RIGHT VENTRICULAR PACING IMPROVES RIGHT HEART FUNCTION IN EXPERIMENTAL PULMONARY ARTERIAL HYPERTENSION: A STUDY IN THE ISOLATED HEART

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ABSTRACT

Right heart failure in pulmonary arterial hypertension (PH) is associated with mechanical ventricular dyssynchrony, which leads to impaired right ventricular (RV) function, and - by adverse diastolic interaction - to impaired left ventricular (LV) function as well. However, therapies aiming to restore synchrony by pacing are currently not available. In this proof-of-principle study, we determined the acute effects of RV-pacing on ventricular dyssynchrony in PH.

Chronic PH with right heart failure was induced in rats by injection of monocrotaline (80 mg/kg). To validate for PH-related ventricular dyssynchrony, rats (6 PH, 6 controls) were examined by cardiac magnetic resonance imaging (9.4 Tesla), twenty-three days after monocrotaline- or sham-injection. In a second group (10 PH, 4 controls), the effects of RV-pacing were studied in detail, using Langendorff-perfused heart preparations.

In PH, septum bulging was observed, coinciding with a reversal of the trans-septal pressure gradient, as observed in clinical PH. RV-pacing improved RV systolic function, compared to unpaced condition (RV dP/dt_\text{max}: +8.5 \pm 1.3 \%, p < 0.001). In addition, RV-pacing markedly decreased PTI_{RV-P>LVP}, an index of adverse diastolic interaction (-24 \pm 9 \%, p < 0.01), and RV-pacing was able to resynchronize time of RV and LV peak-pressure (Δt_\text{peak} unpaced: 9.8 \pm 1.2 ms vs. paced: 1.7 \pm 2.0 ms, p < 0.001). Finally, RV-pacing had no detrimental effects on LV function or coronary perfusion, and no LV pre-excitation occurred.

Taken together, we demonstrate that in experimental PH, RV-pacing improves RV function and diminishes adverse diastolic interaction. These findings provide a strong rationale for further in vivo explorations.
INTRODUCTION

Pulmonary arterial hypertension (PH) is characterized by progressive pulmonary vascular remodeling. During the progression of the disease, right ventricular (RV) afterload continues to rise and eventually right heart failure develops in the majority of patients.

In PH-patients, signs of mechanical RV dyssynchrony along with signs of adverse interventricular diastolic interaction are often observed. This results in inefficient pumping of the heart. In essence, the duration of RV contraction is lengthened due to increased RV afterload. As a consequence, time-to-peak shortening of the RV free wall is delayed, even beyond closure of the pulmonary valves. Loss of a coordinated ventricular contraction results in impaired RV systolic function. In addition, the prolonged RV contraction in early left ventricular (LV) diastole causes the already relaxing interventricular septum to bulge into the left ventricle. This negatively influences early LV filling, eventually contributing to the impairment of LV diastolic function as well.

To this date, no specific treatment is available for the failing right ventricle. Cardiac resynchronization therapy is a well-established treatment for LV dyssynchrony related to left heart failure, and might be an interesting therapeutic option for right heart failure as well. However, our research group recently demonstrated that the origin of PH-related ventricular dyssynchrony lies in regional differences in the duration of the contraction, rather than regional differences in onset of the contraction (e.g. due to a conductance delay). For this reason, PH-related ventricular dyssynchrony is essentially different from dyssynchrony associated with left heart failure.

In the present proof-of-principle study, we tested whether RV-pacing could synchronize pressure generation across the septum, resulting in an improvement of RV systolic function and a reduction of adverse diastolic interaction. First, we validated the monocrotaline rat model, a well-established model for chronic PH, for the presence of ventricular dyssynchrony. Subsequently, we evaluated the acute effects of RV-pacing on cardiac performance and PH-related ventricular dyssynchrony in isolated Langendorff-perfused heart preparations. This approach allows relatively easy manipulation and offers a high degree of preparation stability in which LV and RV load can be varied independently, with derivation of cardiac-specific functional data.

METHODS

All experiments were approved by the Institutional Animal Care and Use Committee of the VU University Amsterdam.

Experimental model of pulmonary arterial hypertension

In total, 26 male Wistar rats were included in the study (150-175g; Harlan, Horst, the Netherlands). PH was induced (n = 16) by a single subcutaneous injection of monocrotaline (80 mg/
RV-pacing

kg dissolved in sterile saline; Sigma-Aldrich, Zwijndrecht, The Netherlands). This resulted in a PH-phenotype, followed by right heart failure approximately 23 days after injection. The control group was injected with saline only (n = 10).

Cardiac magnetic resonance imaging

Twenty-three days after monocrotaline-injection, the presence of ventricular dyssynchrony in vivo was assessed in PH-rats and compared to controls (6 for each group), by measuring cardiac function and the behavior of the interventricular septum with cardiac magnetic resonance imaging (CMR; 9.4 Tesla; Varian Medical Systems, Palo Alto CA), as previously described. After CMR-scanning, all rats were euthanized and their organs weighed.

Images were analyzed off-line using Segment (version 1.698; http://segment.heiberg.se). Endocardial borders of both ventricles were automatically detected for all slices of the heart and for each frame in the heart cycle. LV and RV volume curves were constructed using the modified Simpson's rule, from which end-diastolic and end-systolic volume, peak filling rate, stroke volume, heart rate, cardiac output, and ejection fraction were derived. Septum curvature was calculated as previously described. In short, the anterior, middle and posterior positions of the interventricular septum at mid-ventricular level were determined, through which a circle was fitted. The reciprocal of the radius of this circle was used to quantify septum curvature (1/R), and was defined positive if the septum bowed toward the right ventricle.

Isolated Langendorff–perfused heart preparation

To characterize the hearts of PH-rats and controls (10 PH-rats, 4 controls; no CMR performed), and to study ventricular dyssynchrony in detail, a Langendorff-setup was used as previously described, with balloons in left and right ventricle (Figure 1). The heart was perfused (at 35-37°C) using a modified Krebs-Henseleit solution (composition in mM: 118.5 NaCl, 4.7 KCl, 1.4 CaCl2, 25 NaHCO3, 1.2 MgCl2, 1.2 KH2PO4, and 11 glucose) that was continuously gassed with 95% O2 / 5% CO2 (pH 7.4). Coronary perfusion pressure was set at a constant value of 80 mmHg to minimize edema formation. Electrodes were placed at the right atrium, and at a vessel-free area of the LV and RV free wall (LV: posterolateral - midventricular; RV: RV “anterolateral”, opposite to the LV electrode), after which normal atrial and subsequent ventricular activation were checked to verify that the intrinsic conductance system was intact. In addition, signals of LV and RV electrodes were compared to detect potential differences in electrical activation of left and right ventricle. Atrial and ventricular threshold stimuli were determined, and the heart was atrial-paced at 4.0 Hz (pulse duration 1.0 ms, at twice the threshold). During the whole experiment, electrical activity and stimuli, LV and RV pressures, and coronary flow were continuously recorded with a sample rate of 2.0 kHz.

After stabilization (10 min), the volumes at maximal developed pressure (Vmax) of both ventricles were determined by small stepwise increases and decreases in balloon volume (in analogy to Lmax, used in isolated muscle studies), subsequently the pressure-volume relationship of the
RV-pacing protocol

RV-pacing was only performed in PH-hearts; RV-pacing experiments in normal hearts were not performed, since it is known that this results in loss of synchrony and worsening of cardiac function. LV volume was set at 75% $V_{\text{max}}$, and RV volume was set at 95% $V_{\text{max}}$. These volumes correspond with LV and RV end-diastolic pressures of 5 and 10 mmHg respectively (Figure 2), as observed in PH-patients, and in monocrotaline-treated rats in vivo. The intrinsic atrioventricular delay (AV-time) was defined as the time-interval between atrial (A) and ventricular (V) electrical activation (Figure 1).

RV-pacing was performed by direct stimulation of the RV free wall (using the RV electrode), triggered from atrial activation, starting with an AV-time equal to the intrinsic AV-time. Subsequently, AV-time was shortened in steps of 10 ms (AV-shortening). Effects of RV-pacing stabilized within 5 seconds. After the experiment, all hearts were dissected in left (including interventricular septum) and right ventricle, and weighed.

Functional assessment of RV-pacing

The isovolumic pressure recordings were evaluated off-line using MATLAB (version R2007b, The MathWorks, Natick MA). Signals were averaged over approximately hundred beats (25 seconds). The effects of RV-pacing on both intra- as well as inter-ventricular aspects of PH-related dysynchrony were evaluated. Intra-ventricular dyssynchrony was measured by RV $\text{dP/dt}_{\text{max}}$ and RV systolic pressure (RV SP). The time difference between RV and LV peak-pressure was used as an index for inter-ventricular dyssynchrony ($\Delta t_{\text{peak}}$).
RV-pacing

Figure 2

PTI\textsubscript{RVP\textgreater{}LVP} was used to quantify the interventricular diastolic interaction in isolated hearts. It measures the degree as well as the duration of reversed pressure differences across the interventricular septum (i.e. RV pressure > LV pressure) during a heartbeat, which is considered the driving force that causes the septum to bulge into the left ventricle, impairing LV filling. This parameter is especially sensitive (it decreases) for improvements in synchronic pressure generation across the septum (due to RV-pacing). PTI\textsubscript{RVP\textgreater{}LVP} expresses the pressure-time integral of the trans-septal pressure gradient when RV pressure exceeds LV pressure, and was calculated by:

$$PTI_{RVP>LVP} = \int_{1\text{ beat}} (\text{RV pressure} - \text{LV pressure})dt \text{ when } \text{RV pressure} - \text{LV pressure} > 0$$

The onset of LV and RV contraction was defined as the time-point at which pressure rose to 5% of developed pressure above diastolic pressure. The difference between the onset in RV and LV contraction was used to identify presence of LV pre-excitation ($\Delta t_{\text{onset}}$). LV pre-excitation refers
to depolarization of the LV myocardium that is earlier than would occur by conduction of an impulse through the AV node (in this case LV depolarization triggered by artificial pacing of the RV free wall), and is known to be detrimental for LV function in the long-term.23 This phenomenon can be recognized from pressure recordings, when the difference in onset no longer changes at larger AV-shortening intervals (see Figure 1, Figure 5D); in that case RV-pacing no longer solely advances RV contraction, but prematurely activates the left ventricle as well.

The duration of RV and LV contraction was defined as the time-interval between 5% rise and 95% fall in developed pressure. Coronary perfusion was measured by average total coronary flow.

**Statistical analysis**

All data were verified for normal distribution, and values were expressed as mean±SEM, unless stated otherwise. A p-value < 0.05 was considered significant. Group differences were analyzed by unpaired Student T-test. Septum curvature, ventricular volume curves and pressure-volume relationships were analyzed by two-way ANOVA for repeated measurements. Paired Student T-test was performed to evaluate the effect of RV-pacing.

**RESULTS**

**General characteristics of PH-rats vs. controls**

In PH-rats, CMR revealed significantly smaller cardiac output, stroke volume, lower heart rate and RV ejection fraction, and significantly larger RV end-diastolic volumes, compared to control (Table 1). Autopsy showed a significant increase in (wet) lung mass and RV / (LV+S) mass ratio (Table 1). An upward shift in systolic and diastolic pressure-volume relationships for the right ventricle in PH was observed; The pressure-volume relationships for the left ventricle were not different between PH and control (Figure 2). These results indicate PH-induced RV remodeling and RV dysfunction in monocrotaline-treated rats.

**Septum bulging and PH-related ventricular dyssynchrony in vivo**

In PH-rats, CMR revealed that the interventricular septum at the midventricular level was less curved throughout the cardiac cycle, compared to controls (Figure 3A,B; average 1/R, PH: 0.50 ±0.15 cm\(^{-1}\) vs. control: 2.07 ±0.05 cm\(^{-1}\), p < 0.001). In addition, solely in PH-hearts septum bulging was observed. At early LV diastole, the septum temporarily protruded into the left ventricle (negative 1/R; Figure 3A,B). Furthermore, we found significantly smaller LV end-diastolic volumes and lower LV peak filling rates for PH (Table 1).
RV-pacing

Reversed trans-septal pressure gradient and ventricular dyssynchrony in isolated hearts

Pressure measurements revealed no differences in the onset between RV and LV contraction in PH-hearts (onset delay RV-to-LV, PH: 5.1 ±0.6 ms vs. control: 5.5 ±0.4 ms, n.s.). This finding was confirmed by the lack of a difference in electrical activation between right and left ventricle (activation delay RV-to-LV, PH: 0.1 ±0.8 ms vs. control: 0.7 ±1.0 ms, n.s.). In contrast, we found a prolonged duration of RV contraction in PH-hearts (Figure 3C; duration of RV contraction, PH: 197 ±3 ms vs. control: 168 ±4 ms, p < 0.001). As a consequence, only in PH-hearts RV pressures were found to exceed LV pressures during late systole in the heart cycle, resulting in a temporary reversal of the trans-septal pressure gradient (Figure 3D).

When comparing in vivo septum measurements (Figure 3B) with the pressure measurements obtained in isolated hearts (Figure 3D), it was found that time of peak negative trans-septal pressure gradient (t = 66 ±2 %RR-interval) coincided with the occurrence of maximal septum bulging in PH (t = 64 ±2 %RR-interval).

In addition, we found that in PH-hearts, PTI_{RV,P>LVP} (an index of diastolic interaction) was RV-volume dependent, whereas this relationship was not observed in controls (Figure 4).

Effects of RV-pacing

The effects of RV-pacing in PH-remodeled hearts were studied at different AV-shortening intervals. The intrinsic AV-time at baseline (no pacing of the RV free wall) was 89 ±3 ms (AV-time, control: 92 ±3 ms). At maximal RV dP/dt_{max}, AV-shortening was found to be 15 ±2 ms (p < 0.001), which was considered as the optimal pacing interval (Fig 5B). At this interval, there
was no evidence for LV pre-excitation (Figure 5D), as LV pre-excitation only occurred at longer AV-shortening intervals (AV-shortening at the transition point to LV pre-excitation: 32 ±2 ms; p < 0.001 vs. optimal pacing interval).

Compared to baseline, pacing at optimal interval improved RV systolic function in all experiments; RV dP/dt_max (baseline PH: 1.75 ±0.04 *10^3 mmHg/s, control: 0.88 ±0.08 *10^3 mmHg/s) increased by 8.5 ±1.3 % (p < 0.001; Figure 6A), and peak RV systolic pressure increased by 2.7 ±0.6 % (p < 0.01; Figure 6B). Pacing also decreased the time-difference between RV and LV peak-pressure (Δt_peak, PH baseline: 9.8 ±1.2 ms vs. paced: 1.7 ±2.0 ms, p < 0.001; Δt_peak, control: -3.5 ±0.6 ms; Figure 6C). In addition, RV-pacing positively influenced the diastolic interaction, as PTI_RVP>LVP decreased by 24 ±9 % (p < 0.01; Figure 6D). Furthermore, RV-pacing shortened

PH-related ventricular dyssynchrony in monocrotaline-treated rats. A) Examples of short-axis CMR-images at the midventricular level of control- and PH-hearts at time points t = 0, and t = 65 %RR-interval. Epi- and endocardial borders are indicated by the thin lines. The interventricular septum is highlighted by the dotted line. Crosses indicate anterior, middle and posterior positions of the interventricular septum that were used to calculate septum curvature (1/R). B) Septum curvature was less pronounced in PH vs. control throughout the heart cycle, and septum bulging (negative 1/R, arrow) was observed in all PH-hearts (mean ±SEM, both groups: n = 6). C) Examples of LV and RV pressure recordings in isolated Langendorff-perfused hearts of control and PH, used to construct the trans-septal pressure gradient. D) In PH, RV contraction is prolonged and as a consequence RV pressure exceeds LV pressure at early LV diastole, causing a momentary reversal of the trans-septal pressure gradient (arrow). No reversal was observed in control hearts.

Data are presented as mean ±SEM, PH: n = 10, control: n = 4.
Figure 4

A) Examples of LV and RV pressure measurements in a PH-heart for different RV volume settings: RV70, RV95 = RV pressure curves at 70 or 95 %Vmax (thick red lines; thin red lines represent RV pressure curves at intermediate RV volume settings). LV pressure was minimally affected, and for the sake of clarity only one LV pressure curve is shown. B) Only in isolated PH-hearts, interventricular dyssynchrony (quantified by PTIRVP>LVP; gray area) increased with increasing RV volume. Data are presented as mean ±SEM, PH: n = 10, control: n = 4. Abbreviations: PTIRVP>LVP, pressure-time integral, when RV pressure exceeds LV pressure.

Figure 5

A) Example of a RV pressure curve at baseline (dashed line) and when optimally paced (solid line). For every experiment, the same series of AV-shortening were tested. Notice that pacing implies earlier start of RV contraction. B) RV dP/dt max as function of AV-shortening. Optimal pacing interval was defined when RV dP/dt max was highest. Notice the initial rise in RV dP/dt max at short AV-shortening intervals and the subsequent fall at longer AV-shortening intervals. C) Diastolic interaction (PTIRVP>LVP) decreased precipitously with AV-shortening. Optimal RV dP/dt max was found at relatively low values of AV-shortening. D) Difference in onset of RV vs. LV contraction (∆tonset) as function of AV-shortening (overall, ∆tonset at LV-pre-excitation was -6.3 ±1.2 ms, ranging from -0.5 to -13.0 ms). LV pre-excitation only occurred at higher AV-shortening interval than when optimally paced.
the duration of RV as well as LV contraction (RV duration at baseline: 197 ± 2 ms, change in RV duration after pacing: -1.0 ± 0.4 %, p < 0.05; LV duration at baseline: 191 ± 2 ms, after pacing: -1.3 ± 0.3 %, p < 0.001).

No significant effects of RV-pacing were observed on RV diastolic function (RV DP, baseline: 8.5 ± 1.2 mmHg, paced: 0.9 ± 1.2 %; RV dP/dt_{min}, baseline: -819 ± 28 mmHg/s, paced: -2.0 ± 2.2 %; both n.s.). Also, no effects of RV-pacing were observed, either on LV function (LV SP, baseline: 95 ± 2.2 mmHg, paced: 0.2 ± 0.3 %; LV DP, baseline: 2.4 ± 0.4 mmHg, paced: -3.2 ± 2.6 %; both n.s.), or on coronary perfusion (mean Qcor, baseline: 15 ± 1 ml/min, paced: 0.3 ± 0.3 %; n.s.).

The minimal rundown of the functional properties (decline in developed pressure: < 5%/hr, increase in diastolic pressure: < 5%/hr), during our short-lasting experiment (< 30 min), suggest minimal effect of edema formation.

**DISCUSSION**

After validation of the monocrotaline-rat model for PH-related ventricular dyssynchrony, we demonstrated that in chronic PH:

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RV-pacing improved RV function and reduced interventricular diastolic interaction. A,B) At optimal pacing interval, RV-pacing significantly improved RV dP/dt_{max} and RV systolic pressure (RV SP), compared to baseline, and (partially) restored intra-ventricular synchrony. C) RV-pacing significantly reduced the time-difference between RV and LV peak (Δt_{peak}), and restored inter-ventricular synchrony. D) RV-pacing markedly decreased PTI_{LVP>Qcor}, an index of adverse diastolic interaction. Data are shown as mean ±SEM (aside) and as paired individual observations (center) N = 10 (all PH). Baseline, paced: before pacing, and when optimally RV-paced (AV-shortening = 15 ± 2 ms).
1) RV-pacing improved RV systolic function, characterized by enhanced RV $dP/dt_{\text{max}}$ and peak RV systolic pressure.

2) RV-pacing diminished adverse interventricular diastolic interaction, by resynchronizing time between RV and LV peak-pressure ($\Delta t_{\text{peak}}$), and reducing PTI $RVP>LVP$.

In addition, RV-pacing slightly shortened the duration of RV as well as LV contraction; No (detrimental) effects on LV function or coronary perfusion were observed, and there was no evidence for LV pre-excitation.

By providing this proof-of-principle, the findings may give support for the potential role of RV-pacing as a novel treatment for PH-induced right heart failure.

Validation of the monocrotaline rat model for ventricular dyssynchrony

The monocrotaline rat model is a well-established model for chronic PH in general, but so far this model has not specifically been validated for PH-related ventricular dyssynchrony. Therefore, we first investigated whether signs of ventricular dyssynchrony were present in vivo.

We used sophisticated CMR-techniques to accurately quantify septum curvature and LV and RV function in the monocrotaline rat model. CMR offers superior imaging quality and allows generation of cross-sectional images in virtually any plane, both of major advantage, especially when visualizing septum bulging. Our CMR measurements confirmed the pulmonary hypertensive state of the monocrotaline-treated rats, with clear signs of right heart failure. Moreover, CMR demonstrated the presence of septum bulging, low LV end-diastolic volumes and low LV peak filling rates, comparable to the clinical situation. As observed in clinical PH, ventricular dyssynchrony in monocrotaline-induced PH was explained by regional differences in duration, rather than in onset of contraction (as measured by ECG and pressure recordings). Prolonged RV contractions and reversal of trans-septal pressure gradients in our PH-model were demonstrated by biventricular pressure measurements in isolated Langendorff-perfused heart preparations, which is in line with what was previously shown by Boissiere et al. It is important to note that the expected coincidence in time of septum bulging and peak reversed trans-septal pressure gradient (RV pressure exceeds LV pressure; Figure 3) was also found in the isolated hearts.

These observations demonstrate that the monocrotaline rat model is an appropriate model to study PH-related ventricular dyssynchrony, and in addition, that ventricular dyssynchrony can be studied in detail in a Langendorff-setup with balloons in both ventricles. This approach has major advantages. It allows relatively easy manipulation with a high degree of preparation stability. Furthermore, it allows derivation of robust functional data with cardiac-specific parameters. Finally, in the Langendorff-setup LV and RV load can be varied independently, by changing ventricular volumes, which enabled us to reveal the relationship between ventricular dyssynchrony and RV load.
Beneficial effects of RV-pacing

To the best of our knowledge, our study is the first that explored the effects of RV-pacing on intra- and inter-ventricular dyssynchrony in chronic PH. We found a modest, but highly significant improvement in RV systolic function. Moreover, we observed an important reduction in interventricular diastolic interaction, without detrimental effects on LV function or coronary perfusion. At the optimal RV-pacing interval, there was no evidence for LV pre-excitation, which is known to be detrimental for LV function at the long-term.

The early activation of the RV free wall probably compensated for the longer RV contraction period and therefore the delay in time-to-peak-shortening of the RV free wall relative to the interventricular septum and LV free wall. Pacing helped to restore synchrony of the left and right ventricle, and as a result RV systolic function improved. The time of activation is critical: if the RV free wall is activated too early synchrony is lost again, which explains the initial rise and then fall in RV dP/dt max with increasing AV-shortening (Figure 5B).

Another beneficial effect of pacing was the reduction in interventricular diastolic interaction, expressed by PTI RVP>LVP. Pacing-induced earlier activation of the RV free wall and the shortened RV contraction resulted in an earlier start of RV relaxation. The partially restored synchrony in the relaxation of both ventricles explains the observed reduction of the PTI RVP>LVP. Although isovolumic pressure measurements in our Langendorff-setup cannot directly provide this information, a marked decrease in PTI RVP>LVP together with a shortened duration of LV contraction would predict less septum bulging and improvement in early LV filling.

Recently, Quinn et al. also reported positive effects of pacing in a different model of RV pressure overload. However, their findings are only partially applicable to the PH-patient group, because they applied an acute pressure overload in a pig-model with the conductance system artificially damaged by ethanol injection. A few clinical studies have explored the effect of RV-pacing on RV dysfunction secondary to congenital heart disease (studies on systemic right ventricles are not discussed here). These studies aimed to restore RV electromechanical dyssynchrony related to a complete right bundle branch block, a late complication of surgical repair. However as mentioned earlier, ventricular dyssynchrony in PH is based on prolonged contraction, rather than disturbances in the electrical conductance system.

Limitations – the isolated heart vs. in vivo

This study supports the potential role of RV-pacing for the treatment of PH-related ventricular dyssynchrony and right heart failure. However the results cannot be translated directly to the in vivo situation yet; Future studies in a large animal model or (acute) RV-pacing experiments in PH-patients are necessary.

In the Langendorff preparation the mediating role of RV afterload remains unknown, which limits the prediction of the effects of RV-pacing and improved RV contractility on stroke volume and cardiac output. Nonetheless, related studies reported an improvement of cardiac output after RV-pacing to the same extent as the improvement in RV contractility. RV-pacing could also
potentially worsen tricuspid regurgitation through elevation of RV systolic pressures. On the other hand, it was recently shown that resynchronization therapy in left heart failure actually reduced pre-existing mitral regurgitation.\textsuperscript{31}

Another important issue is the role of the pericardium. In our isolated Langendorff-perfused hearts, the pericardium was removed, which is known to reduce the interventricular diastolic interaction in the case of RV pressure overload.\textsuperscript{32} This might explain why we did not observe a significant reduction in LV diastolic pressures / LV filling pressures by RV-pacing (that were already low at baseline) in our isolated heart preparations.\textsuperscript{33} The effects of RV-pacing will probably be more pronounced in vivo with the pericardium intact.

Crystalloid based Langendorff-perfused hearts are prone to edema formation, which could affect diastolic properties. However, with a coronary perfusion pressure of 80 mmHg, this was reduced to a minimum.\textsuperscript{20,21} In addition, edema formation was found to have only limited functional effects during our experiments, as we observed a minimal rundown of the functional properties during our short-lasting experiments and, we were also able to detect clear differences in diastolic properties between control and PH-heart.

We found longer PR-intervals than are reported for (PH-)rats in vivo (~90 vs. ~60 ms).\textsuperscript{34} However, no differences were observed between PR-intervals of isolated PH- and control hearts. We therefore conclude that the prolonged PR-interval, compared to the in vivo situation, is most likely to be attributed to the Langendorff set-up in general and unlikely to be related to differences in cardiac condition between PH-hearts and controls. Furthermore, the apparently prolonged PR-interval is of little relevance for the interpretation of our finding, as the intervention studied involves ventricular activation, which follows after the PR-interval.

As a last point, clinical effective medical therapies, such as epoprostenol, are known to have a relatively small impact on hemodynamic measures, which nonetheless translate to improved survival.\textsuperscript{35} Therefore, the small acute improvements in RV function found here, may in the long-term translate into substantial benefit.

\textbf{Conclusions}
In our experimental PH-model, RV-pacing improved cardiac performance through alleviation of PH-related ventricular dyssynchrony. The promising results of this study identify RV-pacing as a potential novel treatment for right heart failure in PH, and provide a strong rationale for future investigations evaluating the effects of RV-pacing in vivo.

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Disclosures
None

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GENERAL DISCUSSION

PERSPECTIVES ON NOVEL THERAPEUTIC STRATEGIES FOR RIGHT HEART FAILURE IN PULMONARY ARTERIAL HYPERTENSION: LESSONS FROM THE LEFT HEART

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Right heart function is the main determinant of prognosis in pulmonary arterial hypertension (PH). Yet, no treatments are currently available that directly target the right ventricle, as we demonstrate in this perspective; Meta-analysis of clinical trials in PH revealed that current PH-medication seems to have limited cardiac-specific effects, when analyzed by the pump-function graph. Driven by the hypothesis that "left" and right heart failure might share important underlying pathophysiological mechanisms, we evaluated the clinical potential of left heart failure (LHF) therapies for PH, based on currently available literature.

Like in LHF, the sympathetic nervous system and the renin-angiotension-aldosterone system are highly activated in PH. From LHF we know that intervening in this process - by e.g. ACE inhibition or beta-blockade - is beneficial in the long run. Therefore, these medications could be also beneficial in PH. Furthermore, the incidence of sudden cardiac death in PH could be reduced by implantable cardioverter-defibrillators. Finally, pilot studies have demonstrated that interventricular dyssynchrony, present at end-stage PH, responded favorably to cardiac resynchronization therapy as well.

To conclude, therapies for LHF might be relevant for PH. However before they can be implemented in PH-management, safety and efficacy should be evaluated first, in well-designed clinical trials.
INTRODUCTION

Pulmonary arterial hypertension (PH) is characterized by excessive pulmonary vascular remodeling, resulting in a marked increase in right ventricular (RV) afterload. The thin-walled, crescent-shaped right ventricle in the normal situation needs to remodel to a thick-walled, more spherical-shaped high-pressure pump, to overcome the often four-fold (!) increase in pressure in the case of PH. Eventually, the right ventricle is not able to cope with the increase in load and right heart failure develops.\textsuperscript{1,2} Despite the successful introduction of several new pulmonary-selective vasodilating therapies in the last decade, the prognosis of PH-patients remains poor.\textsuperscript{3,4}

The relationship between RV afterload (mainly determined by pulmonary vascular resistance or PVR, and pulmonary arterial compliance\textsuperscript{5}) and RV dysfunction is not straightforward. Patients with systemic sclerosis associated PH (relatively low load / low pressure) have a worse prognosis, compared to patients with idiopathic PH, whereas patients with PH associated with congenital heart disease (high load / high pressure) have a relative good prognosis.\textsuperscript{6} Also in PH, mean pulmonary artery pressure (mPAP) and PVR are of limited prognostic value, while the strongest predictors of survival are reflections of RV (mal)adaptation to its increased load (cardiac index, right atrial pressure, tricuspid annular plane systolic excursion or TAPSE, NT-proBNP plasma levels; Figure 1).\textsuperscript{7-9} Thus, it is not the load \textit{per se}, but the failing right ventricle itself that leads to death.

Current PH-medication (prostacyclines, endothelin receptor blockers, PDE-5 inhibitors, calcium-antagonists) focuses on controlling the excessive vascular remodeling typical for PH, resulting in a reduction in RV load.\textsuperscript{10} Their \textit{cardiac-specific} effects on RV adaptation and remodeling have hardly been studied yet, but they are most likely of limited clinical relevance, as we will demonstrate later (see ‘Cardiac effects of current PH-medication’). Therefore, there is still unexploited potential for therapies that directly target the right ventricle.\textsuperscript{11}

In left heart failure (LHF), it is well accepted that the process of cardiac remodeling \textit{itself}, regardless the initial cardiac event, is - although compensatory at first - detrimental in the long run.\textsuperscript{12} There is now convincing evidence that intervening in the process of remodeling importantly reduces morbidity and mortality in patients with LHF.\textsuperscript{13,14} We hypothesize that the RV remodeling observed in PH-patients, shares important pathophysiological mechanisms with the cardiac remodeling observed in LHF-patients. This implies that the adverse RV remodeling could possibly be treated with the same well-established therapies for LHF.

To get better insight into the processes involved, it is essential to clinically distinguish cardiac-specific effects of treatment from their effects on load (pulmonary vasodilation), which also \textit{indirectly} affect the heart. In the first part of this review, we therefore discuss how this separation of effects can be studied, and we will evaluate the cardiac-specific effects of current PH-treatments. In the second part of the review, we explore the potential relevance of current evidence-based LHF-therapy (Table 1) for right heart failure secondary to PH.
Hemodynamic changes during the progression of pulmonary arterial hypertension (PAH). The continuous rise in pulmonary vascular resistance (PVR) during the progression of the disease is initially compensated by concentric remodeling of the right ventricle; right atrial pressure (RAP) remains at normal levels, and there is a steep increase in mean pulmonary artery pressure (mPAP) as cardiac index at rest (CI) is preserved. In the next stage, the right ventricle is not able to fully compensate for the further increase of PVR, it starts to decompensate and eccentric RV remodeling is observed; there is a modest rise in mPAP as CI is starting to fall as well, at this stage RAP remain at near-normal levels. In the final stage of overt right heart failure, there is a severe drop in CI, a steep rise in RAP, and even though PVR still increases, mPAP drops because of the low-output state.

Changes in RV function very well fits to the different disease stages in PAH, and explain the prognostic importance of CI and RAP over mPAP. In systemic sclerosis associated (ssc-) PAH, the ability for the right ventricle to adapt to the increasing PVR seems to be limited, and therefore the heart fails at lower PVR. The aim of specific RV-therapies is to improve the ability of the heart to adapt to its afterload.

Table 1 Summary of current left (systolic) heart failure therapy*, data taken from 13,14

| 1. Treat underlying cause when possible (e.g. coronary artery disease, arterial hypertension) |
| 2. General measurements (self-care management, avoid drugs that adversely affect the clinical status whenever possible) |
| 3. Diuretics (and moderate salt restriction) |
| 4. Beta-blockers (initiated in very low doses, followed by gradual increment) |
| 5. Angiotension-converting enzyme inhibitors (or angiotensin II receptor blockers, if intolerant for ACE inhibitors) |
| 6. Aldosterone antagonists (only when renal function is preserved and closely monitored) |
| 7. Exercise training (adjunct to optimal medical therapy) |
| 8. Implantable cardioverter-defibrillator (patients at high-risk for life-threatening arrhythmic disorders) |
| 9. Cardiac resynchronization therapy (symptomatic heart failure patients despite optimal medical treatment, with signs of cardiac dyssynchrony) |
| (10.) Digoxin, hydrazaline / nitrate, LV assist devices, heart transplantation |

* Therapies marked in bold are not standard in current PAH-management
How can we distinguish the cardiac-specific effects of PH-therapy from the pulmonary vasodilating effects in patients?

The right ventricle and the pulmonary vascular bed are functionally coupled. As a consequence, it is difficult to distinguish cardiac-specific from pulmonary-specific effects of an intervention with the use of standard diagnostic tools (i.e., right heart catheterization, echocardiography). For example, bosentan treatment has been shown to partially restore cardiac dimensions and function (compared to placebo, bosentan-treatment improved cardiac output: 0.4 L/min/m², p < 0.01; and RV:LV diastolic area ratio: -0.64, p < 0.01), but these effects are most likely the result of the decrease in RV load (difference in PVR reduction, bosentan-treatment vs. placebo: -415 ± 99 dyn.s.cm⁻⁵, p < 0.001), and are therefore not cardiac-specific. Similar observations have been reported for epoprostenol, sildenafil, and after successful pulmonary endarterectomy or lung transplantation.

In an experimental setting, this problem can be circumvented by using models with a fixed RV afterload (e.g., pulmonary arterial banding). Herein, we describe two methods that are also applicable in a clinical setting.

Pressure-volume relationship

It is well accepted that from combined ventricular pressure and volume measurements, parameters of cardiac function and contractility can be derived that are independent of the arterial load. An example of a load-independent parameter of systolic function is the end systolic elastance (Ees or Emax), which is measured by the slope of the fitted line connecting end-systolic pressure volume points (Figure 2B); Also, load-independent parameters of diastolic function can be derived. This method has been used successfully in describing LV performance in multiple disease conditions, and more recently its use has been validated in PH-patients for the right ventricle as well. The construction of PV-loops requires simultaneous measurements of instantaneous pressure- and volume-signals (Figure 2A,B), which can only be obtained using specialized equipment (e.g., conductance catheters). Moreover, to accurately determine Ees, it is necessary to vary cardiac load (usually by a temporary partial occlusion the inferior vena cava), which might be unacceptable in patients that are hemodynamically compromised, like PH-patients. Fortunately, mathematical techniques (e.g., ‘single-beat estimation’) have been developed that allow reasonable estimation of Ees and only requires a high-quality RV pressure curve and a reliable stroke volume measurement during steady-state. Recent studies that compared the separate cardiac and pulmonary effects of norepinephrine, dobutamine and levosimendan in an experimental model for right heart failure, are examples of the usefulness of pressure-volume relation (including single-beat estimation).

Pump-function graph

An interesting alternative for studying cardiac-specific vs. pulmonary-specific effects is the pump-function graphs. A major advantage of this method is that only instantaneous pres-
sure and average flow measurements suffice, and that its analysis does not require instantaneous volume-signals. Average RV pressure is plotted against stroke volume (the ‘working point’), and using the same single-beat estimation as discussed above, a pump-function graph can be constructed (Figure 2C,D). An increase in ‘$P_{iso}$’ while ‘$SV_{max}$’ remains unchanged (abbreviations: see legend Figure 2), indicates improved cardiac contractility: in this case the new working point moves to the upper right (Figure 2C). A change in cardiac load has a different effect: when load decreases by pulmonary vasodilation (and cardiac contractility remains unchanged) the working point moves to the lower right (Figure 2D). With the use of the pump-function graph, we

**Figure 2**

Distinguishing cardiac- from pulmonary-specific effects in PAH-patients. A) Pressure curves of the right ventricle and the main pulmonary artery are shown; by sine wave fit, maximal isovolumic pressure is estimated ($P_{iso}$). B) Pressure-volume loops can be constructed from instantaneous pressure (y-axis) and volume (x-axis) measurements by use of e.g. conductance catheters. End-systolic elastance ($E_{es}$) is considered a load-independent measure of RV contractility and is measured from the slope of the connecting line between end-systolic pressure ($P_{es}$) and $P_{iso}$. C,D) An alternative approach for describing heart function is the pump-function graph. Here, average RV pressure vs. stroke volume at steady-state are plotted (the ‘working point’) and by the same single-beat estimation ($P_{iso}$), a pump-function graph is constructed (black curved line). The slope of the line from the origin through the working point is a measure for pulmonary vascular resistance divided by heart period (PVR/T) and therefore a measure for RV afterload. When RV contractility increases (2C), this is observed in the pump-function graph by increased $P_{iso}$ while $SV_{max}$ remains unchanged; the new working point has moves to the upper right (‘1’). When RV afterload is reduced (PVR/T decreases; 2D), the pump-function graph remains unchanged, while the new working point moves to the lower right (‘2’).
recently demonstrated lower cardiac contractility in systemic sclerosis associated PH compared to idiopathic PH, that could well explain their worse prognosis despite lower PVR. When studying chronic (as opposed to acute) effects of an intervention, both methods (PV-loops or pump-function graph) may be insufficient due to RV remodeling. However, they can be further refined, by incorporating measures of RV remodeling (RV wall thickness; RV diameter) in the analysis, in which case RV wall stress (σ; estimated by Laplace’s law) is used instead of RV pressure. We conclude that by an integral approach, it is well-possible to distinguish the cardiac-specific from the pulmonary-specific effects of an intervention in PH-patients.

**Perspective** – Often, it is very difficult in patients to distinguish the cardiac- from the pulmonary-specific effects of PH-therapy. For this purpose, the pressure-volume relation and the pump-function graph have been developed. We propose the use of the pump-function graph over the pressure-volume relation, as it is more easily obtained in patients, using routine RV catheterization.

**Cardiac effects of current PH-medication**

The cardiac-specific effects of current PH-therapies, in contrast to their pulmonary vasodilating effects, have only been studied in a small number of papers. The few relevant experimental studies are discussed first.

**Experimental studies**

Zierer et al. investigated the effects of diltiazem (a calcium-channel blocker) on RV function in a chronic model of RV pressure overload, using pressure-volume analysis. Administration of diltiazem during constant RV afterload acutely depressed cardiac output, and this was mainly related to depressed right atrial function and RV filling. Kerbaul et al. investigated the effects of prostacyclines in an acute model of RV pressure overload, also using pressure-volume analysis. Epoprostenol improved cardiac output, and this was explained by a marked decrease in RV afterload without detectable changes in RV contractility. These observations have been confirmed by others. Two recent papers studied the effects of chronic treatment of sildenafil, in a model where RV pressure overload was induced by pulmonary artery banding. Both studies reported an increase in RV hypertrophy and/or improvement of RV function, which implies that there is a direct effect of sildenafil on the heart. Earlier, Nagendran et al. reported upregulation of PDE-5 in hypertrophied, but not in normal, rat and human RV myocardium, and also demonstrated acute inotropic effects of sildenafil in the isolated Langendorff-perfused heart. In summary, experimental data suggest acute detrimental effects of calcium-channel blockers, a neutral effect of prostacyclines, and possibly beneficial cardiac-specific effects of sildenafil on RV function and RV remodeling. Currently, no (experimental) data is available on the cardiac-specific effects of endothelin receptor blockers on the right ventricle in the setting of PH; So far these substances have only been evaluated in models, in which RV afterload was not fixed.
Meta-analysis of clinical studies

To the best of our knowledge, no clinical studies exist that specifically separated the cardiac from pulmonary effects of current PH-therapies. We therefore re-evaluated all placebo-controlled randomized clinical trials in PH that included serial invasive hemodynamic data, recently summarized by Galie et al.\textsuperscript{33}, by use of the pump-function graph (Figure 3). MPAP was used as a surrogate measure for mean RV pressure, stroke volume indexed for body surface area (SVi) was recalculated by dividing cardiac output by heart rate and body surface area (estimated 1.82 m\textsuperscript{2} if not reported). Concomitant evaluation of the hemodynamic changes in mPAP and SVi by the pump-function graph, during a typical study period of 12 weeks (range 8 weeks – 12 months), suggests that current PH-therapies have predominantly pulmonary vasodilating effects. (compare Figure 3 with the situation 2 in Figure 2D). Although future clinical studies are necessary that are specifically designed to address this issue, this observation demonstrates that there is a strong rationale for developing novel PH-therapies, which specifically target the right ventricle.\textsuperscript{11}

Figure 3

Meta-analysis of PAH-trials by the pump-function graph. Each individual arrow shows the general absolute change in indexed stroke volume (ΔSVi) and mean pulmonary artery (ΔmPAP; as a surrogate measure for mean RV pressure) per study group (red, placebo / control group; blue, intervention group) of all placebo controlled randomized clinical trials in PAH that have reported serial hemodynamic measurements.\textsuperscript{33} During the study period, a decrease in SVi was always accompanied by an increase in mPAP in the placebo groups, implying increase in PVR without relevant changes in cardiac contractility. For the intervention groups, an increase in SVi was always accompanied by a decrease in mPAP, implying reduction in PVR without important changes in cardiac contractility. Therefore, current PAH-medications have predominantly pulmonary vasodilating effects, with only limited cardiac-specific effects.
Perspective - Right heart function is the main determinant of prognosis in PH. Current medication (endothelin receptor blockers, PDE-5 inhibitors, and prostacyclines) seems to have limited cardiac-specific effects (when analysed by RV pump-function graph). Novel therapies that specifically improve right heart function in PH are needed.

RELEVANCE OF LEFT HEART FAILURE THERAPIES FOR PH-RELATED RIGHT HEART FAILURE?

The cornerstones of current (systolic) LHF-therapy are: (loop)diuretics; a beta-blocker; angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers if ACE inhibitors are not tolerated (Table 1). In case of persisting symptoms, an aldosterone antagonist or an angiotensin blocker is added, if the patient’s renal function permits. Exercise training is regarded an adjuvant therapy. For selected LHF–patients, an implantable cardioverter-defibrillator and/or cardiac resynchronization therapy can be considered. These therapies are well-established, and are based on numerous well-designed randomized controlled trials (more details on current LHF-therapy can be found in current guidelines\(^{13,14}\)). Of note, clinical benefit in these trials was demonstrated irrespective of the etiology of LHF. This supports the current idea that the process of cardiac remodeling, after the initial hit, is similar and independent of its cause (e.g. ischaemia or hypertension).\(^{12}\) However, it has been argued that therapy efficacy might be different in systolic vs. diastolic heart failure (different LHF-phenotype).\(^{34}\) Therefore, as the cardiac remodeling observed in PH-patients with right heart failure is comparable to that of systolic LHF (reduced ejection fraction, ventricular dilatation),\(^9\) only these recommendations will be discussed in this perspective.

It is tempting to extrapolate the LHF-recommendations to right heart failure, even though there are important structural, functional and developmental differences between the left and right ventricle.\(^{1,2}\) Nevertheless, there is already some overlap in recommendations between the LHF- and PH-guidelines,\(^3,4,13,14\) which suggests that, at least from a therapeutic perspective, there might be some interesting similarities. For example, loopdiuretics are widely used to achieve fast symptomatic relieve, both in PH as well as in LHF. Also, moderate exercise training is nowadays accepted as an adjuvant therapy for PH-patients that are clinically stable and under optimal medical treatment.\(^{35-37}\)

Since loopdiuretics and exercise training are already part of the recommendations of current PH-guidelines, we shall not discuss these therapeutic modalities any further here. We will also not discuss therapies for LHF that are still experimental. Instead, this perspective focuses on the clinical potential of: 1) beta-blockers as modulators of the sympathetic nervous system; ACE inhibitors, 2) angiotensin blockers and aldosterone antagonists as modulators of the renin-angiotensin-aldosterone system (RAAS); and 3) the potential of electrical cardiac interventions, like implantable cardioverter-defibrillators and cardiac resynchronization therapy, as novel
General discussion

Add-on therapies for PH (Figure 4). Because there are hardly any prospective controlled data available that investigated the relevance of these LHF-therapies in PH, we will mainly focus on the relevance of the underlying pathophysiological mechanisms for PH that are affected by these interventions.

**Figure 4**

Yet unexplored pathophysiological mechanisms in PAH.

| Abbreviations (in alphabetical order): ACEIs, angiotensin-converting enzyme inhibitors; aldost. ant., aldosterone antagonists; ARBs, angiotension receptor blockers; AT1R, cardiomyocyte angiotensin type 1 receptor; βAR, cardiomyocyte beta1-adrenergic receptor; CRT, cardiac resynchronization therapy; ETRAs, endothelin receptor antagonists; HRV, heart rate variability; ICD, implantable cardioverter-defibrillator; MSNA, muscle sympathetic nervous activity; PAH, pulmonary arterial hypertension; PDE-5 inhibitors, phosphodiesterase-5 inhibitors; RAAS, renin-angiotensin-aldosterone system; RHF, right heart failure; RV (afterload), right ventricular; SNS, sympathetic nervous system; ventr. arrhythmias, ventricular arrhythmias.

**Neurohumoral activation and PH**

The combined use of a beta-blocker (more specifically bisoprolol, carvedilol, or sustained released metoprolol) with either an ACE inhibitor, angiotensin blocker, and/or an aldosterone antagonist, in addition to symptomatic treatment by loopdiuretics, significantly reduces morbidity and mortality in LHF.13,14 These medications modulate the underlying "neurohumoral activation", which is nowadays considered pathological in the long run, as they promote cardiac remodeling and progression of the disease.12,38 Neurohumoral activation in LHF can be seen as a state, in which neural and hormonal systems, designed to maintain adequate organ perfusion, are increased to
excessively high levels. This activation includes many components, of which the sympathetic nervous system and RAAS are, from a therapeutic perspective, the most relevant.13,14,38

**Sympathetic nervous system**

Autonomic dysbalance with dominance of the sympathetic system already occurs at early stages of LHF,39 and is mainly attributed to reduced baroreceptor discharge. Baroreceptors, mainly located in the aortic arch, carotid arteries and in the left ventricle, are normally triggered by mechanical stretch and respond by tonically inhibiting the central sympathetic neural outflow. In case of LHF, both systemic arterial pressures and baroreceptor sensitivity are reduced. Sympathetic overdrive leads to chronically elevated levels of norepinephrine, resulting in overstimulation and selective downregulation of the cardiac-specific beta_1_-adrenergic receptors in the left ventricle. This stimulus not only leads to increased cardiac mechanical stress (by inotropic, chronotropic and vasoconstrictive effects), but also has direct cardiotoxic effects.40 As a consequence, LV remodeling progresses with further functional deterioration.38 Beta-blockers are able to stop this vicious circle of heart failure, by antagonizing the beta-adrenergic receptor.41 Of interest, the therapeutic effects of digoxin are nowadays no longer solely attributed to its weak inotropic effects, but also to its modest neurohumoral effects: digoxin indirectly sensitizes the cardiac baroreceptor, and in this way reduces sympathetic outflow of the central nervous system.42

Although sympathetic activity is difficult to measure in the clinical setting, several methods have been developed to demonstrate sympathetic overdrive in LHF-patients.39 Of these, measurements of regional norepinephrine spillover or microneurography (which directly measures post-ganglionic muscle sympathetic nerve activity, often abbreviated as MSNA) quantify sympathetic activity best. A sophisticated non-invasive alternative is the use of ^123^I-MIBG tracers (heart-to-mediastinum ratio falls when the sympathetic nervous system is chronically activated). A more crude but easy method is the assessment of heart rate variability (which is reduced when the sympathetic nervous system is over-activated).

**Renin-angiotensin-aldosterone system**

Another relevant system in this context, closely interrelated with the sympathetic nervous system, is the RAAS.43 This system is triggered by impaired renal perfusion due to reduced cardiac output. In that case, the juxtaglomular cells in the kidneys react by secreting renin. Renin increases angiotensin I levels, from which angiotensin II is formed by angiotensin-converting enzyme (abundantly present in the lung endothelium). Angiotensin II mediates multiple processes: it is a potent vasoconstrictor, and it has inotropic, natriuretic and antidiuretic properties; in the setting of LHF, all impose cardiac stress and are detrimental in the long run. Like norepinephrine, elevated levels of angiotensin II overstimulate and selectively downregulate its angiotensin II type 1 (AT_1_-)-receptor in the left ventricle, directly promoting cardiac remodeling. Furthermore, angiotensin II stimulates the secretion of aldosterone as well as vasopressin (also called antidiuretic hormone). Both have natriuretic and antidiuretic effects and also directly promote cardiac
remodeling. ACE inhibitors, angiotensin blockers, and aldosterone antagonists interfere in this process by suppressing specific components of the RAAS.\textsuperscript{13,14}

RAAS activity is relatively easily quantified by directly measuring renin or angiotensin II activity in plasma; A simple but indirect alternative to measure chronically activated RAAS is the assessment of hyponatremia.\textsuperscript{38}

**Over-activation of the sympathetic nervous system in PH**

Since the primary trigger of neurohumoral activation in LHF (reduction in cardiac output) is also an important clinical feature in PH, one would expect that the sympathetic nervous system and RAAS be highly activated in PH as well. Indeed, measurements of the sympathetic and RAAS activation in PH are comparable to those in LHF.\textsuperscript{44,45}

Measurements in PH-patients, as in LHF, revealed elevated levels of norepinephrine in plasma,\textsuperscript{46,47} although this was not consistently found in other studies.\textsuperscript{48} Furthermore, increased MSNA,\textsuperscript{48} reduced cardiac uptake of \textsuperscript{123}I-MIBG,\textsuperscript{49} reduced heart rate variability,\textsuperscript{50} and selective downregulation the beta\textsubscript{1} -adrenergic receptors in the right (but not left) ventricle have been observed in PH-patients,\textsuperscript{51} which are all indicators of increased sympathetic activity affecting the right ventricle. Moreover, these findings were correlated with disease severity.

The RAAS is also involved in PH-induced right heart failure. Forfia et al. recently identified hyponatremia, which indirectly indicates RAAS activation, as an important independent prognostic factor in PH.\textsuperscript{52} Parameters that more directly measure RAAS activation (increased renin activity, elevated levels of angiotensin II, aldosterone, and/or vasopressin) have not been systematically investigated in PH-patients yet. Nevertheless, increased renin activity and elevated aldosterone levels in plasma have been demonstrated in patients with right heart failure due to hypoxic pulmonary hypertension (“cor pulmonale”),\textsuperscript{53} and in different experimental models of PH-induced right heart failure.\textsuperscript{54} Also, selective downregulation of the AT\textsubscript{1} -receptor in the right ventricle has been observed in PH-patients.\textsuperscript{55}

Together, these studies suggest that the sympathetic nervous system and RAAS are highly activated in PH. But in contrast to LHF, there are only a few clinical studies that explored the therapeutic potential of neurohumoral modulation. Rich et al. investigated the effect of i.v. administration of digoxin in PH-patients, and found acute improvement in cardiac output with concomitant reduction in norepinephrine levels, comparable to digoxin-effect in LHF.\textsuperscript{56}

Interestingly, no clinical trial exists in PH-induced right heart failure on the effects of beta-blockers, which have more potent effects on the sympathetic nervous system than digoxin. By common clinical consensus, beta-blocker use is even contra-indicated. Often this is substantiated by the study of Provencher et al.\textsuperscript{57} They reported significant functional improvement, two months after beta-blocker withdrawal in a small series of patients with porto-pulmonary hypertension. However, all patients (treated for prophylaxis of variceal bleeding) were on high-dose propanolol or atenolol. These old beta-blockers are also contraindicated for LHF, because of their profound myocardial depressive and vasoconstrictive effects, in comparison to newer beta-blockers.\textsuperscript{41}
Moreover, it is well-known from LHF, that acute functional improvements do not invariably lead to favourable changes at long-term, and that overall beneficial effects of beta-blockers can typically be expected after chronic use of three months or more.\(^{41}\)

Another (related) argument against beta-blocker use in PH, is the importance of maintenance of RV systolic function. Acute administration of a beta-blocker is known to exacerbates dyspnea, most likely due to its negative inotropic effects, leading to instant ventriculo-arterial uncoupling.\(^{22}\) However, this temporary effect might be better tolerated by careful use of selective beta-blockers (“start low, go slow”), as is successfully demonstrated in LHF-patients.\(^{13,14}\)

Although this is against present consensus, we would like to argue that, like in LHF, the sympathetic nervous system is activated to pathological levels in PH, and that this could be normalized by careful beta-blocker use. Further (preclinical) research is necessary to investigate whether a low-dose of a newer selective beta-blocker might be a tolerable option to abolish the detrimental effects of sympathetic overdrive in PH.

**Activation of the renin-angiotensin-aldosterone system in PH**

The RAAS has long been recognized to have an important role in pulmonary vascular remodeling and pulmonary vasoconstriction.\(^{58,59}\) Therefore, when captopril (the first ACE inhibitor) became commercially available, this new drug was eagerly tested in PH-patients, for whom no effective treatment existed at that time. In the 1980s, 4 small case-series (26 patients in total) reported on the hemodynamic effects of captopril in PH; Three of the studies were positive and found a significant increase in cardiac output,\(^{60,61}\) and exercise capacity.\(^{62}\) One study however, did not observe any hemodynamic changes, neither positive nor negative.\(^{63}\) Surprisingly, no additional clinical studies have appeared ever since. Currently, there is a renewed interest in the RAAS, since the discovery of ACE2, an isoform of the angiotensin-converting enzyme with counteractive (protective) actions.\(^{64,65}\) The theoretical beneficial effects of ACE inhibitors, angiotensin blockers, and/or aldosterone antagonists on the heart in PH have not been addressed in patients yet.

Preclinical studies using different models of PH and right heart failure, however confirmed that the use of ACE inhibitors or angiotensin blockers significantly reduces RV remodeling and improves cardiac function and/or survival.\(^{66-69}\) We conclude that in PH, pharmacological interference in the RAAS could (partially) reverse pulmonary and cardiac remodeling, which warrants a prospective controlled clinical study of the effects of ACE inhibitors, angiotensin blockers, and/or aldosterone antagonists.

**Perspective** – There is convincing evidence that, like in left heart failure, the sympathetic nervous system and the renin-angiotensin-aldosterone system in PH are highly activated. Well-established pharmacological interventions for left heart failure could therefore be relevant for PH as well. However, ACE inhibitors, angiotensin II blockers and selective beta-blockade have not been explored in PH, and clinical investigations of the potential of these drugs are urgently needed. Nevertheless, routine use of these neurohumoral modulators, and
in particular the use of beta-blockers, are currently not recommended in PH, unless future studies can prove that their use is safe and beneficial in PH.

Electrical remodeling and PH

Implantable cardioverter-defibrillators and cardiac resynchronization therapy are relatively new therapeutic modalities in LHF-management. Major heart failure guidelines contain recommendations on implantable cardioverter-defibrillator use since 2001, and recommendations on resynchronization therapy have only been incorporated since 2005. For selected LHF-patient groups, it is nowadays well-accepted that resynchronization therapy significantly reduce morbidity, and both cardioverter-defibrillators and resynchronization therapy significantly reduce mortality, in addition to the beneficial effect of optimal pharmacological LHF-treatment.13,14

Implantable cardioverter-defibrillator

A cardioverter-defibrillator detects and prematurely terminates malignant and life-threatening ventricular arrhythmias, preventing sudden cardiac death. The incidence of ventricular arrhythmias increases with the progression of LHF. Therefore, implantable cardioverter-defibrillator use is currently recommended as secondary prevention for sudden cardiac death in LHF-patients with a (presumed) history of ventricular arrhythmia, or as primary prevention in LHF-patients with a severely reduced LVEF. In both cases LHF-patients must have a reasonable expectation of survival with acceptable functional status of more than one year.13,14 The clinical trials, on which these recommendations are based, reported a relative reduction of all-cause mortality after 24 months of approximately 30% and an absolute risk reduction of approximately 5%,70,71 which implies a number-needed-to-treat of about 20 patients.

Also in PH, sudden cardiac death, presumably due to malignant ventricular arrhythmias, has been recognised as an important clinical risk for these patients.72 Like in LHF, markers for an “electrically instable heart”, such as: prolonged QTc-intervals and increased QT dispersion derived by ECG,73 neurohumoral disturbances (as discussed above), and increase in cardiac fibrosis,74 have been demonstrated in PH-patients. But, in contrast to LHF, the actual incidence of events related to ventricular arrhythmias in PH is considered low. However, the reported percentages of deaths in PH attributed to ventricular arrhythmias vary widely, from 8 to 26%,7,75 and the actual numbers might importantly differ for the different PH-subgroups (e.g. higher for PH associated with congenital heart disease, which might be related to the presence of surgical cardiac scars76). Moreover, these numbers are based on retrospective studies and were partially obtained before the introduction of PH-specific medications. Systematic prospective clinical studies are necessary to accurately determine the current incidence of sudden cardiac deaths in different subgroups of PH. These data will allow a crude estimation of the clinical potential of cardioverter-defibrillators in PH, by calculation of the number-needed-to-treat (extrapolating the effect of cardioverter-defibrillators in LHF). Until then, implantable cardioverter-defibrillators (or pharmacological
anti-arrhythmic agents) are in general not recommended as an (primary) preventive measure for sudden cardiac death in PH-patients.

Supraventricular tachyarrhythmias
In contrast to ventricular arrhythmias, the incidence of supraventricular arrhythmias seems to be much higher, and they are considered an important cause of clinical deterioration in PH-patients. In a retrospective analysis, an annual incidence of supraventricular tachyarrhythmias in PH was found of around 3%: atrial fibrillation and atrial flutter were equally common. In this study, persistent atrial fibrillation was associated with a very poor prognosis (9 out of 11 PH-patients died within 24 months), which may be explained by worsening of RV function due to the loss of atrial "kick" to ventricular filling. Maintenance of sinus rhythm is therefore currently considered an important treatment goal in PH. This is however in contrast to the clinical experience in LHF. The treatment strategy of rhythm-control, compared to rate-control (which is: acceptance of atrium fibrillation, lowering of the ventricular response-rate in combination with adequate anticoagulation), had no superior effect on survival, whereas it required more hospitalization because of the need for repeated cardioversion. We fully support current recommendations to restore and maintain sinus rhythm in PH-patients if possible, by lack of prospective and controlled data. Future trials however, are necessary to test the validity of this treatment strategy.

Cardiac resynchronization therapy
Cardiac dyssynchrony in LHF is characterized by regional differences in electrical and/or mechanical activation of the left ventricle (usually a delay in activation of the LV free wall in relation to the interventricular septum). Dyssynchrony results in inefficient pumping of the left ventricle, and further clinical deterioration. Cardiac resynchronization therapy can acutely restore synchrony of LV contraction, thereby improving overall LV (systolic) performance. In the long run, resynchronization therapy leads to reversed cardiac remodeling, resulting in an even further improvement of LV performance. Although the current clinical selection criteria for resynchronization therapy (wide QRS-complex on ECG) sub-optimally predict clinical benefit for the individual LHF-patient, resynchronization therapy has been shown to significantly reduce morbidity and mortality, and is nowadays a well-established treatment modality in LHF.

Ventricular dyssynchrony is often observed in progressive stages of PH-induced right heart failure as well. Mechanical interventricular dyssynchrony in PH (which is clinically easily recognised by the paradoxical bulging of the interventricular septum) is associated with impaired RV systolic function. Furthermore, through septum bulging, ventricular dyssynchrony is thought to impair LV diastolic function as well. Resynchronization of the right ventricle could therefore be of clinical benefit in PH. However, we recently demonstrated that LV and RV dyssynchrony are essentially different: the origin of PH-related ventricular dyssynchrony lies in regional differences in the duration of the contraction, rather than regional differences in onset of the contraction (e.g. due to a conductance delay); and is highly afterload dependent.
Previously, successful application of cardiac resynchronization therapy has been demonstrated in patients with PH associated with congenital heart disease. However, these patients display a “LHF-like” dyssynchrony due to a complete right bundle branch block as a (late) complication of cardiac surgery, and are therefore not representative for the PH-population in general. We recently explored the clinical potential of resynchronization therapy in an experimental model of PH-induced right heart failure, in the absence of conduction disturbances. We found that pre-excitation of the RV free wall resulted in improved RV systolic function and reduced adverse LV diastolic interaction. Interestingly, these findings very recently have been confirmed by Hardziyenka et al. in a study with patients suffering from right heart failure and ventricular dyssynchrony secondary to chronic thromboembolic pulmonary hypertension. A cohort of 67 patients was preoperatively screened by standard tissue-Doppler echocardiography, and seven patients were selected for a temporary pacing protocol, based on the presence of large diastolic interventricular delay (as a quantification of PH-related ventricular dyssynchrony). Resynchronization therapy acutely reduced ventricular dyssynchrony, enhanced RV contractility and LV diastolic filling, and this resulted in an improvement of stroke volume of more than 10%. These promising results warrant further investigations of cardiac resynchronization therapy as a novel treatment for right heart failure secondary to PH, that should focus on its long-term effects, and on the identification of robust selection criteria for PH-patients that could profit most from cardiac resynchronization therapy.

**Perspective** – In PH, the incidence of malignant ventricular arrhythmias is considered low, but this observation needs prospective validation. For now, the use of implantable cardioverter-defibrillators is not recommended for PH-patients. Supraventricular tachyarrhythmias often lead to clinical deterioration. Based on retrospective data, maintenance of sinus rhythm is an important treatment goal, but this preference of rhythm-over rate-control needs be confirmed in prospective controlled studies, especially because this is opposite to the experiences in left heart failure. Cardiac resynchronization therapy emerges as a promising new treatment modality. Prospective controlled trials are necessary to study its long-term effects and to identify robust selection criteria.

**CONCLUSIONS AND FUTURE DIRECTIONS**

In this perspective, we investigated the potential applicability of current LHF therapy for the treatment of PH-induced right heart failure. Based on available literature, we conclude that:
1) Left and right heart failure share important underlying pathophysiological mechanisms that are amenable for treatment (Figure 4), however;
2) Clinical experience with current LHF treatments in the setting of PH is very limited.
This discrepancy is intriguing, and we can only speculate about its reasons. Firstly, it is difficult to separate cardiac- from pulmonary-specific effects of therapeutic interventions in PH-patients. As a solution, we propose the use of the pump function graph. Secondly, PH remains a rare disease where many other clinical trials have been undertaken in the last two decades. Thirdly, until recently right heart failure was regarded as an inevitable final consequence of PH, whereas nowadays the right ventricle is considered a potential therapeutic target.

So, how do we move forward? Solid clinical evidence is essential, before LHF-therapy can be implemented in clinical PH-management. Therefore, phase I/II-trials need to be conducted first, which must provide insights in safety, tolerability and efficacy of LHF-therapy in PH. Subsequently, randomized clinical trials should be performed that compare current PH-therapy with and without add-on LHF-therapy. An important aspect is sufficient duration of the trial: the experiences in LHF would predict that reversal of cardiac remodeling requires more than the typical 12-week trial duration. In addition, the question remains which endpoint to choose in these types of studies: classical endpoints in PH-trials, such as 6-minute walking distance, might not be sensitive enough, and direct measures for RV remodeling and function are possibly more appropriate. On the other hand, the most ideal endpoint, mortality, might be too stringent, and will require inclusion of unrealistic high numbers of patients.

To conclude, well-designed clinical studies are warranted, as they might us provide supporting evidence for use of novel therapeutic modalities that are relatively easy at hand, to treat this devastating disease. Future will reveal whether going “left” is a step in the “right” direction.

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