Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart

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Handoko ML, Lamberts RR, Redout EM, de Man FS, Boer C, Simonides WS, Paulus WJ, Westerhof N, Allaart CP, Vonk-Noordegraaf A. Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart. Am J Physiol Heart Circ Physiol 297: H1752–H1759, 2009. First published September 4, 2009; doi:10.1152/ajpheart.00555.2009.—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 T, 23 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 transseptal pressure gradient, as observed in clinical PH. RV pacing improved RV systolic function, compared with unpaced condition (maximal first derivative of RV pressure: +8.5 ± 1.3%, P < 0.001). In addition, RV pacing markedly decreased the pressure-time integral of the transseptal pressure gradient when RV pressure exceeds LV pressure, an index of adverse diastolic interaction (−24 ± 9%, P < 0.01), and RV pacing was able to resynchronize time of RV and LV peak pressure (unpaced: 9.8 ± 1.2 ms vs. paced: 1.7 ± 2.0 ms, P < 0.001). Finally, RV pacing had no detrimental effects on LV function or coronary perfusion, and no LV preexcitation 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.

right ventricular dysfunction; artificial cardiac pacing; magnetic resonance imaging; Langendorff preparation

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 dyssynchrony, are often observed (19, 25, 32). This results in inefficient pumping of the heart (3, 9, 22). In essence, the duration of RV contraction is lengthened due to increased RV afterload (14). As a consequence, time-to-peak shortening of the RV free wall is delayed, even beyond closure of the pulmonary valves (9, 21, 22). Loss of a coordinated ventricular contraction results in impaired RV systolic function (18, 21). In addition, the prolonged RV contraction in early left ventricular (LV) diastole causes the already relaxing interventricular septum to bulge into the LV. This negatively influences early LV filling, eventually contributing to the impairment of LV diastolic function as well (12, 28).

To this date, no specific treatment is available for the failing RV (33). Cardiac resynchronization therapy is a well-established treatment for LV dyssynchrony related to left heart failure (23) and might be an interesting therapeutic option for right heart failure as well. However, our laboratory 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 the onset of the contraction (e.g., due to a conductance delay) (22). For this reason, PH-related ventricular dyssynchrony is essentially different from dyssynchrony associated with left heart failure (23).

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 (MCT) 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 (20).

MATERIALS AND METHODS

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

Experimental model of PH. In total, 26 male Wistar rats were included in the study (150–175 g; Harlan, Horst, the Netherlands). PH was induced (n = 16) by a single subcutaneous injection of MCT (80 mg/kg dissolved in sterile saline; Sigma-Aldrich, Zwijndrecht, The Netherlands). This resulted in a PH phenotype, followed by right heart failure ~23 days after injection (8, 15). The control group was injected with saline only (n = 10).

Cardiac magnetic resonance imaging. Twenty-three days after MCT injection, the presence of ventricular dyssynchrony in vivo was assessed in PH rats and compared with controls (6 for each group), by measuring cardiac function and the behavior of the interventricular...
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 LV and RV (Fig. 1) (20). 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 (27, 29). 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 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 LV and RV. 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 length at maximal developed force, used in isolated muscle studies (31)]. Subsequently, the pressure-volume (PV) relationship of the LV was determined (in the physiological range of 70–100% Vmax), with the RV volume set at 75% Vmax (20).

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 (30). LV volume was set at 75% Vmax, and RV volume was set at 95% Vmax. These volumes correspond with LV and RV end-diastolic pressures of 5 and 10 mmHg, respectively (Fig. 2), as observed in PH patients (11) and in MCT-treated rats in vivo (15). The intrinsic atrioventricular delay (AV time) was defined as the time interval between atrial and (right) ventricular activation (Fig. 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 s. After the experiment, all hearts were dissected in LV (including interventricular septum) and RV and weighed.

Functional assessment of RV pacing. The isovolumic pressure recordings were evaluated offline using MATLAB (version R2007b, The MathWorks, Natick, MA). Signals were averaged over ~100 beats (25 s). The effects of RV pacing on both intra- as well as interventricular aspects of PH-related dyssynchrony were evaluated (13). Intraventricular dyssynchrony was measured by the maximal first derivative of RV pressure (RV dP/dtmax) and RV systolic pressure (RV SP). The time difference between RV and LV peak pressure was used as an index for interventricular dyssynchrony (ΔPpeak).

The pressure-time integral of the transseptal pressure gradient when RV pressure exceeds LV pressure (PTI<sub>RVP>LVP</sub>) 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 LV (25), impairing LV filling (12, 28). This parameter is especially sensitive (it decreases) for improvements in synchronic pressure generation across the septum (due to RV pacing). PTI<sub>RVP>LVP</sub> was calculated by:

\[
\text{PTI}_{RVP>LVP} = \int_{1\text{beat}} (\text{RV pressure} - \text{LV pressure}) \, dt,
\]

when RV pressure > 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 (DP). The difference between the onset in LV and RV contraction was used to identify the presence of LV preexcitation. LV preexcitation 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 (30). This phenomenon can be recognized from pressure recordings, when the difference in onset no longer changes at larger AV shortening intervals (see Figs. 1 and 5D); in that case, RV pacing no longer solely advances RV contraction, but prematurely activates the LV 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 analyses. All data were verified for normal distribution, and values were expressed as means ± SE, 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 PV 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 with control (Table 1). Autopsy showed a significant increase in (wet) lung mass and RV/(LV + septum) mass ratio (Table 1). An upward shift in systolic and diastolic PV relationships for the RV in PH was observed. The PV relationships for the LV were not different between PH and control (Fig. 2). These results indicate PH-induced RV remodeling and RV dysfunction in MCT-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 with controls (Fig. 3, A and 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 LV (negative 1/R; Fig. 3, A and B). Furthermore, we found significantly smaller LV end-diastolic volumes and lower LV peak filling rates for PH (Table 1).

Reversed transseptal 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, nonsignificant (NS)]. This finding was confirmed by the lack of a difference in electrical activation between RV and LV (activation delay RV to LV, PH: +0.1 ± 0.8 ms vs. control: +0.7 ± 1.0 ms, NS). In contrast, we found a prolonged duration of RV contraction in PH hearts (Fig. 3C; duration of RV contraction, PH: 197 ± 3 ms vs. control: 168 ± 4 ms, P < 0.001). As a consequence, only in PH hearts were RV pressures found to exceed LV pressures during late systole in the heart cycle, resulting in a temporary reversal of the transseptal pressure gradient (Fig. 3D).

When comparing in vivo septum measurements (Fig. 3B) with the pressure measurements obtained in isolated hearts (Fig. 3D), it was found that time of peak negative transseptal pressure gradient (t = 66 ± 2% RR interval) coincided with...
In addition, we found that, in PH hearts, PTIRVP_LVP (an index of diastolic interaction) was RV volume dependent, whereas this relationship was not observed in controls (Fig. 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 preexcitation (Fig. 5D), as LV preexcitation only occurred at longer AV shortening intervals (AV shortening at the transition point to LV preexcitation = 32 ± 2 ms; P < 0.001 vs. optimal pacing interval).

Compared with 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; Fig. 6A), and peak RV SP increased by 2.7 ± 0.6% (P < 0.01; Fig. 6B). Pacing also decreased the 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; Fig. 6C). In addition, RV pacing positively influenced the diastolic interaction, as PTIRVP-LVP decreased by 24 ± 9% (P < 0.01; Fig. 6D). Furthermore, RV pacing shortened the duration of RV as well as LV contraction (RV duration at baseline: 197 ± 2 ms).

the occurrence of maximal septum bulging in PH (t = 64 ± 2% RR interval).

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ms; change in RV duration after pacing: $-1.0 \pm 0.4\%$, $P < 0.05$; LV duration at baseline: $191 \pm 2$ ms; after pacing: $-1.3 \pm 0.3\%$, $P < 0.001$).

No significant effects of RV pacing were observed on RV diastolic function (RV DP, baseline: $85.5 \pm 2.2$ mmHg; paced: $+0.9 \pm 1.2\%$; RV dP/dt$_{min}$, baseline: $-819 \pm 28$ mmHg/s; paced: $-2.0 \pm 2.2\%$; both NS). Also, no effects of RV pacing were observed, either on LV function (LV SP, baseline: $2.4 \pm 0.4$ mmHg, paced: $-3.2 \pm 2.6\%$; both NS), or on coronary perfusion (mean coronary perfusion, baseline: $15 \pm 1$ ml/min, paced: $+0.3 \pm 0.3\%$; NS).

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

**DISCUSSION**

After validation of the MCT rat model for PH-related ventricular dyssynchrony, we demonstrated that, in chronic PH, 1) RV pacing improved RV systolic function, characterized by enhanced RV dP/dt$_{max}$ and peak RV SP; and 2) RV pacing diminished adverse interventricular diastolic interaction, by resynchronizing $\Delta t_{peak}$ and reducing PTIRVP$_{LVP}$.

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 preexcitation.

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 MCT rat model for ventricular dyssynchrony. The MCT rat model is a well-established model for chronic PH in general (34), 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 MCT 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 (2). Our CMR measurements confirmed the pulmonary hypertensive state of the MCT-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 (3, 22).

As observed in clinical PH, ventricular dyssynchrony in MCT-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 transseptal 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. (6). It is important to note that the expected coincidence in time of septum bulging and peak reversed transseptal pressure gradient (RV pressure exceeds LV pressure; Fig. 3) was also found in the isolated hearts.

These observations demonstrate that the MCT 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 interventricular 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 preexcitation, which is known to be detrimental for LV function at the long term (30).

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 (6, 22). Pacing helped to restore synchrony of the LV and RV, 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 (Fig. 5B).

Another beneficial effect of pacing was the reduction in interventricular diastolic interaction, expressed by PTIRVP-LVP. Pacing-induced earlier activation of the RV free wall and the short-
en ed 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 PTIRVP. Although isovolumic pressure measurements in our Langendorff setup cannot directly provide this information, a marked decrease in PTIRVP, together with a shortened duration of LV contraction, would predict less septum bulging and improvement in early LV filling (12, 28).

Recently, Quinn et al. also reported positive effects of pacing in a different model of RV pressure overload (24). 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 RVs are not discussed here) (7, 10). 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 (22).

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 (10, 24). RV pacing could also potentially worsen tricuspid regurgitation through elevation of RV SPs. On the other hand, it was recently shown that resynchronization therapy in left heart failure actually reduced preexisting mitral regurgitation (35).

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 (4). This might explain why we did not observe a significant reduction in LV DP/LV filling pressures by RV pacing (that were already low at baseline) in our isolated heart preparations (5). 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 (27, 29). 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) (17). However, no differences were observed between PR intervals of isolated PH and control hearts. We, therefore, conclude that the prolonged PR interval, compared with the in vivo situation, is most likely to be attributed to the Langendorff setup 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 (1). Therefore, the small acute improvements in RV function found here may, in the long term, translate into substantial benefit.

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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