Right-to-Left Ventricular Diastolic Delay in Chronic Thromboembolic Pulmonary Hypertension Is Associated With Activation Delay and Action Potential Prolongation in Right Ventricle

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Background—Delayed left ventricle (LV)–to–right ventricle (RV) peak shortening results in cardiac output reduction in patients with chronic thromboembolic hypertension (CTEPH) and other types of pulmonary arterial hypertension. Why the synchrony between LV and RV is lost is unknown. We hypothesized that RV electrophysiological remodeling, notably, conduction slowing and action potential prolongation, contribute to this loss in synchrony.

Methods and Results—We conducted epicardial mapping during pulmonary endarterectomy in 26 patients with CTEPH and compared these findings with clinical, hemodynamic, and echocardiographic variables. We consecutively placed a multielectrode grid on the epicardium of the RV free wall and LV lateral wall. These regions corresponded to RV and LV areas where echocardiographic Doppler sample volumes were placed to measure RV-to-LV diastolic interventricular delay. RV and LV epicardial action potential duration was assessed by measuring activation-recovery interval. Onset of diastolic relaxation of RV free wall with respect to LV lateral wall (diastolic interventricular delay) was delayed by 38±31 ms in patients with CTEPH versus −12±13 ms in control subjects (P<0.001), because, in patients with CTEPH, RV completed electric activation later than LV (65±20 versus 44±7 ms, P<0.001) and epicardial action potential duration, as assessed by activation-recovery interval measurement, was longer in RV free wall than in LV lateral wall (253±29 versus 240±22 ms, P<0.001).

Conclusion—Additive effects of electrophysiological changes in RV, notably, conduction slowing and action potential prolongation, assessed by epicardial activation-recovery interval, contribute to diastolic interventricular delay in patients with CTEPH. (Circ Arrhythmia Electrophysiol. 2009;2:555-561.)

Key Words: chronic thromboembolic pulmonary hypertension ■ echocardiography ■ electrophysiological remodeling ■ diastolic interventricular dyssynchrony

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We aimed at resolving the pathophyslogic basis of DIVD. We hypothesized that it results, at least in part, from RV electrophysiological remodeling, that is, changes in RV electrophysiological properties secondary to RV hypertrophy/failure, analogous to LV electrophysiological remodeling during LV hypertrophy/failure.6 Previous studies in CTEPH patients have indicated that RV completes activation and repolarization later than LV.7 Moreover, RV action potentials are prolonged in humans8 and experimental animals9 with RV dysfunction associated with severe heart failure and RV
hypertrophy caused by chronic RV pressure overload\textsuperscript{10} and RV volume overload.\textsuperscript{11} In support of our hypothesis, we found that these changes in RV activation and action potential duration are associated with DIVD in CTEPH.

**Methods**

**Patient Assessments**

We prospectively studied 26 consecutive CTEPH patients (mean age, 58.2±13 years; 14 women) who were referred between August 2004 and November 2007 for pulmonary endarterectomy (PEA) and had analyzable tissue Doppler imaging (TDI) echocardiographic recordings at preoperative assessment. CTEPH was diagnosed as reported previously.\textsuperscript{12} PEA was performed using standardized surgical techniques\textsuperscript{13} and anesthesia protocols. Before surgery, all patients underwent transthoracic TDI echocardiography, 12-lead ECG recording, pulmonary angiography, and RV catheterization. Thirteen age-sex-matched individuals (mean age, 54.8±9 years, 8 women) without cardiovascular disease served as control subjects to establish normal echocardiographic values. All subjects gave written informed consent. Investigations were approved by the local institutional review board.

**DIVD Analysis: TDI Echocardiography**

Echocardiographic recordings were made with a 1.6- to 3.2-MHz transducer, following the guidelines of the American Society of Echocardiography. Chamber dimensions, LV early diastolic eccentricity index (a measure of early diastolic leftward IVP bowing), and Doppler flow parameters were analyzed as reported previously.\textsuperscript{14,15} The color-coded TDI tracings were recorded and analyzed off-line by positioning sample volumes in the middle of the basal portions of the RV free wall and LV lateral wall segments (Figure 1 and supplemental Figure 1). From these traces, RV and LV peak velocities during systole (Sm) and early diastole (E\textprime{}) were measured. Time to E\textprime{} was measured as time between onset of the QRS complex and onset of the E\textprime{} wave (early diastolic relaxation).\textsuperscript{16} DIVD was calculated by subtracting RV time to E\textprime{} from LV time to E\textprime{} (supplemental Figure 1).\textsuperscript{16,17} To minimize the influence of heart rate, all times were corrected to the R-R interval between 2 QRS complexes and expressed as percentage of cycle length.\textsuperscript{18} The averages of at least 2 consecutive beats were used for comparisons.

**Electrophysiological Remodeling: Epicardial Mapping**

Twenty-six patients underwent epicardial mapping during PEA (body core temperature, 36.0° to 36.5°C). At the time of measurement, spontaneous circulation was maintained and pulmonary arterial and systemic pressures were virtually identical to preoperative values obtained during right heart catheterization. A complete mapping protocol consisted of the following. In all patients, multielectrode grids (144 or 126 electrodes, 1×1 or 0.4×0.4 mm interelectrode distance, respectively) were consecutively placed on the epicardium of the RV free wall and LV lateral wall. Both areas corresponded to the basal RV and LV areas where echocardiographic Doppler sample volumes were placed during TDI recordings. These regions have been previously shown to be the last activated in CTEPH patients\textsuperscript{19} and in the intact human heart.\textsuperscript{16,19} As reference, we used a reference electrode placed on fat tissue of the chest wall. Unipolar electrograms were recorded during sinus rhythm and during constant pacing from the central electrode of the grid. The interval between a Reference time and the moment of the maximal negative dV/dt of the electrogram was used as activation time (Figure 2). The earliest deviation from baseline in recorded electrograms served as reference time. We validated that this moment coincides with the onset of the QRS complex. Mean activation time of RV free wall and LV lateral wall was the average activation time of all electrograms of the multielectrode grid recorded during sinus rhythm. RV-to-LV activation delay was the difference between activation times of RV and LV. To assess RV and LV action potential durations, we measured activation-recovery intervals (ARIs)\textsuperscript{20} in electrograms recorded during constant pacing at the central electrode (500 or 600 ms basic cycle length). ARIs were the time intervals between the maximum negative dV/dt of the local QRS complexes (local activation) and maximum dV/dt of the local T-wave (local repolarization)\textsuperscript{20} (Figure 3). Mean ARIs of RV and LV were the average ARI of all electrograms of the multielectrode grid placed on RV and LV, respectively. RV-to-LV difference in ARI was calculated by subtracting mean ARI of RV from mean ARI of LV. RV-to-LV delay in end of repolarization (delay between ends of repolarization of RV and LV) was the sum of RV-to-LV activation delay and RV-to-LV difference in ARI. The longitudinal and transversal conduction velocities were calculated from ellipsoid activation patterns as described previously (Figure 3).\textsuperscript{21} Intersitial fibrosis was assessed in histological sections of hearts obtained at postmortem analysis in 6 randomly taken regions of RV and LV each.\textsuperscript{22} We studied 3 CTEPH patients who died during surgery (1 underwent electrophysiological study during PEA) and 6 age-sex-matched patients who died of noncardiac causes. Postmortem analysis in the remaining CTEPH patient who died during surgery was declined by his relatives.

**Statistics**

The statistical analysis was performed using SPSS version 16.0. Data are mean±SD or median with interquartile range. Paired and unpaired Student t test, 1-way ANOVA with Bonferroni post hoc correction or nonparametric Wilcoxon signed rank tests were used.
for comparison when appropriate. There was no censoring in the time-to-event measurements. Pearson and Spearman correlation analyses, logistic regression, or linear regression analysis were conducted where appropriate to study an association between echocardiographic, hemodynamic, and electrophysiological parameters. \( P < 0.05 \) was considered statistically significant.

**Results**

**Baseline Patient Characteristics**

Baseline patient characteristics are summarized in Table 1. All patients used oral anticoagulants for at least 3 months before referral, 7 used the dual endothelin receptor antagonist bosentan, and none used antiarrhythmic drugs (including calcium channel blockers and \( \beta \)-blockers). Patients with CTEPH had, on average, dilated RV (as shown by significantly larger RV end-diastolic diameter) with impaired early diastolic relaxation (reduced \( E' \)) and contractility (reduced RV peak Sm and tricuspid annulus plane systolic excursion). Reduced LV end-diastolic diameter was accompanied by decreased early diastolic relaxation velocity and leftward shift of the IVS (LV early diastolic eccentricity index). Patients with CTEPH had significantly increased QRS and QTc duration (Table 1) and DIVD (Table 2) compared with control.

**Electrophysiological Basis of DIVD**

To test the hypothesis that increased DIVD results from RV electrophysiological remodeling, we conducted epicardial mapping during PEA. The mean interval between echocardiographic and epicardial mapping was 16±6 days. On average, epicardial activation occurred significantly later in RV free wall than in LV lateral wall (65±20 versus 44±7 ms, \( P < 0.001 \)) due to significantly slower longitudinal (47±6 versus 58±10 cm/s, \( P < 0.001 \)) and transversal (12±1 versus 18±4 cm/s, \( P < 0.001 \)) conduction velocities in RV. Moreover, mean ARI was significantly longer in RV than in LV (253±29 versus 240±22 ms, \( P < 0.001 \)). Thus, mean LV-to-RV activation delay and difference in ARI were 21±20 ms and 15±21 ms, respectively. This resulted in RV-to-LV delay in end of repolarization of 37±30 ms. DIVD positively correlated both with RV-to-LV activation delay (Figure 4A) and RV-to-LV difference in ARI (Figure 4B), confirming the roles of both slower conduction and ARI prolongation in RV. Of note, DIVD correlated even stronger with RV-to-LV delay in end of repolarization, that is, the added effects of activation delay and ARI prolongation in RV. Among all patients, CTEPH patients without right bundle-branch block (RBBB) had significantly increased DIVD (28±28 ms) and longer QRS duration (95±14 ms) than control (\( P < 0.001 \) and \( P = 0.031 \), respectively) and RV-to-LV delay in activation of 16±17 ms. Not surprisingly, 4 patients with RBBB had more pronounced increase in DIVD of 78±19 ms (\( P < 0.001 \) and \( P = 0.001 \) versus control subjects).
Catheterization RV completed activation significantly later than LV, even in NYHA class I/II/III/IV 0/10/12/4 finding is in line with a previous study, which showed that increase was more prominent in patients without RBBB. This less of whether or not RBBB was present, although this We found increased DIVD in patients with CTEPH, regarding whether or not RBBB was present, although this We found increased DIVD in patients with CTEPH, regarding whether or not RBBB was present, although this

Mechanisms Contributing to DIVD
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Table 1. Baseline Characteristics and ECG Data of Patients With CTEPH and Control Subjects

<table>
<thead>
<tr>
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<th>Patients (n=26)</th>
<th>Control Subjects (n=13)</th>
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<tr>
<td>NYHA class</td>
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<tr>
<td>Systolic arterial</td>
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<td>pressure, mm Hg</td>
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<td>Diastolic arterial</td>
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<td>pressure, mm Hg</td>
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<tr>
<td>Mean arterial</td>
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<tr>
<td>pressure, mm Hg</td>
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<tr>
<td>ECG</td>
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<tr>
<td>PQ duration, ms</td>
<td>167±29</td>
<td>157±16</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>100±20</td>
<td>84±8*</td>
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<td>QT, duration, ms</td>
<td>422 (41)</td>
<td>406 (21)†</td>
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<tr>
<td>Catherization</td>
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<td>Mean pulmonary arterial pressure, mm Hg</td>
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<td>41±15</td>
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<tr>
<td>Total pulmonary resistance, dyne/cm²</td>
<td>818±507</td>
<td>818±507</td>
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<td>RV stroke volume index, mL/m²</td>
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<tr>
<td>Cardiac index, L/min/m²</td>
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<td>Pulmonary capillary wedge pressure, mm Hg</td>
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<td>8 (10) (n=17)</td>
</tr>
<tr>
<td>Mixed venous blood oxygen saturation, %</td>
<td>64 (20) (n=25)</td>
<td>64 (20) (n=25)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or median (interquartile range). NYHA indicates New York Heart Association. *P=0.004 versus patients; †P=0.006 versus patients.

and patients without RBBB, respectively) and QRS duration of 137±6 ms (P<0.001 versus control patients and patients without RBBB) and RV-to-LV activation delay of 49±10 ms (P<0.001 versus patients without RBBB).

To study one possible cause of slower RV conduction velocities, we analyzed the extent of interstitial fibrosis.Interstitial fibrosis in RV was significantly increased in CTEPH patients compared with patients who died of noncardiac causes (12.0±1.7 versus 7.1±2.5%, P=0.02) but not different in LV between both groups (8.0±1.4 versus 5.7±1.7%, P=0.4).

Discussion
We found that CTEPH is associated with augmented differences in electrophysiological properties between RV and LV, notably slower conduction velocities and longer action potential durations in RV. These differences may contribute to increased DIVD in CTEPH patients because they may delay the completion of systole and the start of diastole of RV with respect to LV (Figure 5).

Mechanisms Contributing to DIVD
We found increased DIVD in patients with CTEPH, regardless of whether or not RBBB was present, although this increase was more prominent in patients without RBBB. This finding is in line with a previous study, which showed that RV completed activation significantly later than LV, even in CTEPH patients who had no RBBB. Similarly, Marcus et al observed delayed RV peak shortening in patients with pulmonary arterial hypertension without RBBB. Importantly, in most individuals without cardiovascular disease, RV was activated either simultaneously with LV or slightly earlier. In the present study, 15 of 26 CTEPH patients (88%) had RV-to-LV activation delay in excess of 20 ms. Although the possible alterations in the specialized conduction tissue of the right bundle branch in patients with CTEPH cannot completely be ruled out as a partial explanation of our findings, it is most likely that this activation delay is explained by the observed slower longitudinal (∼19%) and transversal (∼33%) conduction velocities in RV that, in turn, may partly be based on increased interstitial fibrosis. In the present study, RV collagen content in CTEPH patients was significantly higher than in patients who died of noncardiac causes. Moreover, collagen contents of CTEPH patients were higher in the RV than in the LV, whereas RV and LV values were similar in patients who died of noncardiac causes, in accor-
dance with previous studies.25 Besides fibrosis, RV ischemia, as documented in patients with pulmonary arterial hypertension,26 may also contribute to conduction slowing.27 Another important cause of delayed RV relaxation and DIVD in the present study is longer action potential duration in the RV, as assessed by ARI. In healthy humans, average LV-ARI exceeds RV-ARI by 32 ms.23 In patients with CTEPH, reduced density of the repolarizing sarcolemmal potassium currents \( I_{Kr}, I_{K1}, \) and \( I_{K2} \) may be a possible mechanism of RV action potential prolongation.8 Similarly, in experimental animals with chronic pulmonary arterial hypertension, RV action potential duration is prolonged in the early stages of hypertrophy because of increased density of the depolarizing sarcolemmal calcium current \( I_{Ca-L} \), whereas at late stages, it may be ascribed to a reduction in \( I_{Ks} \) density.10 Taking into account that the onset of early diastolic relaxation (RV and LV E’s) and, consequently, DIVD coincides in time with the ECG T-wave (Figure 1), it is not surprising that, in the present study, DIVD correlated most strongly with RV-to-LV delay in end of repolarization. The RV-to-LV repolarization delay in CTEPH patients is compatible with the study of Chen et al.7

Increased RV size could also be a contributing factor to delayed RV electric activation and repolarization with respect to LV. For example, in the present study, RV-to-LV activation delay significantly correlated with echocardiographically derived RV end-diastolic diameter \((r=0.56, P=0.003)\) and free wall thickness \((r=0.61, P=0.001)\). Similarly, RV-to-LV delay in end of repolarization was directly related to RV end-diastolic diameter \((r=0.61, P=0.001)\) and RV free wall thickness \((r=0.66, P<0.001)\).

It is possible that other pathophysiologic mechanisms also contribute to prolonged RV contraction, delayed relaxation, and DIVD in patients with RV disease and RV failure. For example, \( \beta \)-myosin heavy chain is upregulated in human end-stage heart failure28 but has slower force generation and decay rates\(^29\) than \(\alpha\)-myosin heavy chain, the transcript present in healthy hearts. Moreover, delayed RV relaxation may result from regional ischemia in the RV,\(^1\) increased RV mass,\(^30\) enhanced collagen deposition in the RV, and abnormal intracellular calcium handling (delayed postcontraction sequestration of calcium into the sarcoplasmic reticulum)\(^31\)

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**Figure 4.** Relation between DIVD and RV-to-LV activation delay (A), RV-to-RV difference in ARI (B), and RV-to-LV delay in end of repolarization (C).

**Figure 5.** Schematic representation of the mechanism by which electrophysiological remodeling may cause DIVD. Averaged action potentials and TDI traces of RV (dotted line) and LV (solid line) are temporally aligned. RV-to-LV repolarization delay constitutes DIVD and is sum of RV-to-LV activation delay (a) and difference in RV-to-LV action potential duration. Note that averaged RV action potential in CTEPH patient is prolonged by gray region compared with normal situation. Filled and open arrows indicate onsets of LV and RV early diastolic filling velocity E', respectively.
observed in RV hypertrophy and failure secondary to pulmonary hypertension. It cannot be ruled out that changes in LV action potential duration and conduction velocities may also occur to some extent in patients with severe CTEPH and RV failure. For instance, chronic pulmonary hypertension and subsequent RV dysfunction resulted in LV myocardial edema and fibrosis in an experimental study.32

**Relation Between DIVD and End-Systolic/Early Diastolic IVS Position**

In the present study, the IVS was shifted leftward in early diastole as evidenced by enhanced LV early diastolic eccentricity index (Table 2). Moreover, DIVD was directly related to this index ($r=0.67$, $P<0.001$). In patients with pulmonary arterial hypertension, the end-systolic and end-diastolic IVS bowing are caused by inverted low transseptal pressure gradient.33 Indeed, in the study of Roeleveld et al,34 the end-systolic/early diastolic IVS bowing in patients with pulmonary arterial hypertension was caused by the transseptal pressure gradient inversion and was related to RV peak contraction delay and, accordingly, the onset of the RV relaxation phase. In the present study, early diastolic IVS septal bowing in CTEPH patients may partly be explained by DIVD. However, the well-known end-diastolic IVS leftward shift in patients with CTEPH and other types of pulmonary arterial hypertension dictated by low or inverted transseptal pressure gradient can hardly be attributed to DIVD. Moreover, whether DIVD contributes to impaired LV diastolic filling in CTEPH remains to be investigated.

**Study Limitations**

We performed only standard longitudinal TDI that allows for simultaneous visualization of RV and LV free walls, although circumferential TDI may more accurately reflect diastolic interventricular delay. Second, RV and LV epicardial activation maps were not recorded simultaneously, and the areas covered by the electrodes were relatively small. However, our electrophysiological data are in close agreement with previously published values by Chen et al,7 who recorded unipolar electrograms from the complete RV and LV epicardial surfaces, and demonstrated that in CTEPH patients, the RV completed activation later than LV, although some patients had early RV epicardial activation breakthrough. Moreover, early RV epicardial activation breakthrough, if it occurred, took place 10 ms later than reported normal values. Based on these observations, we believe that the electrophysiological properties of the mapped parts of both ventricles that we report in the present study adequately reflect the augmented electrophysiological differences between the RV and the LV in CTEPH. Third, we did not investigate the relationship between delayed RV-to-LV delay in end of repolarization and the transseptal pressure gradient that determines IVS position in diastole.33 The next limitation of the present study is that epicardial mapping was performed under general anesthesia when the pericardium was open, whereas DIVD was assessed in conscious patients. Although Blanchard et al7 demonstrated negligible pericardium-mediated interventricular interaction in patients with CTEPH, intrapericardial pressures may well have been increased in the present study, particularly in patients with decompensated heart failure. If so, opening of pericardium may have led to changes in interventricular interaction. Finally, we did not perform epicardial mapping in control subjects. However, our observation that CTEPH patients have significantly longer QRS and QTc durations than control subjects provides further evidence for electrophysiological remodeling.

**Conclusion**

Additive effects of RV electrophysiological remodeling, notably conduction slowing and action potential prolongation, as assessed by measuring activation-recovery intervals, contribute to increased DIVD in CTEPH patients.

**Acknowledgments**

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**Disclosures**

None.

**References**


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CLINICAL PERSPECTIVE

Early studies have indicated that resynchronization therapy may be beneficial in some patients with right ventricular disease. Similarly, studies in animal models of right ventricular pressure overload demonstrated improved interventricular synchrony, right ventricular contractility, left ventricular geometry, and cardiac output when the right ventricle was preexcised with respect to left ventricular during biventricular pacing. Such intervention studies may also prove or refute the possibility that right-to-left ventricular delay in end of repolarization is causally related to diastolic interventricular dysynchrony and thus has a functional impact in chronic thromboembolic pulmonary hypertension. If so, the fact that the right ventricle completes activation and repolarization later than the left ventricle provides the opportunity to preexcite the right ventricle with respect to the left ventricle in an effort to reduce the right-to-left ventricular phase shift. Future studies are required to resolve whether diastolic interventricular dysynchrony can be corrected by cardiac resynchronization therapy, which aims at reducing right-to-left ventricular interventricular delay. Such studies may be conducted in chronic thromboembolic pulmonary hypertension patients who are not eligible for pulmonary artery endarterectomy, the therapy of choice for chronic thromboembolic pulmonary hypertension, or those who did not benefit from it. Similarly, it must be also proven whether the findings of the present study may be clinically relevant in other patient categories with right ventricular hypertrophy/failure, for example, those who suffer from other categories of pulmonary hypertension, especially in combination with right bundle-branch block. However, these studies should be conducted with caution in patients with severe right ventricular failure because systolic septal motion toward the right ventricular free wall was shown to be an important compensatory mechanism.
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Suuplemental Figure 1: Measurement of “Time to E’”. Time to E’ is interval between onset of QRS and onset of early diastolic relaxation movement (E’, filled arrow). A’, atrial phase of diastolic filling.