compartment resistance was calculated as \((P_{vo} - P_v)/\text{flow}\). On venous occlusion, venous pressure increases, initially abruptly and then more slowly. The slope of this second phase and the rate of the flow into the vascular compartment were used to calculate total vascular compliance \(C_v\), as \(C_v = Q/(P_v - P_{vo}/\Delta t)\) [5].

2.8. Estimation of capillary filtration coefficient

Lungs from sham (n=16) and banded (n=15) animals were equilibrated under constant pressure perfusion. Control \(P_{wm}\) was recorded and arterial and venous pressures were then simultaneously elevated by 5 mmHg (to achieve an equal increase in capillary pressure) for 10 min, after which the change of lung weight was recorded and measurement of \(P_{wm}\) was repeated. Arterial and venous pressures were then returned to baseline and the lungs were allowed to equilibrate for 10 min to reach an
isogravimetric state. Capillary filtration coefficient \(K_c\) was calculated from the rate of weight gain \(\Delta W/\Delta t\) during the last 2 min of the \(P_m\) increment as \(K_c = (\Delta W/\Delta t)/\Delta P_m\) and expressed per gram blood-free dry weight.

### 2.9. Statistical analysis

Values are expressed as mean±standard error of the mean. Where appropriate, relationships were analysed using linear regression analysis. Regression lines were compared by testing the difference between the slope and intercept using Student’s t-tests. Statistical analysis of data using Student’s unpaired t-test enabled the comparison of groups (an F value calculation was also performed to test for unequal variance between the groups. If significant variance was found, t-tests with Welch’s correction for unequal variance were used). All statistical analysis was performed using Prism analysis software (v2.01, GraphPad, San Diego, CA, USA) \(P<0.05\) indicating statistical significance.

### 3. Results

#### 3.1. Morphology

Following 150±8 days of aortic banding, heart weight:body weight ratio was increased by 72% compared with sham controls (Fig. 1). This reflected marked increases in the LV (58%), RV (100%) and atrial (211%) mass \((P<0.001\) in each case). In addition, lung weight:body weight ratio was increased by 61% \((P<0.001\), while kidney weights remained unchanged. These changes represent an increase in organ weight as the body weight of banded and sham control groups were similar (1098±30 vs. 1093±19 g).

Lung water content was significantly \((P<0.001\) reduced (5.5%) in chronically banded animals (Fig. 2A), but was unchanged in any of the other organs. This decrease in lung water content was only observed after chronic (150 days) aortic banding; banding for 6 days resulted in a significant increase in lung water \((2.3%, P<0.01\) which normalised by 58 days (Fig. 2B).

#### 3.2. Systemic haemodynamics

Haemodynamic data at 150 days are shown in Table 1. Aortic banding resulted in a systolic pressure gradient of 22.1±2.7 mmHg between the LV and the carotid artery. This was accompanied by reduced aortic flow (49%), increased peripheral resistance (60%), increased LV end-diastolic pressures (150%, respectively), all \(P<0.05\) in each case and a trend for reduced LV \(dP/dt\) (29%). There was a substantial increase in LA systolic (186%) and diastolic pressures (4-fold) and increased RV end-diastolic (104%) pressures, all \(P<0.05\). Heart rate derived from ECGs was unchanged. Banding increased QRS R wave voltage (58%), duration (40%) and QTc interval (17%), all \(P<0.05\).

#### 3.3. Lung morphology

Morphometric analysis of sections of perfusion fixed lung from banded and sham control animals showed evidence of considerable thickening of the alveolar septa, Table 2. Septal area expressed as a percentage of tissue area was significantly increased from 23.06±3.40 to 28.33±4.55 \% \((P<0.05\). Morphometric analysis of pulmonary blood vessels revealed a significant increase in wall thickness \((19.7±2.4 \mu m\) vs. \(13.1±1.2 \mu m\)) and wall thickness/lumen ratio in small arterioles \((<250 \mu m\), Table 2) from heart failure lungs compared with controls \((P<0.001\). Similarly, there was a significant increase in wall thickness \((9.6±0.4 \mu m\) vs. \(6.8±0.4 \mu m\)) and wall thickness/lumen ratio in venules \((<250 \mu m\) from lungs of banded animals compared with controls \((P<0.001\), Table 2. Fig. 3 shows electronmicrographs of capillary/alveolar ultrastructure in control and heart failure lungs, illustrating a marked thickening of the basal laminae, cellular infiltration and increased cell size in the heart failure lung.

#### 3.4. Isolated perfused lungs

In constant flow perfused lungs, baseline mean \(P_a\) (sham: 12.9±1.6 mmHg; banded: 13.9±1.3 mmHg) and \(P_{aw}\) (sham: 20.6±1.3 mmHg; banded: 19.8±1.9 mmHg) were similar in control and heart failure lungs. Transient increases in venous outflow pressure (VOP) produced corresponding increases in \(P_a\), \(P_{aw}\) and lung weight, but to a much reduced extent in heart failure lungs, Fig. 4A and B. The total pulmonary resistance fell slightly and to a similar degree with increased VOP in both groups (Fig. 4C). In sham control lungs, lung weight increased in direct
Fig. 2. (A) Organ water content at 150 days postoperation. Values are plotted as mean ± SEM. Sham: n = 24; banded n = 32. Lung water content was significantly reduced, but unchanged in other organs, as indicated. ***, P < 0.001. (B) Water content in lungs studied at various times following aortic banding or sham operation. Values are plotted as mean ± SEM. Water content was significantly increased at 6 ± 1 days in banded animals, but was significantly reduced at 150 days, as indicated. **, P < 0.01; ***, P < 0.001.

Table 1
Haemodynamic and electrocardiographic data from anaesthetised aortic banded and sham operated animals at 150 days. Values are given as mean ± SEM; n values and level of difference between banded and corresponding sham data as indicated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham</th>
<th>Banded</th>
<th>Significance</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic carotid pressure (mmHg)</td>
<td>48.4±5.6</td>
<td>39.1±2.9</td>
<td>NS</td>
<td>16</td>
</tr>
<tr>
<td>Diastolic carotid pressure (mmHg)</td>
<td>32.6±4.6</td>
<td>30.1±2.3</td>
<td>NS</td>
<td>16</td>
</tr>
<tr>
<td>LV systolic pressure (mmHg)</td>
<td>47.2±5.6</td>
<td>61.2±4.0</td>
<td>P &lt; 0.05</td>
<td>16</td>
</tr>
<tr>
<td>LV end diastolic pressure (mmHg)</td>
<td>3.6±0.6</td>
<td>9.0±0.9</td>
<td>P &lt; 0.01</td>
<td>16</td>
</tr>
<tr>
<td>LV+dp/dt</td>
<td>2599±317</td>
<td>1835±202</td>
<td>NS</td>
<td>16</td>
</tr>
<tr>
<td>LV−dp/dt</td>
<td>1858±259</td>
<td>1230±95</td>
<td>P &lt; 0.05</td>
<td>16</td>
</tr>
<tr>
<td>LA systolic pressure (mmHg)</td>
<td>2.35±0.92</td>
<td>6.72±0.47</td>
<td>P &lt; 0.01</td>
<td>7</td>
</tr>
<tr>
<td>LA end diastolic pressure (mmHg)</td>
<td>0.67±0.63</td>
<td>3.76±0.37</td>
<td>P &lt; 0.01</td>
<td>7</td>
</tr>
<tr>
<td>RV systolic pressure (mmHg)</td>
<td>10.1±1.9</td>
<td>13.0±0.6</td>
<td>NS</td>
<td>7</td>
</tr>
<tr>
<td>RV end diastolic pressure (mmHg)</td>
<td>2.5±0.7</td>
<td>4.5±0.4</td>
<td>P &lt; 0.05</td>
<td>7</td>
</tr>
<tr>
<td>Aortic flow (ml/min)</td>
<td>52.5±4.7</td>
<td>26.9±4.9</td>
<td>P &lt; 0.01</td>
<td>10</td>
</tr>
<tr>
<td>Peripheral vascular resistance (dynes s cm⁻³)</td>
<td>63 651±6140</td>
<td>102 046±12 240</td>
<td>P &lt; 0.05</td>
<td>10</td>
</tr>
<tr>
<td>Aortic gradient (mmHg)</td>
<td>0.5±0.9</td>
<td>22.1±2.7</td>
<td>P &lt; 0.001</td>
<td>16</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>244±6</td>
<td>230±8</td>
<td>NS</td>
<td>16</td>
</tr>
<tr>
<td>R-wave height (mV)</td>
<td>0.82±0.05</td>
<td>1.30±0.08</td>
<td>P &lt; 0.001</td>
<td>12</td>
</tr>
<tr>
<td>QRS interval (ms)</td>
<td>46.33±4.84</td>
<td>64.95±5.93</td>
<td>P &lt; 0.05</td>
<td>12</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>326.22±13.84</td>
<td>381.06±16.28</td>
<td>P &lt; 0.05</td>
<td>12</td>
</tr>
</tbody>
</table>
proportion to VOP (Fig. 4D) however, this response was much reduced and was independent of VOP in heart failure lungs.

3.5. Vascular permeability

Evans blue accumulation in response to a 20-mmHg increase in VOP (Fig. 5A) was significantly lower in lungs from banded animals (163±12 μg g⁻¹ dry lung weight) compared with controls (240±33 μg g⁻¹) P<0.05. Fluid accumulation based on these measurements was also significantly less in heart failure lungs (0.83±0.06 vs. 1.23±0.16 ml g⁻¹ dry lung weight, Fig. 5B).

3.6. Pulmonary haemodynamics

During isogravimetric constant pressure perfusion, arterial (10.8±0.4 mmHg; sham vs. 10.5±0.4 mmHg; banded) and venous pressures (3.1±0.2 vs. 3.6±0.3 mmHg) and flow (32.8±2.1 vs. 26.7±2.2 ml min⁻¹ g⁻¹) were similar in control and heart failure lungs. Total pulmonary resistance based on a simple two-resistance single compliance model [16] tended to be higher in heart failure (0.342±0.052 mmHg ml⁻¹ min⁻¹ g⁻¹) than controls (0.241±0.02 mmHg ml⁻¹ min⁻¹ g⁻¹). Baseline resistance of the arterial compartment was significantly increased (61%) in heart failure lungs animals compared with controls (P<0.05), Fig. 6A. Similarly, the baseline pulmonary venous resistance was greater (50%) in heart failure lungs (P<0.05, Fig. 6B). However, microvascular resistance was similar in both groups.

3.7. Capillary filtration coefficient

The increase in lung weight in response to a 5-mmHg increment in Pm was attenuated (40%) in heart failure compared with controls (Fig. 7, upper panel). The Kf,c value calculated from these weight changes was also markedly reduced (83%, Fig. 7, lower panel) in chronic heart failure lungs compared with controls, P<0.001.

4. Discussion

The principal observations from this study are that in lungs adapted to chronic heart failure: (1) lung water content is significantly reduced (2) arterial and venous resistances are increased and (3) capillary filtration is reduced. Morphological changes in pulmonary vasculature and alveoli suggest that lung remodelling contributes to these physiological changes. Novel observations from this study are the reduction in capillary filtration coefficient and in lung water content in lungs adapted to chronic heart failure, the latter reversing the pattern seen acutely following aortic banding.

In this study, the reduction in aortic flow, increased peripheral vascular resistance and raised LV end diastolic and LA pressures in aortic-banded guinea-pigs confirm the presence of heart failure. This is supported by our previous findings of raised plasma catecholamines and atrionatriuretic peptide in this model [10]. The increases in lung and RV weight:body weight ratio are indicative of chronic heart failure. In addition to the haemodynamic changes described, we observed morphological changes in the lungs (septal thickening, increased septal area, increased
Fig. 3. Photomicrographs of (A) low power magnification (×7625) of control lung showing orientation of capillary (CP) and alveolus (AV); (B) high power magnification (×76710) of control lung, showing detail of basal laminae (BL); (C) low power magnification of heart failure lung, to show orientation of capillary and alveolus and (D) high power magnification of heart failure lung to show detail of basal laminae. Note the thickening of the basal laminae, cellular infiltration and increased cell size in the heart failure lung. EC, endothelial cell; PN, type I pneumocyte.
septal:alveolar volume ratio) and pulmonary vessels (increase in arteriolar and venular wall thickness) which confirmed the presence of heart failure in aortic-banded animals after 150 days. The increases in wall thickness: lumen ratio of small arterioles and venules in heart failure lungs are compatible with the increase in arterial and venous resistances observed. They also confirm previous reports of altered pulmonary arteriolar structure in rats with heart failure [17] and increased total pulmonary vascular resistance in dogs with heart failure [5,6].

These morphological changes are indicative of the occurrence of pulmonary vascular remodelling, which is known to occur in patients with pulmonary hypertension [8] and has been described soon after the onset of experimental LV dysfunction [7]. Remodelling and the development of pulmonary oedema have been observed as a result of chronic infusions of angiotensin II [18,19] together with enhanced pulmonary vasoconstriction in a canine model of heart failure [20]. Thus angiotensin II, which may be elevated in heart failure [21] may have a role in mediating this remodelling. Pulmonary venous remodelling may have the effect of attenuating the transmission of left atrial pressure waves to the pulmonary microcirculation, thereby contributing to resistance to pulmonary oedema in chronic heart failure.

The reduction in water content of lungs adapted to chronic heart failure was a reversal to that seen acutely following aortic banding and has not, as far as we know, been reported previously. Pulmonary oedema and an increase in lung water content are characteristic findings in terminal heart failure. The present model was chosen in order to study mechanisms of adaptation to chronic heart failure and therefore reflects more closely clinical aortic stenosis, which may be tolerated for many years before the occurrence of pulmonary oedema, the onset of which usually heralds a rapid decline in this condition. The finding of reduced lung water content in chronic heart failure may reflect increased deposition of non-water related material. An alternative possibility is that lung remodelling, by reducing water filtration, results in a net loss of lung water. Thickening of the alveolar septae and basal lamina may contribute to the attenuated pulmonary microcirculation, thereby contributing to resistance to pulmonary oedema in chronic heart failure.
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Fig. 5. (A) Evans blue dye accumulation in the lungs in response to a 20-mmHg increase in venous outflow pressure. Dye accumulation was significantly ($P < 0.05$) reduced in lungs adapted to chronic heart failure. (B) Water accumulation in the lungs in response to a 20-mmHg increase in venous outflow pressure. Water accumulation was significantly ($P < 0.05$) reduced in lungs adapted to chronic heart failure. Values are plotted as mean±SEM. Sham: $n = 13$; banded $n = 8$.

from animals with chronic heart failure. These morphological changes would also be expected to reduce capillary/alveolar exchange providing a further mechanism for reduced water filtration. The finding of reduced weight gain in heart failure lungs exposed to increased microvascular pressure and reduced $K_{f,c}$ are consistent with this.

Our observation of reduced $K_{f,c}$ in lungs adapted to chronic heart failure differs from data obtained by Townsley et al. [5] who reported no change in $K_{f,c}$ in isolated lung lobes obtained from a canine model of heart failure induced by cardiac pacing for 28 days. We consider that the most likely explanation for this apparent discrepancy may be related to the relative chronicity of the two preparations since we allowed heart failure to develop for 150 days after aortic banding prior to study. Townsley et al. [5] also make the point that their data do not exclude the possibility that ventricular pacing may be required for such changes to develop. Also, the increase in lung weight in our model is not seen in early heart failure and indicates a chronic condition. Interestingly, the acute increase in lung water content occurring 6 days after aortic banding is normalised by 58 days and becomes a reduction in lung

Fig. 6. (A) Arterial resistance was significantly increased ($P < 0.05$) in lungs adapted to chronic heart failure. (B) Venous resistance was also significantly ($P < 0.05$) increased in lungs adapted to chronic heart failure. (C) Microvascular resistance was unchanged in lungs adapted to chronic heart failure. Values are plotted as mean±SEM. Sham: $n = 14$; banded $n = 10$. *, $P < 0.05$; ***, $P < 0.001$. 
lung water content in lungs adapted to chronic, but not acute heart failure. This is associated with a reduced $K_{fc}$ and increased pulmonary arterial and venous resistances. Pulmonary vascular and alveolar remodelling are likely contributors to these changes in pulmonary vascular resistance and capillary filtration. We hypothesise that these pulmonary adaptations to chronic heart failure provide protection from oedema formation. These changes, while initially protective in helping to prevent oedema formation, are also likely to confer major long-term disadvantages: by (a) augmenting total pulmonary vascular resistance and (b) contributing to impaired gas diffusion, known to occur in chronic heart failure [23]. Another important aspect is that an increase in pulmonary vascular resistance, although imposing increased afterload on the right ventricle, may limit an excessive increase in left ventricular filling pressures, but this was beyond the scope of this study. We are not aware of data on changes in endothelial and alveolar water and electrolyte transport comparable to those which have been described in acute lung injury and hypoxia. Recent studies [24–26] suggest the importance of aquaporin water channels and epithelial sodium transport in alveolar fluid clearance and it will be particularly important for the involvement of these factors to be studied in chronic heart failure. The morphological data that we obtained may serve as an explanation for the decrease in capillary filtration, but does not exclude an altered regulation in fluid clearance. Understanding the mechanisms that underlie pulmonary vascular remodelling in heart failure is therefore of considerable importance.

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