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Vena cava backflow and right ventricular stiffness in pulmonary arterial hypertension

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Abstract

Vena cava (VC) backflow is a well-recognized clinical hallmark of right ventricular (RV) failure in pulmonary arterial hypertension (PAH). Backflow may result from tricuspid regurgitation during RV systole or from impaired RV diastolic filling during atrial contraction. Our aim was to quantify forward and backward flow in the VC and to establish the main cause in PAH.

In 62 PAH patients, cardiac magnetic resonance measurements provided volumetric flows (ml/s) in the superior and inferior VC; time-integration of flow gave volume. "Backward fraction" was defined as the ratio of backward and forward volume in the VC, expressed as percentage. Time of maximum VC backflow was expressed as percentage of the cardiac cycle. RV volumes and aortic stroke volume were determined. Right heart catheterization gave RV and right atrial pressures. RV end-diastolic stiffness was determined with the single beat method.

The backward fraction was 12 (IQR:3-24)% and larger than 20% in 21 patients. Maximum backflow occurred at near 90% of the cardiac cycle, coinciding with atrial contraction. The backward fraction was associated with maximal right atrial pressure (Spearman's r=0.77), RV end-diastolic stiffness (r=0.65), RV end-diastolic pressure (r=0.77), and was negatively associated with stroke volume (r=–0.61; all $p<0.001$).

Significant backward flow in the VC was observed in a large group of PAH-patients and occurred mostly during atrial contraction as a consequence of impaired RV filling due to RV diastolic stiffness. Backward flow due to tricuspid regurgitation was of significance in only a small minority of patients.

Keywords

Pulmonary arterial hypertension, pulmonary heart disease, right heart failure, right ventricular overload, congestive heart failure, diastolic dysfunction

“take home” message:

In 62 patients with pulmonary arterial hypertension, timing of maximal backflow in the vena cava was in late-diastole, during the right atrial contraction. The amount of backflow was associated with right ventricular stiffness. Stroke volume was reduced.

Abbreviations:

α	curve-fitting constant
β	diastolic stiffness constant
CMR	cardiac magnetic resonance imaging
E_{ed}	end-diastolic elastance
P	pressure
PAH	pulmonary arterial hypertension
PA	pulmonary artery
PAP	pulmonary artery pressure
mPAP	mean pulmonary artery pressure
RV	right ventricle
RVBDP	RV begin-diastolic pressure
RVEDP	RV end-diastolic pressure
RVEDV	RV end-diastolic volume
RVESV	RV end-systolic volume
RA	right atrium
RAP	right atrial pressure
RAP_{max}	maximal right atrial pressure
V	volume
VC	vena cava

Introduction

In pulmonary arterial hypertension (PAH), an increased afterload results in right ventricular (RV) dysfunction and ultimately RV failure and death [1, 2]. Clinical signs of RV failure include peripheral oedema and the distension of the jugular veins. Already described in the 19th century by the German physician Dr. Adolf Kussmaul, severe RV failure can result in distension of the internal jugular vein during inspiration. In modern medicine, the sign of venous backflow of intravenous contrast injected during CT angiography is a frequent first sign pointing towards RV failure. The clinical importance of venous backflow lies not only in a potential loss of RV efficiency (the movement of blood requires energy), but also in a worsening of renal function as a result of venous congestion [3, 4].

Despite the wide recognition of venous backflow as an important hallmark of RV failure, still very little is known about its main determinants. While RV blood may flow away from the pulmonary circulation during systole due to tricuspid regurgitation, an alternative explanation is ejection of blood into the venous system during right atrial contraction. Such reversal of flow could become particular prominent when RV diastolic filling is impaired due to increased RV stiffness. While most physiological studies on RV failure have focused on systolic RV dysfunction [5], right atrial (RA) pressure, a surrogate marker of right ventricular stiffness, was of prognostic significance in multiple epidemiological studies [6-8]. The hemodynamic consequences of RV diastolic stiffness are largely unknown but could include the backflow of venous blood and venous congestion.

During the diastolic part of the cardiac cycle, the healthy RV fills with an amount of blood that is approximately equal to stroke volume (SV). A low SV is associated with poor prognosis [9, 10]. The normal direction of flow towards the RV is determined by small pressure differences between central venous-, RA and RV pressure [11, 12]. In pulmonary

arterial hypertension (PAH) a backflow has been observed in the vena cava (VC) [13, 14]. Reversal of flow requires energy, which can only be generated by either right ventricular contraction in the presence of tricuspid regurgitation [15, 16] or by RA contraction in a setting of impaired RV filling due to stiffness. Irrespective of its cause, backflow will decrease cardiac efficiency and may cause deleterious venous congestion of the kidneys, liver and gut. However, until now, the cause, degree and consequences of venous backflow have not been examined. In this study we used cardiovascular MRI (CMR) to quantify magnitude and direction of flow in the VC, in order to determine the relation between VC backflow and RV diastolic stiffness.

Materials and methods

Patients

We analysed data from the prospective registry of PAH patients seen at the Amsterdam UMC, Vrije Universiteit Amsterdam. Patients routinely undergo CMR imaging, right heart catheterization (RHC), six-minute walk testing and blood sampling at diagnosis and during follow-up. CMR and RHC were performed within a 2-day time interval. Patient inclusion occurred without prior knowledge of the current disease severity, medication, or RHC results. The Medical Ethics Review Committee of the VU University Medical Center did not consider the current study to fall within the scope of the Medical Research Involving Human Subjects (WMO), and an informed consent statement was not obtained (approval number 2012288).

CMR measurement of vena cava flow and right ventricular volumes

The patients underwent a CMR investigation to assess cardiac function and the blood flow in the VC. CMR was performed with a Siemens 1.5T 'Avanto' whole body scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 6-element phased-array body coil. Phase-contrast velocity quantification was performed during shallow continued breathing, using a gradient-echo pulse sequence with through-plane velocity encoding and a velocity sensitivity of 150 cm/sec. Triggering was retrospective, field of view = 240 × 320 mm^2, matrix size = 140 × 256, echo time = 3.4 ms, temporal resolution = 22 ms, flip angle = 15°. In the superior VC, the orientation of the image plane was transverse (Fig. 1a), at the position of the right pulmonary artery (PA). In the inferior VC, flow was measured at a position just below the right atrium and above the venous branches to the liver and other abdominal organs (Fig. 1b).

By integrating the forward and backward parts of the flow curve, the forward and backward volumes over the entire cardiac cycle were calculated for the superior and inferior VC. To assess which part of backward volume was caused by tricuspid regurgitation and which part was caused by RA contraction, backward volumes were also separately determined during ventricular systole and diastole, respectively. Total forward and backward volumes were obtained by taking the respective volumes of the superior and inferior VC together. Finally, the VC backward fraction was determined by dividing the total backward volume by the total forward volume per heartbeat and multiplying with 100 %. The time of maximum backflow in the VC was expressed as a percentage of the cardiac cycle time.

By applying short-axis coverage of the RV by cine CMR, the RV end-systolic volume (RVESV) and end-diastolic volume (RVEDV) were determined. Maximal RA size was assessed by calculating RA cross-sectional area on the 4-chamber cine CMR. The time frame just before opening of the tricuspid valve was selected for this calculation. The MASS software (Medis, Leiden, The Netherlands) was used for these calculations. Stroke volume (SV) was obtained by integrating the aortic flow curve [17].

Right Heart Catheterization

Under local anaesthesia, a balloon-tipped Swan-Ganz catheter (834F75, Edwards Lifesciences LLC, Irvine, CA) was inserted via the jugular vein and brought into position. Under constant electrocardiographic (ECG) monitoring, pulmonary artery pressure (PAP), RV and RA pressures were recorded with a 1000 Hz sampling rate. From the RV pressure curve, minimum pressure gave RV begin-diastolic pressure (RVBDP), while the highest diastolic pressure, just before the onset of isovolumic contraction, gave RV end-diastolic pressure (RVEDP). From the RA pressure (RAP) curve, the maximum value, RAP_{max}, was determined.

Single-beat pressure-volume analysis of right ventricular pressures

To determine End-Diastolic Elastance, E_{ed} the three-point method was used [18, 19]. The first point PV point was set at V = 0 ml, P = 0 mm Hg. The other two points were given by V = RVESV, P = RVBDP, and V = RVEDV, P = RVEDP respectively. To avoid the effect of measurement offset errors due to the positioning of the RV catheter pressure transducer, RVBDP was normalized at 1 mm Hg, while the RVEDP was calculated with the following formula: $RVEDP_{normalised} = 1 + (RVEDP – RVBDP)$. Through the three points, an exponential curve was fitted given by the formula [18, 20]: $P = \alpha (e^{V\beta} – 1)$ with P: pressure in mm Hg; α: curve-fitting constant in mm Hg; β: diastolic stiffness constant in ml^{-1}; V: volume in ml. E_{ed} was then calculated as the slope of this curve at EDV [19]: $\alpha \beta e^{\beta EDV}$ and used as measure of RV stiffness (mm Hg ml^{-1}). Single-beat pressure-volume analyses were performed in Mathematica (Wolfram Research, Champaign, IL).

Statistics

Normally distributed variables are presented as mean ± standard deviation, non-normally distributed variables as median (IQR: 25 % - 75 %). Spearman's rank-order correlation was applied to assess the associations between VC backward fraction, haemodynamics and RV function. The level of significance used for testing was $p < 0.05$. The statistics were performed by using Prism 7, GraphPad Software Inc, San Diego, CA.

Results

Patient characteristics

Sixty-two patients were included in this study (48 % idiopathic PAH, 21 % hereditary PAH, 21 % PAH secondary to connective tissue disease, 6 % chronic thromboembolic pulmonary hypertension, 2 % PAH secondary to HIV and 2 % pulmonary veno-occlusive disease). The

majority of patients was female and the average age was 51 ± 14 years. Medication consisted of endothelin receptor antagonists, PDE5-inhibitors, prostacyclins, and calcium antagonist. Double therapy consisted mainly of endothelin receptor antagonists in combination with PDE5-inhibitors; triple therapy included prostacyclins as well. Patient characteristics are summarized in Table 1. The stroke volume from RV volumes was 62 ± 18 ml, not different from the measurement by aortic flow (57 ± 16 ml, $p = 0.128$).

Vena cava backflow

Figure 2 shows the MRI magnitude and velocity images of the flow measurement in the VC inferior. In systole, at a trigger delay (Td) of 101 ms, the direction of blood velocity in the VC is directed towards the heart (coded "bright"). In diastole, at trigger delay 543 ms, the direction of VC blood velocity reverses to the backward direction away from the heart (coded “dark”).

A diagram with simultaneous pressures in the PA, RV and RA in combination with VC flow measurements is given in Figure 3. The CMR flow curves in the superior and inferior VC were aligned over the cardiac cycle using the ECG.

Maximum VC backflow was observed at 86 (82 - 90) % (superior VC) and 92 (89 - 95) % (inferior VC) of the cardiac cycle, coinciding with RV diastole and atrial contraction. In two patients with severe tricuspid regurgitation, maximum backflow was observed in the systolic phase of the cardiac cycle. In the remaining 60 patients, maximum backflow occurred in the diastolic phase (atrial contraction) and amounted to 93 ± 11 % of total backflow during the entire cardiac cycle. The backward fraction (ratio of backward to forward volume) was 12 (3 - 24) % (Figure 4). The backward fraction was significantly associated (all $p < 0.001$, Figure 4) with RAP_{max} ($r = 0.77$), RVEDP ($r = 0.77$), and E_{ed} ($r = 0.65$). In addition, backward

fraction was negatively associated (Table 2) with SV (r = –0.61) and RV ejection fraction (r = –0.61). Only a weak negative correlation could be observed between backward fraction and kidney function expressed as eGFR (r = – 0.27, $p < 0.05$).

Discussion

From this study we conclude that, in a large group of PAH-patients, a backward flow in the VC can be observed in late diastole, which is closely associated with RV diastolic stiffness. Tricuspid regurgitation, although present in almost all PAH patients, caused a maximal systolic backflow in the VC in only two patients. The bulk of backflow was observed during RA contraction.

The underlying mechanism of backflow is summarized in the Figure 5, which shows the pressures and flows during RA contraction. In a normal subject, the flow from the RA is in the forward direction, because the RV is compliant and the RV end-diastolic pressure remains low. However, in a PAH patient with RV diastolic dysfunction, the RV is stiff and RVEDP is elevated. Blood flow will follow the largest downward pressure gradient, and when the pressure in the VC is lower than in the RV, flow will be partially directed back into the VC. As a consequence, venous return to the RV is reduced, leading to a loss of RV stroke volume. This chain of events is presented in Figure 6. Based on the strongest associations with backflow, RV stiffness increase and elevated RVEDP are given the central place in the process. RV volumes showed less tight relations and may be secondary effects. The relation between the backward fraction and RA pressure and also maximal RA area suggest that the volume status of the patient may also be a factor influencing the amount of backflow.

Previously, echocardiographic measurements were used to show that an atrial reversal wave is present in hepatic venous flow [21]. In addition, pulmonary angiography showed reflux of

contrast medium into the inferior VC, and this reflux was associated with pulmonary hypertension [13], or with 30-day survival after pulmonary embolism [14]. In these angiography studies the timing of backflow in the cardiac cycle was not determined. We could demonstrate for the first time that VC backflow is mainly a phenomenon occurring during diastole and is therefore closely associated with RV diastolic stiffness. The finding that the backward fraction was also positively associated with E_{es}, while negatively associated with RVEF and stroke volume can be clarified as follows. In the pressure overloaded RV, hypertrophy is required to increase E_{es} in order to remain coupled to the load [5]. Hypertrophy implies wall thickening, which in turns entails a stiffer RV and increased E_{ed}. In this instance, RVEF and stroke volume are not measures of contractility.

Clinical practice

Our study introduces a new concept of backflow in the VC related to RA contraction. Instead of filling the RV, the RA pumps a part of its volume back into the VC. An impact on stroke volume is suggested by the negative association between the backward fraction and SV. Through this mechanism, diastolic failure of the RV is linked with systolic RV failure, since loss of diastolic blood supply also implies loss of systolic stroke volume.

Therefore, this study demonstrates the potential detrimental effect of increased RV diastolic stiffness on RV systolic adaptation. Previous studies have shown that stiffening of the RV is not just the consequence of hypertrophy but is partially mediated by increased collagen deposition and hypophosphorylation of the giant sarcomeric protein titin [18, 19, 22]. Until now no therapeutic strategies are available that directly target the RV [23]. Our current study, delineates once again the potential clinical importance of RV diastolic stiffness in PAH, and efforts should be made to obtain further insights in the pathophysiological mechanisms possibly giving impetus to novel treatments.

Limitations

In our study, only associations were studied and further research is necessary to establish cause and effect relations. Another limitation is the lack of pressure recordings in the VC. The relative levels of the pressure in the VC and the pressure in the RV will determine which fraction of blood is reversed by RA contraction.

Finally, although the backflow could contribute to venous congestion [4], in our study, only a weak association could be observed between backward fraction and kidney function. This could possibly be explained by the fact that altered eGFR levels can be both a reflection of forward and backward failure. Unfortunately, in only a small percentage of patients, levels of gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were determined, limiting correlation analyses. From our data it was not possible to determine to influence of the volume status on backflow. Future studies may investigate the effect of diuretics on the backward fraction.

Conclusion

In the PAH patients of this study, the timing of maximal backflow in the VC was in late-diastole, during the RA contraction. The backward fraction was associated with RV stiffness. Because the RV loses part of its venous return, the RV stroke volume is reduced.

Perspectives

It is generally assumed that VC backflow is caused by tricuspid valve insufficiency, and thus would occur during systole. In the PAH patients of this study, the VC backflow was mainly during atrial contraction and was associated with RV end-diastolic stiffness.

The VC backflow limits the venous return to the RV, reducing RV stroke volume. Also, the VC backflow may contribute to venous congestion in these patients. Between patients, quite

some differences in backflow are seen. Further research may elucidate the causes of backflow in the individual patient.

The clinical implications of our findings remain to be determined. Our report contributes to an improved understanding of right heart inefficiency, a previously documented phenomenon associated with progressive RV failure [24]. Right heart inefficiency in PAH is likely partly based on the cellular and molecular changes characteristic of heart failure, but also on mechanical inefficiency. Previously recognised contributors to mechanical inefficiency in right heart failure are post systolic contraction [25] and tricuspid insufficiency. Here we demonstrate the contribution of right atrial contraction related VC backflow to mechanical inefficiency. As mechanical inefficiency may contribute to the progression of RV failure, interventions to restore efficiency have been proposed, including RV-LV resynchronisation therapy and tricuspid valve repair. Also, further research is needed to investigate the pathophysiological causes of RV diastolic stiffness in order to develop novel treatment strategies directly targeting the right ventricle.

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Author Disclosures

Dr. Marcus received fees as a consultant for Actelion Pharmaceuticals. The remaining authors have nothing to disclose.

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TABLES

Table 1. Patient characteristics and measurements

General characteristics	
Age (years)	51 ± 14
Gender (female/male)	49/13
6MWD (m)	459 ± 151
NTproBNP (ng/L)	363 (122 - 1150)
Disease type	
Idiopathic/hereditary PAH	43
PAH associated with connective tissue disease	13
HIV associated PAH	1
Pulmonary veno occlusive disease	1
Chronic thromboembolic pulmonary hypertension	4
Treatment at time of assessment	
None	12
Mono therapy	11
Double therapy	34
Triple therapy	5
Right heart catheterisation	
HR (beats/min)	75 ± 11
Stroke volume (ml)	77 ± 25
mPAP (mmHg)	48 ± 12
mRAP (mmHg)	8 ± 5
SvO_2 (%)	68 ± 10

PAWP (mmHg)	9 ± 3
PVR (dynes*s/cm^5)	518 (362 - 1417)
CO (l/min)	5.8 ± 1.9
Cardiac magnetic resonance imaging	
HR (beats/min)	75 ± 13
Stroke volume (ml)	57 ± 16
RVEDV (ml)	163 ± 64
RVESV (ml)	101 ± 64
RVEF (%)	42 ± 14
Maximal RA size (cm^2)	30 ± 10
LVEDV (ml)	104 ± 30
LVESV (ml)	40 ± 18
LVEF (%)	63 ± 9

Data are presented as mean ± SD or median (25-75% percentile) dependent on normal distribution. Abbreviations: 6MWD, six minute walk distance; NTproBNP, N-terminal pro-brain natriuretic peptide; HR, heart rate; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; SvO_2, mixed venous oxygen saturation; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; CO, cardiac output; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction; RA: right atrium; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

Table 2: Associations between backward fraction and clinical parameters

Parameter	Spearman R	p-value
mPAP	0.69	$p < 0.001$
Stroke volume	–0.61	$p < 0.001$
Ees	0.61	$p < 0.001$
Ees/Ea	–0.15	$P = 0.45$
RVEF	–0.61	$p < 0.001$
RVEDV	0.35	$p < 0.01$
RVESV	0.51	$p < 0.001$
Maximal RA size	0.59	$p < 0.001$
Ln(NT-proBNP)	0.71	$p < 0.001$
6MWD	–0.33	$p < 0.01$
eGFR	–0.27	$p < 0.05$

Abbreviations: mPAP, mean pulmonary artery pressure; Ees, end-systolic elastance; Ees/Ea, ventricular-arterial coupling; RVEF, right ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; NTproBNP, N-terminal pro-brain natriuretic peptide; 6MWD, six minute walk distance; eGFR, estimated glomerular filtration rate.

FIGURES

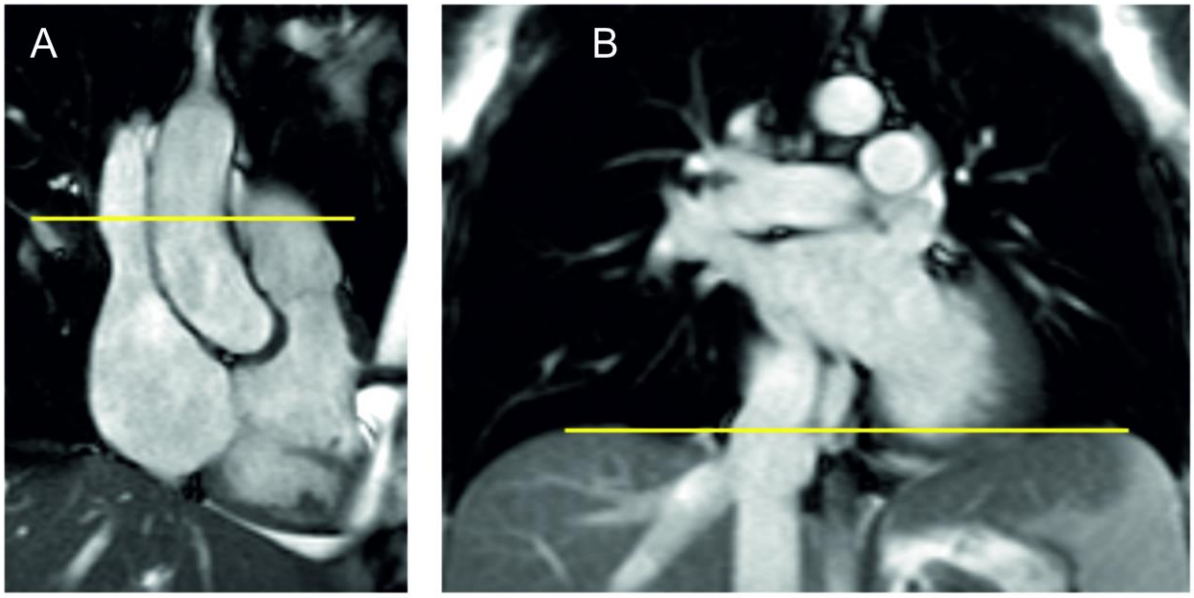

Figure 1. Planning of the CMR velocity quantification.

Imaging of the vena cava superior **(A)** and vena cava inferior **(B)**. The yellow lines indicate the projections of the imaging planes used for through-plane velocity quantification.

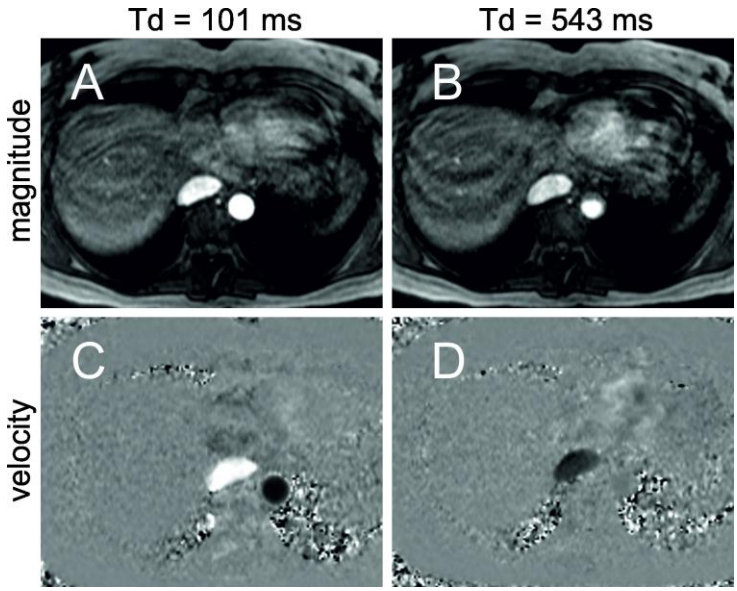

Figure 2. CMR velocity quantification in the vena cava inferior.

Magnitude (**A, B**) and velocity (**C, D**) images of the vena cava inferior at two time points in the cardiac cycle. In the velocity images, "bright" indicates velocity towards the heart, and "dark" velocity away from the heart. Td is the trigger delay after the ECG R-wave. At Td = 101 ms, the velocity in the vena cava is directed towards the heart. At Td = 543 ms, the velocity in the vena cava has reversed, and is now directed away from the heart.

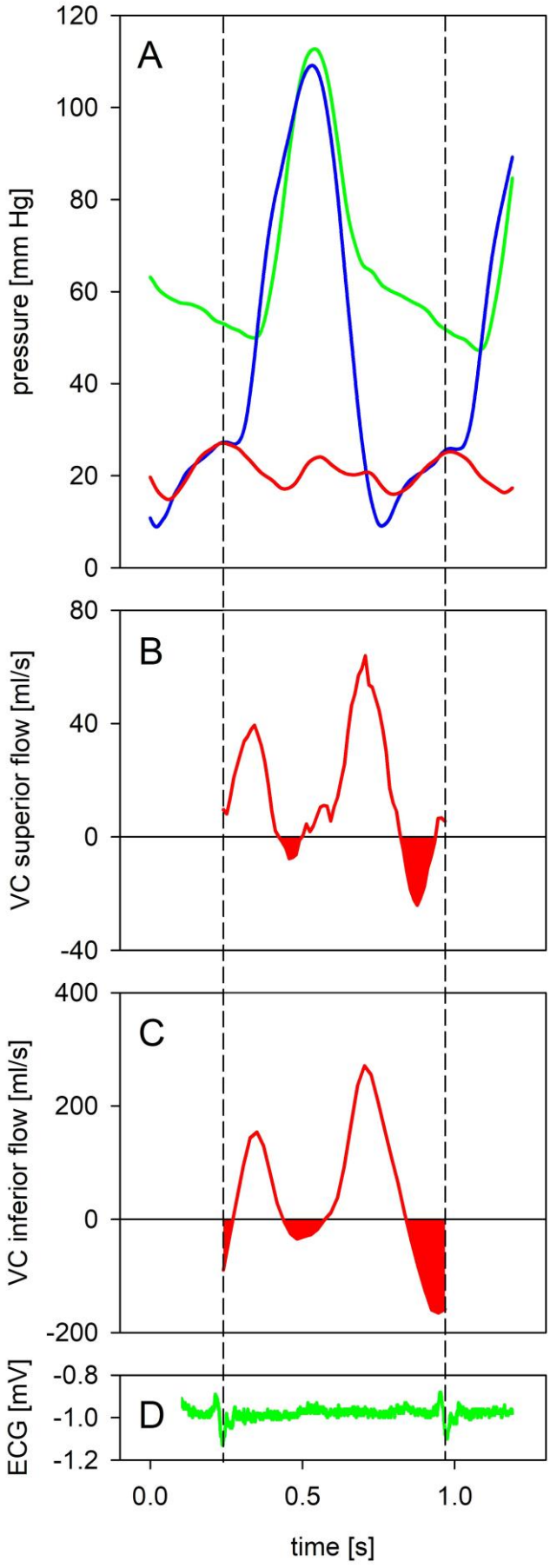

Figure 3. Pressure and flow measurements during the cardiac cycle.

Simultaneous pressure recordings **(A)** in a PAH patient: in the pulmonary artery (green), right ventricle (RV, blue), and right atrium (red) pressure by right heart catheterization. Note in the RV pressure recording, that after the beginning of diastole (lowest RV pressure value), the RV pressure increases quite steeply, which indicates that the RV wall is stiff (diastolic dysfunction).

For the same patient, MRI-derived volumetric flow in the vena cava (VC) **(B)** superior and inferior **(C)** are plotted. The time scale is synchronized using the ECG tracing **(D)**. Flow towards the heart is positive, flow away from the heart is negative (backflow). The backward volumes are shown as red filled areas. The largest backward volume is late in the cardiac cycle, synchronous with the atrial contraction. In this patient, the total backward fraction is 40% (14% for the VC superior and 47% for the VC inferior).

The backflow which occurs at the time when the pressure in the RV rapidly increases, and which stops when the RV pressure starts decreasing, is likely caused by tricuspid valve insufficiency. The low pressure in the RA at that moment is caused by the stretching of the RA by RV contraction. The jet generated by the RV through the insufficient tricuspid valve has a high velocity but involves little volume, so that the pressure increase in the RA by the regurgitation is limited and the backflow into the VC is small.

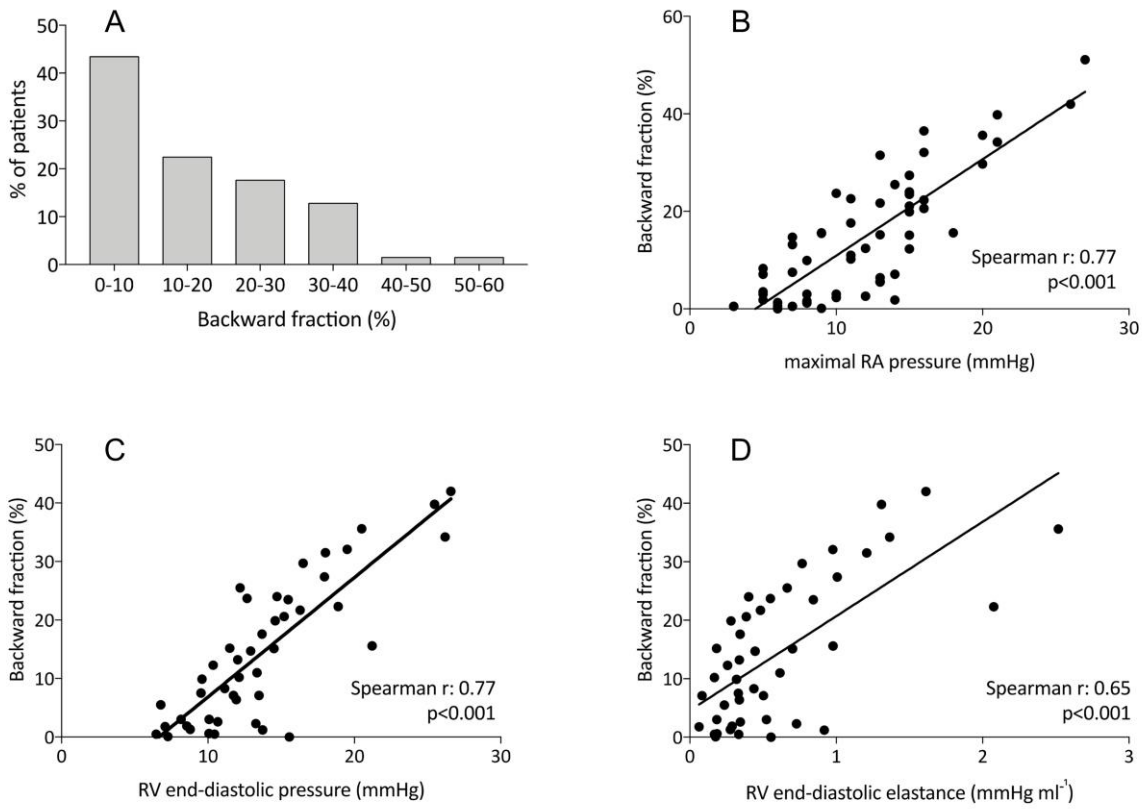

Figure 4. Association with the backward fraction

The backward fraction (defined as the ratio of backward volume and forward volume, expressed as percentage) as distributed over the patient population is shown in **A**. The backward fraction is plotted versus maximal right atrial (RA) pressure **(B),** versus right ventricular end-diastolic pressure **(C)** and versus RV end-diastolic elastance as measure of RV stiffness **(D)**.

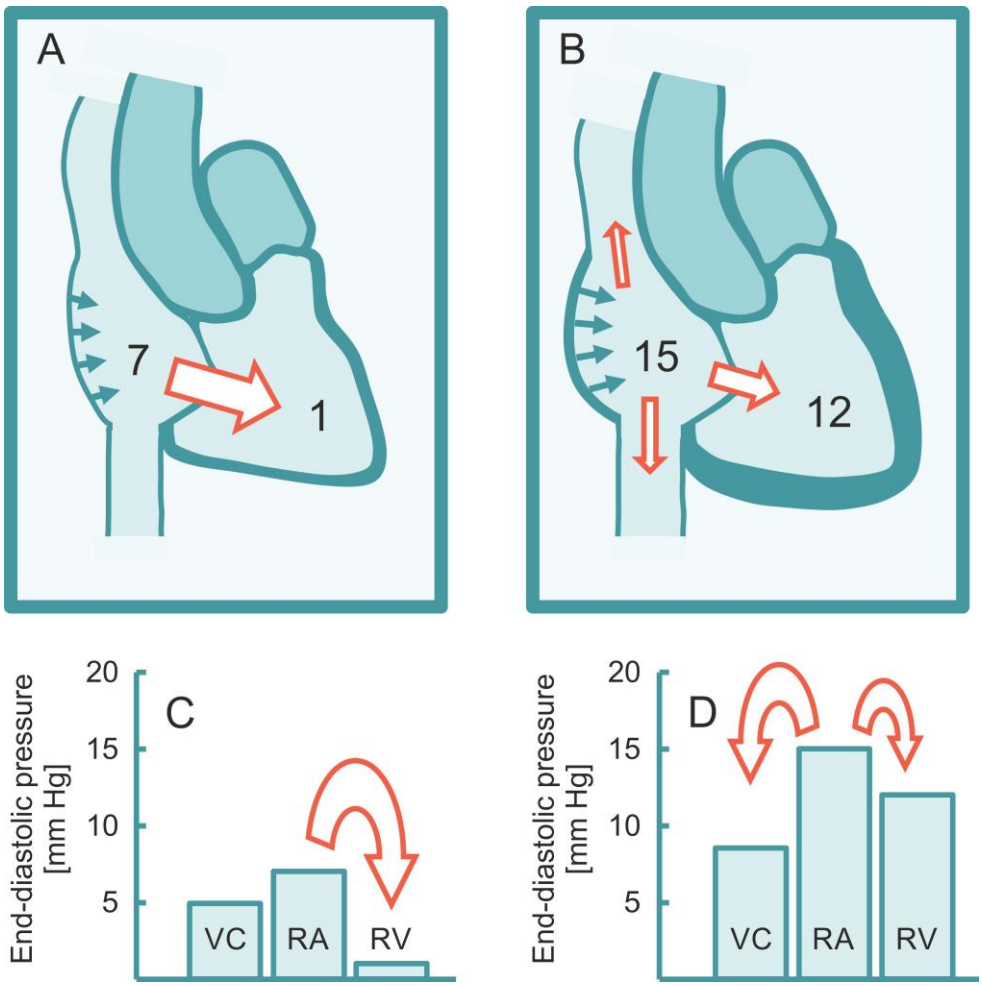

Figure 5. Pressures and flows in a normal and a stiff right ventricle.

Cartoons of the right heart at end-diastole, during the atrial contraction. Numbers in the figures are representative pressures in mm Hg. The bar graphs below indicate these pressures in the vena cava (VC), right atrium (RA) and right ventricle (RV).

The top left panel (**A**) shows a normal subject: because of the compliant RV wall and the low RV end-diastolic pressure, the RA ejects fully forward into the RV (curved arrow in the left bar graph **C**). The right upper panel (**B**) shows a patient with pulmonary arterial hypertension: due to the stiff RV wall and the high RV end-diastolic pressure, the RA ejects partly in the reverse direction, back into the VC (curved arrows in the right bar graph, **D**).

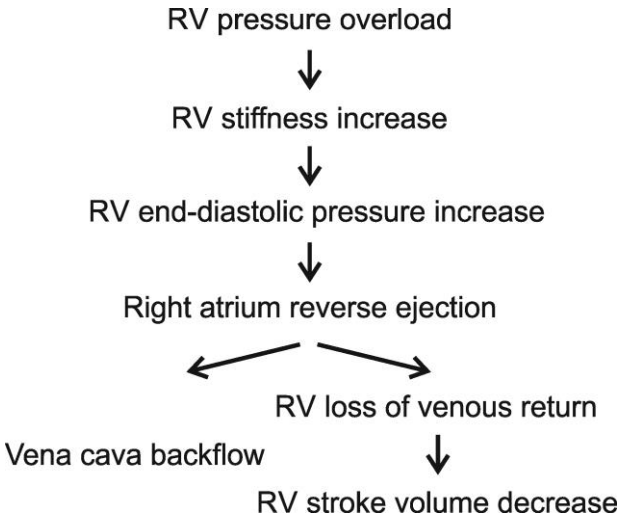

Figure 6. Flowchart: from right ventricular end-diastolic stiffness to vena cava backflow.

This flowchart shows the proposed mechanism explaining how Right Ventricular (RV) stiffness leads to vena cava backflow and decreased RV stroke volume.