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Right coronary artery flow impairment in patients with pulmonary hypertension

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Aims This study investigates whether increased right ventricular (RV) pressure in pulmonary hypertension (PH) impairs right coronary artery (RCA) flow and RV perfusion.

Methods In 25 subjects, five patients with idiopathic pulmonary arterial hypertension, nine patients with chronic thromboembolic pulmonary arterial hypertension, and 11 healthy controls, flow of the RCA and left anterior descending (LAD) artery was measured with MR flow quantification.

Results In PH, RCA peak systolic and mean systolic flow were lower, 1.02 $\pm$ 0.62 mL/s and 0.42 $\pm$ 0.30 mL/s, than peak and mean diastolic flow, 2.99 $\pm$ 1.97 mL/s ($P < 0.001$) and 1.73 $\pm$ 0.97 mL/s ($P < 0.001$); a pattern similar to the LAD. In contrast, in controls, RCA peak and mean flow in systole, 1.63 $\pm$ 0.58 mL/s and 0.72 $\pm$ 0.23 mL/s, were comparable to peak and mean flow in diastole, 1.72 $\pm$ 0.48 mL/s and 0.93 $\pm$ 0.28 mL/s (NS).

The systolic-to-diastolic flow ratio in the RCA, and mean flow per gram RV tissue, were inversely related to RV mass, $R = -0.61$ ($P = 0.009$), and $R = -0.73$ ($P < 0.001$) and to RV pressure, $R = -0.83$ ($P < 0.001$), and $R = -0.57$ ($P = 0.033$).

Conclusion Although in controls, RCA flow is similar in systole and diastole, in PH there is systolic flow impediment, which is proportional to RV pressure and mass. In patients with severe RV hypertrophy total mean flow is reduced.

Keywords Coronary artery flow • Pulmonary hypertension • Right ventricle • Magnetic resonance imaging • Chronic thromboembolic pulmonary hypertension

Introduction

The right ventricle (RV) serves the pulmonary circulation. The RV is thin-walled with much less myocardial mass than the left ventricle (LV). In experiments in which the RV wall was damaged, no decrease in overall cardiac function was observed.[1–3] As a result of these observations, a passive conduit function with minor circulatory function was allocated to the RV. However, in conditions of increased RV afterload, RV function becomes increasingly important. In 1936, Fineberg and Wiggers[4] first postulated that 'circulatory failure following obstruction of the pulmonary circuit had no other cause than fatigue of the RV'. Animal studies investigating RV function under stressed conditions found that RV function becomes increasingly important and that the ability of the RV to compensate is limited by RV perfusion, i.e. right coronary artery (RCA) flow.[5–9]

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In patients with pulmonary hypertension (PH), the increased RV afterload causes RV hypertrophy which requires increased perfusion. Impairment of coronary flow might lead to cardiac dysfunction.[10] Thus, a reduced right coronary flow might contribute importantly to RV failure in patients with PH. In a study of PH in dogs, it was found that RV pressure overload induces a reduction in RCA flow in systole.[11,12] However, a reduced RCA flow in systole, possibly resulting in decreased perfusion per gram of cardiac tissue, has not been reported in patients with increased RV afterload due to PH.

The purpose of this study was to investigate the coronary artery flow pattern of the RCA in patients with PH in comparison with healthy controls and to investigate the influence of RV pressure and RV hypertrophy on the RCA flow.

Methods

Patients

Between March 2006 and September 2006, 48 patients were evaluated because of suspected PH. After initial evaluation, 30 patients were eligible for inclusion. Twenty patients underwent both a right heart catheterization and a cardiac MRI within 1–2 days and were included in the study. In three patients, it was not possible to obtain adequate measurements. Three study subjects, who were catheterized because of suspected PH, turned out to have normal pulmonary artery pressures and were included in the group of 11 healthy volunteers. The other healthy volunteers only had a cardiac MRI. The healthy volunteers were selected age and sex matched controls, without a history of coronary or cardiac disease, obtained from staff members of the Departments of Pulmonary Diseases and Physics and Medical Technology of the VU University Medical Center and from the Department of Cardiology of the Leiden University Medical Center and from their relatives. In total, 25 subjects were included in the study, five patients with idiopathic pulmonary arterial hypertension (IPAH), nine patients with chronic thromboembolic PH (CTEPH) and 11 healthy volunteers. The characteristics of the study subjects are summarized in *Table 1*. All patients had a mean pulmonary artery pressure >25 mmHg at right heart catheterization and a pulmonary capillary wedge pressure <15 mmHg. PH related to connective tissue disease, congenital heart disease, portal hypertension, HIV infection, or a hypoxic origin was excluded by further diagnostic work-up.[13] Patients with CTEPH were diagnosed by pulmonary angiography. The institutional ethics review commission approved the study protocol and all patients gave informed consent. The study complies with the Declaration of Helsinki.

Right heart catheterization

Right heart catheterization was performed to obtain measurements of pulmonary artery pressure, RV pressure, right atrial pressure, pulmonary capillary wedge pressure, cardiac output, pulmonary vascular resistance, and mixed venous oxygen saturation. Cardiac output was determined using the Fick method. Oxygen consumption was measured during right heart catheterization. All patients had a vasodilatory test with inhaled nitric oxide (20 p.p.m.).

Cardiac magnetic resonance imaging

Cardiac MRI was performed with a 1.5T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany) with simultaneous ECG recording. Subjects were imaged in the supine position, using a circularly polarized phased array body coil attached to the chest.

Table 1 Demographic and haemodynamic characteristics

	PH ($n = 14$)	Control ($n = 11$)	*P*-Value
Age, years	51 ± 13	51 ± 9	0.961
Gender (F/M)	7 / 7	6 / 5	0.912
Height, m	1.73 ± 0.11	1.82 ± 0.07	0.255
Weight, kg	81 ± 12	86 ± 13	0.344
Body surface area, m^2	2.0 ± 0.2	2.1 ± 0.2	0.153
Haemodynamic characteristics (patients)			
Systemic arterial pressure, mmHg			
Systole	126 ± 15	122 ± 8	0.391
Diastole	78 ± 11	76 ± 12	0.668
Mean	96 ± 11	90 ± 12	0.270
Pulmonary arterial pressure, mmHg			
Systole	81 ± 26	nm	nm
Diastole	28 ± 12	nm	nm
Mean	48 ± 15	nm	nm
Right atrial pressure, mm Hg	5.0 ± 3.1	nm	nm
Pulmonary vascular resistance, dyne s/cm^5	600 ± 254	nm	nm
Cardiac output, L/min	5.5 ± 2.0	nm	nm
Mixed venous O_2, %	67 ± 6	nm	nm
Morphometric characteristics			
RV mass, g	107 ± 37	61 ± 14	<0.001
LV mass, g	129 ± 36	117 ± 34	0.406
RVEDV, mL	174 ± 61	106 ± 34	<0.001
LVEDV, mL	99 ± 33	96 ± 35	0.773

PH, pulmonary hypertension; RV, right ventricle; LV, left ventricle; RVEDV, right ventricular end-diastolic volume; LVEDV, left ventricular end-diastolic volume; nm, not measured.

Measurement of right and left ventricular mass and volume

Short-axis images of the heart from apex to base were acquired, covering the whole LV and RV. For the cine images, a gradient-echo pulse sequence (True-FISP by Siemens) was applied (repetition time/echo time, 34/1.6 ms; flip angle, 60°; field of view, 280 × 340 mm^2; matrix, 150 × 256 pixels; pixel size, 1.9 × 1.3; slice thickness, 6 mm; slice distance, 4 mm). The endo- and epicardial contours of the RV and LV were delineated manually by a blinded observer and processed using MASS software (Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands) to obtain RV and LV masses and end-diastolic volumes.

Measurement of right coronary artery and left anterior descending flow

Coronary artery flow measurements were performed according to a previously described protocol, with minor modifications.[14] In addition, MR contrast, (0.2 mmol/kg gadolinium-diethylene triamine pentaacetic

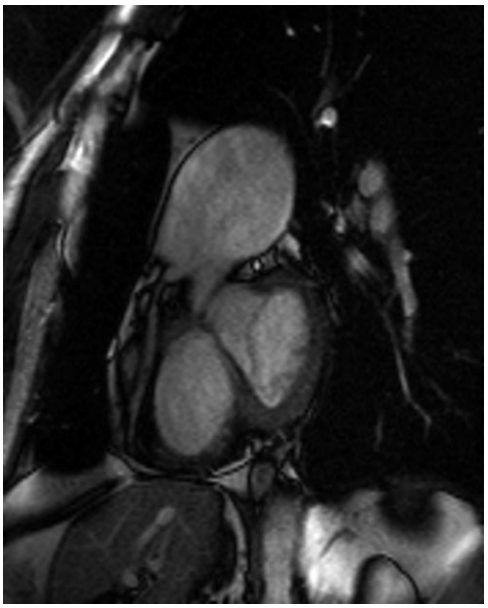

Figure 1 Example of a localizing image to identify the origin of the right coronary artery. In this particular image, the left anterior descending artery is also seen perpendicular to the image plane

acid) was used to enhance the angiographic images. First, localizing images using a pulse sequence (gradient echo, 11 k_y lines per heartbeat, echo time 6.2 ms, repetition time 14 ms) were obtained to identify the origins of the RCA and left anterior descending (LAD). Then an oblique plane was obtained, showing a longitudinal section of the RCA and LAD (*Figure 1*). For the flow measurements, an image plane orthogonally to these longitudinal sections was positioned at 20 mm from the origin of the RCA and LAD. The flow in the coronary arteries was then determined in this image plane using a two-dimensional, spoiled gradient echo pulse sequence, and a one-dimensional velocity signal parallel to the flow in the coronary artery (velocity sensitivity, 40 cm/s; repetition time ms/echo time ms, 24/5; flip angle, 30°; field of view, 125 × 250 mm^2; matrix 100 × 256 pixels; pixel size 1.16 × 0.98; slice thickness 6 mm). One fat saturation pulse was applied per cardiac cycle, directly after the R-wave trigger. Scan duration was maximal 960 ms, acquiring 40 frames. To prevent wrap-around artifacts, the posterior elements of the phased array coil were switched of and the field of view was positioned close to the anterior wall. Subtraction of velocity encoding phase maps was used to correct for inhomogeneity of the magnetic field, leaving only phase changes related to velocity. The velocity maps were analysed with the FLOW software (Department of Radiology, Leiden University Medical Center, Leiden). The magnitude image was used to select the position and size of the coronary artery cross-section. This area was selected as region of interest. The region of interest was repositioned manually in each temporal frame of the cardiac cycle. The area of the region of interest was kept constant during the cardiac cycle. Background motion was corrected by subtracting the velocity in the region of interest with the average velocity of a circular reference contour surrounding the coronary arteries with 3 pixel distance. If this reference contour incorporated a nearby blood vessel, it was manually corrected. The flow (mL/s) was calculated as the product of the coronary artery cross-sectional area and area averaged velocity.

For each patient and control, a flow curve of the RCA and LAD flow was obtained (*Figure 2*). The R-wave on the electrocardiogram indicated the start of systole. The duration of systole was obtained from the contractile phase of short-axis cine images. The diastolic phase of the cardiac cycle was defined as the start of relaxation on the short-axis cine images until the next R-wave on the electrocardiogram. Peak systolic and diastolic flows were defined as the maximal flow measured during systole or diastole, respectively. Mean systolic flow was defined as the averaged flow during the systolic phase of the cardiac cycle. Mean diastolic flow was defined as the averaged flow during the diastolic phase of the cardiac cycle. Finally, the mean flow during one heartbeat was calculated by averaging the flow over the entire cardiac cycle. To average instantaneous flows over the groups, time was normalized by presenting it as percentage of heart period.

Statistical analysis

All data are expressed as mean ± SD. Comparisons between groups were made by the two-sided *t*-test, and chi-square test. To reduce Type I error due to multiple testing, *P*-values <0.03 were considered significant. To asses the difference in flow profiles in LAD and RCA between PH patients and the healthy controls, we used a multilevel analysis. This technique takes into account that the same subjects are repeatedly measured and it uses all the available data, irrespective of the number of repeated measurements. Furthermore, multilevel analysis is capable of dealing with variations in the duration of the cardiac cycle between patients.[15] We used a random intercept model with as level 2 patient ID and as level 1 time. As independent variables, we used the dummy variable indicating the patient group and the interaction between the time during the cardiac cycle and patient group to see whether the effect of flow profile differed for patients with PH and healthy controls. We also considered non-linear effects of time by including the second and the third power of time in the model and its interaction with patient group. For each dependent variable, we choose the best fitting model based on the log-likelihood function. Pearson correlations were used to assess the relationship between coronary artery flow with RV and LV mass and pressures. The variables were normally distributed, or normalized with a log-transformation. In these analyses, *P*-values <0.05 were considered significant.

Results

The demographic, haemodynamic and morphometric characteristics of the study subjects are summarized in *Table 1*. Mean pulmonary artery pressure, pulmonary vascular resistance, RV mass, and RV volume were not different between the patients with IPAH and the patients with CTEPH. Systemic pressure did not differ between patients and controls. Mean pulmonary artery pressure of the patients with PH was 48 ± 15 mmHg and pulmonary vascular resistance was 600 ± 254 dyne s/cm^5. RV mass in the PH patients was significantly increased compared to the RV mass of healthy controls, 107 ± 37 g vs. 61 ± 14 g ($P < 0.001$). The mean RVEDV in the PH patients, which was 174 ± 61 ml, was significantly increased compared to the mean RVEDV of healthy controls, which was 106 ± 34 ml ($P < 0.001$).

Coronary flow profiles

The flow profiles of the LAD and RCA, mean ± SD, with normalized time, are presented in *Figure 3*, and detailed information is

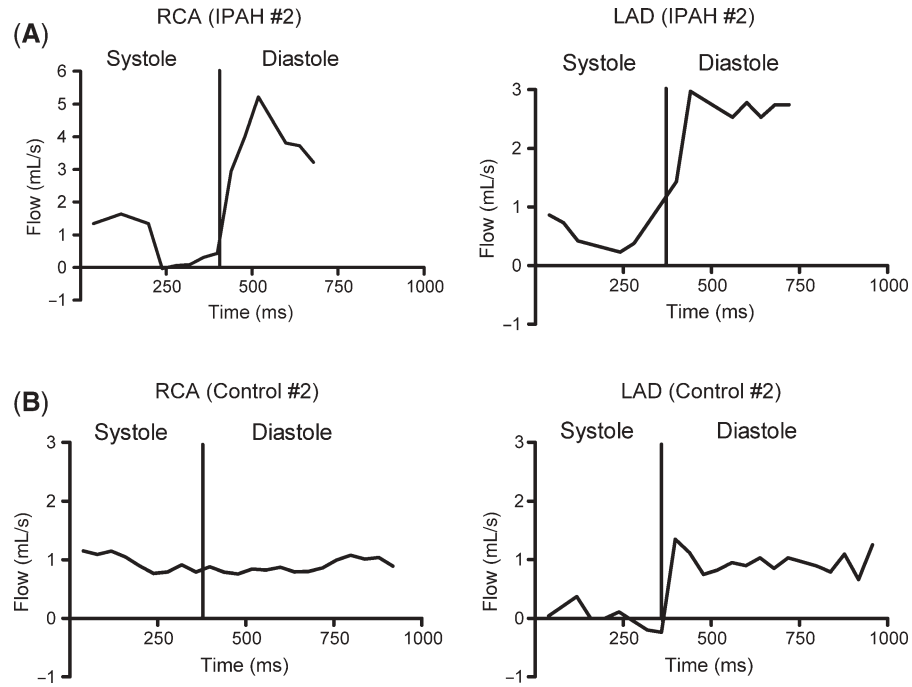

Figure 2 Representative examples of the right coronary artery and left anterior descending flow curve in a patient with idiopathic pulmonary arterial hypertension (above) and a healthy control (below). Systolic and diastolic phase in the cardiac cycle are indicated

given in *Table 2*. The coronary artery flow profiles in the LAD are similar in PH patients and control subjects. The flow profiles in the RCA of the PH patients show a biphasic flow profile, whereas this flow profile in control subjects is smooth and does not depend on contraction. In PH patients, RCA flow in systole is markedly reduced while diastolic flow is increased. We also compared the flow profiles between patients with PH and the healthy controls directly with a multilevel analysis. For RCA, a significant interaction effect was found between patient group and time. For patients with PH, the best model that fitted the RCA flow was a biphasic s-shaped curve, whereas for healthy patients a smoother profile was found (*Figure 4*). For LAD, there was no difference found between the flow profiles. The mean RCA flow over the entire cardiac cycle is increased in PH patients compared with healthy controls, 1.25 ± 0.69 mL/s compared with 0.86 ± 0.19 mL/s ($P = 0.017$).

The systolic-to-diastolic flow ratios are also reported in *Table 2* and show that patients with PH have a significantly smaller mean systolic-to-diastolic flow ratio in the RCA compared with controls, 0.39 ± 0.28 compared with 0.82 ± 0.43 ($P = 0.007$). For the LAD, mean systolic-to-diastolic flow ratios were not different between PH patients and healthy controls.

Relation of coronary flow to ventricular pressure

The total mean flow in the RCA correlated with RV systolic pressure, $R = 0.57$ ($P = 0.033$). Total mean flow per gram myocardial tissue in the RCA also correlated with RV pressure, $R = -0.57$ ($P = 0.033$). In addition, mean diastolic flow in the RCA correlated with diastolic coronary perfusion pressure, defined as diastolic aortic pressure subtracted by end-diastolic ventricular pressure, $R = 0.67$ ($P = 0.003$). There was no significant correlation between the systolic coronary perfusion pressure and mean systolic flow in the RCA, $R = 0.27$ ($P = 0.318$). The contribution of RV pressure to the biphasic flow pattern in the RCA of patients with PH was investigated by correlating the systolic-to-diastolic flow ratio of the RCA to RV systolic pressure. There was a strong correlation between the mean RCA systolic-to-diastolic flow ratio and the RV systolic pressure, $R = -0.83$ ($P < 0.001$) (*Figure 5*).

Relation of coronary flow to ventricular mass

Total mean coronary flow in the RCA correlated with RV mass, $R = 0.81$ ($P < 0.001$). When we calculated mean systolic and diastolic coronary blood flow per gram myocardial mass, both PH patients and healthy controls have an average flow per mass of around 1 mL/min/g during diastole, in the LV as well as in the RV (*Table 2*). As expected, during systole, flow per mass was reduced in the LAD of both groups and in the RCA of patients with PH. The reduction of RCA flow during systole, expressed as the RCA systolic-to-diastolic flow ratio, correlated with RV mass, $R = -0.61$ ($P = 0.009$). Although the total mean coronary blood flow per gram myocardial tissue over the entire group combined was not significantly different in PH patients compared to controls, for both the RV and LV, we found that total coronary

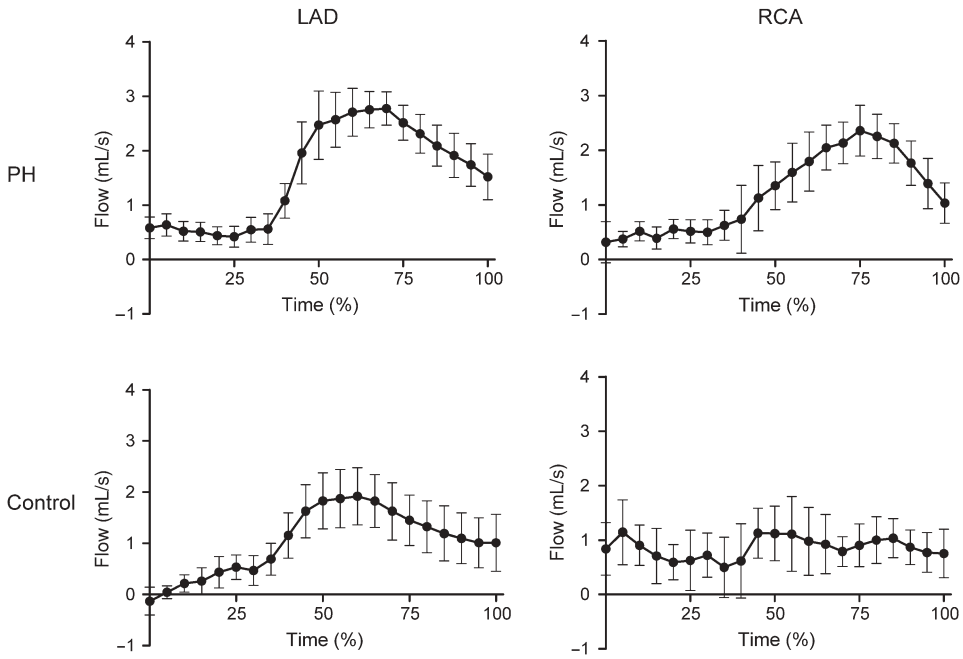

Figure 3 Coronary artery flow profiles in the right coronary artery (RCA) and left anterior dscending (LAD) artery of patients with pulmonary hypertension (PH) and control subjects. Time starts at the ECG R-wave. To average over the groups time is expressed as percentage of duration of one heartbeat. The error bars show ± 1 SD

blood flow per gram myocardial mass declines in proportion to the amount of RV hypertrophy, $R = -0.73$ ($P < 0.001$) (*Figure 6*).

Discussion

We found that in patients with PH RCA flow becomes strongly biphasic with reduced flow in systole and higher flow in diastole. The phasic pattern starts to resemble the profile observed in the LAD. Our results also show that the reduction in systolic RCA flow is related to systolic RV pressure and to RV mass. In addition, we found that in patients with PH, the mean RCA flow per gram myocardial tissue over the entire group was similar to that of controls, but decreased in proportion to the extent of RV hypertrophy. It is thus expected that, especially in subendocardial layers, flow is insufficient in severe RV hypertrophy.

Animal studies have demonstrated a biphasic flow pattern in the left coronary artery but approximately equal systolic and diastolic right coronary artery flow.[16] These observations have later been confirmed in human studies using the intracoronary Doppler guidewire[17] and in non-invasive human studies using MR velocity measurements of the LAD and RCA.[14]

In animal models of RV stress, however, biphasic coronary flow profiles were observed in the RCA. This was seen in models of pulmonary embolism inducing acute RV stress,[5–9] in models of congenital chronic RV stress,[11,18] and in acquired chronic RV stress.[12] In humans, little information is available about the effects of RV stress on RCA flow. Case studies of patients with congenital RV hypertension[19] and patients with PH secondary to atrial septal defect[20] report biphasic coronary flow profiles of the RCA and reversal of this pattern after cardial surgery, suggesting a relation between biphasic RCA flow and RV hypertension. One study by Akasaka *et al.*[21] investigated the relation between RCA flow and PH in humans using intracoronary Doppler velocity measurements. Akasaka *et al.*[21] studied 40 subjects, of which 17 patients had PH defined as a systolic pulmonary artery pressure >35 mmHg during right heart catheterization. The study included three patients with IPAH, nine patients with CTEPH, and five patients with PH secondary to connective tissue disease. They found a decreased systolic-to-diastolic flow ratio in the RCA of patients with PH and that the magnitude of this decrease in flow ratio was proportional to the coronary driving pressure. It was concluded that in the absence of differences in aortic pressure between patients with and without PH, the decreased systolic-to-diastolic flow ratio is attributed to increased RV pressure. This is in agreement with our data. Akasaka *et al.*[21] found no differences in absolute systolic or diastolic RCA flow between patients with and without PH, which seems not in agreement with our present findings. However, their conclusion was based on flow measurements by means of Doppler in the proximal part of the RCA, which also includes flow to the right atrium and LV, since reliable measurement in a more distal RCA branch was only possible in 10 PH patients and nine controls of the 40 study subjects included in the study.

The main factors that determine systolic coronary flow impediment are RV pressure, muscle contractility, muscle thickening, and possible changes in the microcirculation. The RV pressure increase is the most obvious candidate here. Changes in the microcirculation were not studied but these changes are not expected to

Table 2 Systolic and diastolic coronary artery flow in patients and control subjects

		PH ($n = 14$)	Control ($n = 11$)	*P*-Value
Mean systolic flow (mL/s)	RCA	0.42 ± 0.30	0.72 ± 0.23	0.012
	LAD	0.59 ± 0.58	0.22 ± 0.26	0.069
Mean diastolic flow (mL/s)	RCA	1.73 ± 0.97	0.93 ± 0.28	0.014
	LAD	2.26 ± 1.35	1.62 ± 0.63	0.159
Peak systolic flow (mL/s)	RCA	1.02 ± 0.62	1.63 ± 0.58	0.021
	LAD	1.05 ± 0.72	0.79 ± 0.43	0.317
Peak diastolic flow (mL/s)	RCA	2.99 ± 1.97	1.72 ± 0.48	0.047
	LAD	3.54 ± 2.14	2.40 ± 0.75	0.106
Total mean flow during cardiac cycle (mL/s)	RCA	1.25 ± 0.69	0.86 ± 0.19	0.017
	LAD	1.55 ± 0.92	1.02 ± 0.65	0.036
Mean syst/diast flow ratio	RCA	0.39 ± 0.28	0.82 ± 0.43	0.007
	LAD	0.29 ± 0.25	0.15 ± 0.16	0.123
Peak syst/diast flow ratio	RCA	0.46 ± 0.26	0.92 ± 0.57	0.013
	LAD	0.29 ± 0.13	0.36 ± 0.19	0.326
Myocardial mass (g)	RV	107 ± 65	61 ± 15	0.031
	LV	130 ± 35	117 ± 34	0.376
Mean flow/mass diastole (mL/min/g)	RV	1.16 ± 0.52	0.98 ± 0.42	0.343
	LV	1.10 ± 0.48	0.88 ± 0.41	0.171
Mean flow/mass systole (mL/min/g)	RV	0.36 ± 0.32	0.81 ± 0.37	0.003
	LV	0.28 ± 0.26	0.13 ± 0.15	0.100
Total mean flow/mass (mL/min/g)	RV	0.83 ± 0.35	0.90 ± 0.35	0.438
	LV	0.76 ± 0.38	0.75 ± 0.39	0.712

PH, pulmonary hypertension; RCA, right coronary artery; LAD, left anterior descending artery; RV, right ventricle; LV, left ventricle.

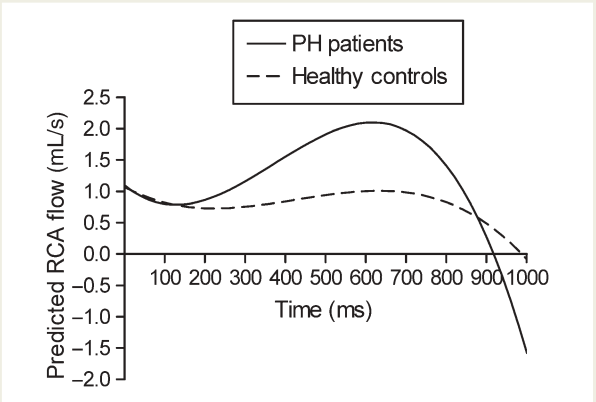

Figure 4 Multilevel analysis was performed to construct predicted right coronary artery (RCA) flow curves using a random intercept model. The curve that corresponded most to the pulmonary hypertension (PH) patients flow profiles was a biphasic s-shaped curve, whereas in healthy controls, a smooth curve was obtained from the model

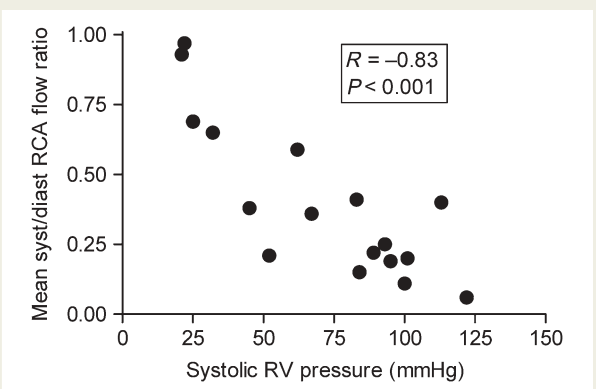

Figure 5 Inverse correlation between systolic right ventricular (RV) pressure and mean systolic-to-diastolic flow ratio in the right coronary artery (RCA) in patients with pulmonary hypertension and three controls, $R = -0.83$ and $P < 0.001$

be large because mean flow (over the whole cardiac cycle) is not decreased.

In patients with severe PH, with reduced systemic pressure because of RV failure and decreased cardiac output, attempts to increase coronary driving pressure with phenylephrine have been unsuccesfull.[23] Although RCA driving pressure increased with phenylephrine, RV performance and cardiac output decreased, possibly due to vasoconstriction.

Myocardial systolic compression also contributes to reduction of RCA flow. Systolic compression of myocardial fibers decreases the diameter of the myocardial microvascular bed and increases vascular resistance, even in an isobaric compression.[22] In patients with PH, who have a RV, which is hypertrophied to withstand systolic pressures close to systemic pressures, this may be an important factor leading to a reduced RCA flow to the RV. In this study, the patients with PH had an increased RV mass and the reduction of RV perfusion was related to the extent of RV hypertrophy. This suggests that the RCA flow in patients with severe PH operates beyond the point of autoregulatory coronary flow reserve, despite the greater coronary flow reserve of the RV.[24] Therefore, it is possible that PH patients with RV hypertrophy are more susceptible to subendocardial ischaemia similar to patients with LV hypertrophy. Indeed, Murray and Vatner[25] have demonstrated that the subendocardial flow is reduced in dogs with RV hypertrophy and Gomez *et al.*[10] reported the presence of RV ischaemia measured by myocardial scintigrapy in nine of 23 patients with PH. Further studies are necessary to evaluate to contribution of decreased RCA blood flow to RV dysfunction in patients with PH and to evaluate whether this decrease in RCA flow leads to RV ischaemia contributing to RV failure.

Study limitations

Measurements were performed in the RCA and LAD but not the circumflex coronary artery. Furthermore, there are anatomical

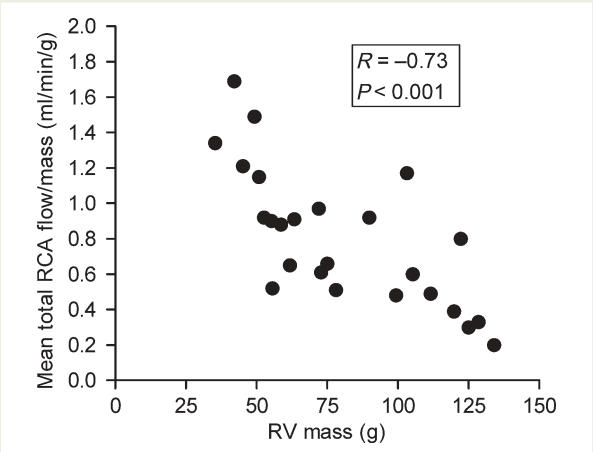

Figure 6 Relation between right ventricular (RV) mass and coronary artery flow of the right coronary artery (RCA) per gram myocardial mass of the RV. There is a strong relation between reduced blood flow per gram myocardial tissue in proportion to the amount of right ventricular hypertrophy in patients with pulmonary hypertension, $R = -0.73$, $P < 0.001$

variations in the RCA and LAD between individual patients, in some patients a small part of the perfusion of the LV is supplied by the RCA. However, it is unlikely that these anatomical variations explain the differences in right coronary flow between PH patients and healthy controls. Similarly, is it unlikely that this explains the decline in right coronary flow in proportion to RV mass in the PH patients.

Conclusion

Systolic RCA flow is impaired in PH. This reduction is proportional to RV mass and pressure.

Conflict of interest: none declared.

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