Assessment of cardiac function and hemodynamics in children and adults with right ventricular pressure overload: role of cardiac magnetic resonance imaging
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Citation for published version (APA):
Romeih, S. (2014). Assessment of cardiac function and hemodynamics in children and adults with right ventricular pressure overload: role of cardiac magnetic resonance imaging

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Recovery of right and left ventricular function after acute pulmonary embolism

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Abstract

**Objective:** To evaluate recovery of cardiac function after acute pulmonary embolism (PE).

**Methods:** Routine breath-held computed tomography (CT)-pulmonary angiography was performed in patients with suspected PE to confirm or exclude the diagnosis of PE at initial presentation. Electrocardiogram (ECG)-triggered cardiac CT was performed to assess biventricular function. After 6 months, cardiac magnetic resonance imaging (MRI) was performed. In total, 15 consecutive patients with PE and 10 without were studied. A significant change in ventricular volume was defined as a >15% change in end-diastolic or systolic volumes (EDV, ESV), and significant ventricular function improvement as a >5% increase in ejection fraction (EF) as based on reported cut-off values.

**Results:** Right and left ventricular (RV and LV) EDV and ESV changed non-significantly (<1.3%) in the patients without PE, indicating good comparability of those values measured by CT and MRI. PE patients with baseline normal RV function (RVEF ≥ 47%) revealed a >5% improvement in the RVEF (+5.4 ± 3.1%) due to a decrease in the RVESV. Patients with baseline abnormal RV function showed a >5% improvement in the RVEF (+14 ± 15%) due to decreases in both the RVESV and RVEDV. Furthermore, the LVEDV increased in this latter patient group.

**Conclusion:** The present study demonstrated an improvement in RV function in the majority of patients with PE, independent of baseline RV function. The degree of RV and LV recovery was dependent on the severity of baseline RV dysfunction.
Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of the pulmonary arteries, and has frequently been associated with acute pulmonary embolism (PE).\(^1\) This obstruction of the pulmonary artery causes an increase in pulmonary vascular resistance and as a consequence chronic right ventricular (RV) dysfunction.\(^1,2\) Although CTEPH is considered to be a rare disease after acute PE, signs of RV dysfunction can be observed in half of the patients with acute PE.\(^1-5\) This acute RV function impairment is caused by increased afterload of the RV by the pulmonary embolus.\(^2\) The natural history of RV recovery after acute PE is largely unknown and, therefore, complicates the diagnostic management of CTEPH. Detailed information of the cardiac function at the time of the PE and general understanding of the subsequent ventricular recovery mechanisms might simplify the diagnostic workup of patients with persistent dyspnoea or heart failure after acute PE. Magnetic resonance imaging (MRI) is widely accepted as the reference standard for evaluating cardiac volumes.\(^6\) Also electrocardiogram (ECG) -gated multidetector computed tomography (MDCT) has been shown to be a reliable method to assess ventricular volumes and ejection fraction (EF) and can be combined with CT pulmonary angiography to establish the diagnosis of PE.\(^7-9\) Furthermore, CT and MRI can be used interchangeably as ventricular volumes assessed by both techniques show excellent correlation.\(^8-11\) The hypothesis of the present study was that acute RV dysfunction associated with acute PE will improve in the majority of patients over time after anticoagulant treatment, except for those patients who develop CTEPH. The rate of this recovery is dependent on individual patient characteristics, such as prior cardiac function, embolus load, and fibrinolytic potential. A further hypothesis was that cardiac MRI would be a feasible tool to study the RV function recovery after acute PE and additionally would involve less radiation exposure than MDCT. Accordingly, the aim of the present study was to evaluate biventricular cardiac function using cardiac MDCT at baseline and MRI at 6 months follow-up in consecutive patients with suspected PE.

Patients and methods

Patients

Consecutive normotensive outpatients with clinically suspected acute PE and an indication for CT pulmonary angiography were enrolled in this prospective observational study. PE suspicion was based on clinical signs and symptoms including sudden onset dyspnoea, deterioration of existing dyspnoea, and/or sudden onset pleuritic chest pain. An indication for CT pulmonary angiography was defined as a likely clinical probability for PE according to the Wells rule or an abnormal VIDAS D-dimer (BioMerieux, Marcy L’Etoile, France) test
result. Patients with confirmed PE were treated according to hospital policy, initially with therapeutic unfractioned or low-molecular-weight heparin, followed by vitamin K antagonists for 6 months. Exclusion criterion was a contraindication for MRI, e.g., pregnancy, aneurysm clip in the brain, implanted neural stimulator, implanted cardiac pacemaker or defibrillator, or severe claustrophobia. As this was a proof of concept study, the aim was to study 15 consecutive patients with PE and 10 consecutive patients without PE. The Institutional Review Board approved the study and all participants consented to participation.

Baseline MDCT examination
All patients underwent MDCT (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) of the chest during breath holding. Section collimation of 0.5- or 1 mm was used for acquisition. A separate image acquisition using retrospective ECG-synchronized dynamic cardiac MDCT was performed to assess RV and left ventricular (LV) function. All examinations were performed according to a standardized protocol as described previously. The diagnosis of PE was confirmed by the presence of at least one filling defect in the pulmonary artery tree. For cardiac analysis, 2 mm thick sections focused on the heart were reconstructed and analysed with dedicated cardiac function analysis software MASS ® (Medis, Leiden, The Netherlands). The phase in which the ventricular sizes were maximal and minimal were selected to represent the end-diastolic and end-systolic phase. End-diastolic and end-systolic endocardial border contours were drawn for both ventricles on every other transverse section (i.e., each 4 mm) covering the entire ventricles up to the pulmonary valve and aortic valve. All contours were manually drawn by an observer (2 years experience with cardiac CT), supervised by a radiologist (8 years experience with cardiac CT) who were both blinded for the patients’ conditions. End-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, and EF were calculated for both the right and left ventricles. Patients with PE were categorized in two groups characterized by normal or abnormal baseline systolic RV function. RV ejection fraction < 47% was defined as abnormal. Patients without PE comprised a third study group.

Follow-up MRI
MRI examinations were performed using a 1.5 T MRI system (Intera, Philips Medical Systems, Best, The Netherlands). A five-element, phased-array cardiac coil placed on the chest was used for signal reception. After a series of thoracic scout images that were used for planning purposes, a stack of 14-18 transverse sections (dependent on the size of the heart) was obtained using a steady-state free-precession sequence for biventricular volume measurements. Each section was acquired with breath holding at end-expiration. Scan parameters were: section thickness= 10 mm with no gap, field of view = 450 mm, scan matrix = 256 x 195, with reconstructed voxels = 1.37 x 1.37 x 8.0 mm, flip angle =
35°, repetition time = 3.2 ms, echo time = 1.6 ms, one signal average was used. Gated cardiac synchronization was used with 30 reconstructed phases per cardiac cycle; yielding a temporal resolution of 20 -35 ms. Parallel imaging was used (Sensitivity encoding SENSE, with sense factor 2). Endocardial contours at end-systole and end-diastole were manually drawn using the MASS software package. All endocardial contours were manually drawn by an observer (2 years experience with cardiac MRI), supervised by a radiologist (11 years experience with cardiac MRI) who were both blinded for the patients’ conditions. (Figure 1b)

Statistical analysis
Ventricular volume changes were studied in 3 subgroups, i.e., patients with PE and abnormal baseline RV function, patients with PE and normal baseline RV function, and patients without PE. Significant change in ventricular volumes was defined as a decrease in volumes of more than 15%. Significant ventricular function improvement was defined as an increase in ejection fraction greater than 5%. Differences in ventricular recovery between the three study groups were assessed by post hoc least significant difference (LSD) testing for parameters that proved statistically significant on analysis of variance (ANOVA). P values less than 0.05 were considered significant.
Results

Study patients
To achieve the required sample size 27 consecutive patients with acute PE and 15 consecutive patients in whom PE was ruled out were recruited into the study. Of these patients, three had died during the 6 months follow-up period and 14 were excluded because of implanted cardiac pacemaker, unwillingness to cooperate, or claustrophobia. The remaining 15 patients diagnosed with PE and 10 patients without PE underwent both a CT examination at entry and MRI at 6 months follow-up, and were included for analysis. The baseline characteristics of patients with PE and without were comparable (Table 1); overall mean age was 53 ±11 years and 11 (40%) of the patients were male. There was no difference in the presence of cardiopulmonary comorbidity. Median follow-up duration was 205 days (range, 165 ± 301 days).

Table 1: General characteristics of study patients

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Patients without PE (n = 10)</th>
<th>Patients with PE (n = 15)</th>
<th>Total population (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years, ± SD)</td>
<td>52 ± 13</td>
<td>53 ± 10</td>
<td>53 ± 11</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>3 (30)</td>
<td>8 (53)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>History of venous thrombosis (n, %)</td>
<td>0 (0)</td>
<td>6 (40)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>COPD (n, %)</td>
<td>2 (20)</td>
<td>3 (20)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Pre-existent left heart failure (n, %)</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Qanadli score [median, IQ range (max 40)]</td>
<td>NA</td>
<td>15 (2.26)</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up duration (days; mean, ± SD)</td>
<td>202 ± 36</td>
<td>226 ± 42</td>
<td>217 ± 41</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease; IQ, interquartile; NS, not significant; NA, not applicable.

Of the 15 PE patients, seven were diagnosed with RV dysfunction at time of the PE (47%, 95% CI 21-73). RV dysfunction was not found in any of the patients without PE (0%, 95% CI 0-30). None of the patients with PE or without PE experienced a clinical event or medication change other than the acute PE that could have influenced their cardiac function in the follow-up period. The PE patients with baseline RV dysfunction did not differ in age, gender, or the prevalence of cardiopulmonary comorbidity from the PE patients with baseline normal RV function.

Ventricular volume changes
Patients with RV dysfunction had higher right ventricular ESV and EDV at baseline than the patients with normal RV function and patients without PE. LV volumes were not different between the three groups. (Table 2) In the cohort without PE, the overall relative change in the EDV (+ 0.48 ± 6.0 mL for the RV and 0.93 ± 5.7 mL for the LV) and ESV (+0.88 ± 4.3
mL for the RV and 0.75 ± 3.1 mL for the LV) in both ventricles did not meet the previously stated definition of significant volume changes. (Table 2) Also, none of the individual patients without PE was found to have changed RV or LVEF after 6 months. PE patients with normal RV function at baseline showed a >5% overall increase in the RVEF (+ 5.4 ± 3.1%) due to a relative decrease in the ESV (-17 ± 7.9%). Overall, no volume changes of the LV were observed in these patients. (Table 2) Individually, of the eight PE patients with normal RV function at baseline, one (13%) showed significant decrease in the RVEDV, six (75%) in the RVESV, and two showed no volume changes. The LVESV increased in four patients (50%). A > 5% increase in the RVEF was found in five of these eight patients (63%), with a concomitant increase of >15% in the LVEDV in one patient

<table>
<thead>
<tr>
<th>Table 2: Ventricular volume changes during follow-up.</th>
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<tbody>
<tr>
<td>Patients without PE (n = 10)</td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Baseline RV ESV (ml; mean ± SD)ab</td>
</tr>
<tr>
<td>Baseline RV EDV (ml; mean ± SD)ab</td>
</tr>
<tr>
<td>Baseline RV EF (%; mean ± SD)ab</td>
</tr>
<tr>
<td>Follow-up RV EF (%; mean ± SD)</td>
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<tr>
<td>Deltac RV EF (%; mean ± SD)a</td>
</tr>
<tr>
<td>Deltac RVEDV (ml; mean ± SD)ab</td>
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<tr>
<td>Relative RVEDV change (%; mean ± SD)ab</td>
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<tr>
<td>Deltac RVESV (ml; mean ± SD)ab</td>
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<tr>
<td>Relative RVESV change (%; mean ± SD)ab</td>
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<tr>
<td>Baseline LV ESV (ml; mean ± SD)</td>
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<tr>
<td>Baseline LV EDV (ml; mean ± SD)</td>
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<tr>
<td>Baseline LV EF (%; mean ± SD)ab</td>
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<tr>
<td>Follow-up LV EF (%; mean ± SD)a</td>
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<td>Deltac LV EF (%; mean ± SD)a</td>
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<tr>
<td>Deltac LVEDV (ml; mean ± SD)a</td>
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<tr>
<td>Relative LVEDV change (%; mean ± SD)a</td>
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<tr>
<td>Deltac LVESV (ml; mean ± SD)a</td>
</tr>
<tr>
<td>Relative LVESV change (%; mean ± SD)</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; RV, right ventricular; LV, left ventricular; SD, standard deviation; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume.

a Significant differences between patients without PE and PE patients with baseline RV dysfunction (P < 0.05).
b Significant differences between PE patients with baseline normal RV function and PE patients with baseline RV dysfunction (P < 0.05).
c Delta = follow-up scan - baseline scan.
d Significant ventricular volume changes (delta EF >5%; delta volume >15%).
e Significant differences between patients without PE and PE patients with baseline normal RV function (P < 0.05).
Overall, the seven patients with abnormal RV function at baseline had a >5% improvement in the RVEF (+14 ±15%) due to a relative decrease in both the ESV (-34 ± 27%) and EDV (-20 ± 19%). Furthermore, the LVEDV increased >15% (15 ± 11%, Figure 1). On an individual basis, five out of seven patients (71%) with RV dysfunction at baseline were found to have a >15% decrease in the RVEDV and six patients (86%) were found to have a >15% decrease in the RVESV after 6 months of treatment. The LVEDV increased by >15% in four patients (57%) and the LVESV in two patients (29%). As a result, a >5% increase in the RVEF was found in six patients (86%) and in the LVEF in two patients (29%). Three patients with PE had a RVEF <47% after the treatment period. In only one patient, this RVEF remained unchanged and poor. After further clinical work-up, this patient was diagnosed with peripheral, inoperable CTEPH.

Discussion

This study shows that the degree of RV recovery after 6 months treatment of acute PE is dependent on the severity of RV dysfunction at the time of the acute event. RVEF improved due to a decrease in end-systolic volumes and, although to a lesser extent, a decrease in end-diastolic volumes. Patients with more severe RV dysfunction at baseline were additionally shown to have LV volume changes due to an increase in end-diastolic volumes. This indicates that restoration of LV function is dependent on the restoration of the RV, which is a manifestation of inter-ventricular dependence.

The following explanations are proposed to explain the findings of the present study: the concept of ventricular recovery starts with the initial effect of an obstruction of the pulmonary artery by a thrombus, causing a sudden rise in afterload of the RV. RV ESVs and EDVs increase, followed by reduced RV EF and stroke volume.2,16 Depending on prior cardiopulmonary status and the extent of embolic obstruction, the impending resulting reduction of pulmonary blood flow leads to a decrease in LV filling and eventually decreased LV stroke volume. During the naturally occurring thrombolysis of the embolus, RV afterload will be reduced leading to RV and LV volume changes and improvement of stroke volume and ventricular output.2,16 Notably, all but three patients with acute PE from this study were found to have a decrease in RV ESV after 6 months of treatment, even with baseline RVEF within the normal range. One of the three patients that showed no RV ESV change was subsequently diagnosed with CTEPH; the other two had low PE-obstruction scores (data not presented) and excellent RV function (EF > 60%) at baseline. These observations suggest that in most patients acute PE is associated with increased RV volumes although not clinically relevant in all cases. Data from a recent study suggest that approximately 50% of first time patients diagnosed with sub massive PE have RV dysfunction at time of diagnosis, of whom 36% continue to have RV dysfunction at 6-month follow-up.17,18 The results of the present study, combining cardiac MDCT and MRI, confirm these data. It has
been previously shown that cardiac evaluation after PE by echocardiography helps predict future pulmonary hypertension.\textsuperscript{17} One potential advantage of using cardiac MRI as opposed to echocardiography in cardiac evaluation after PE is the possibility of direct comparison of the cardiac volumes to MDCT images, as demonstrated in this study. As CT is the current imaging method of choice for diagnosing PE, patients are not required to undergo additional echocardiography in the acute phase of the disease, although ECG-gated MDCT of the heart involves increased radiation and contrast medium exposure. Furthermore, MRI has been demonstrated to accurately measure pulmonary haemodynamic parameters that correlate closely to invasive measurements.\textsuperscript{19} The strengths of the present study include the prospective design and the inclusion of consecutive patients. The CT and MRI protocols performed were well validated. Furthermore, the previously described reliable assessment of RV and LV function with MDCT when compared to MRI is underlined by the present study.\textsuperscript{8,9} A limitation of the study is that as this was a proof of concept study, only a limited number of patients were selected to test the hypothesis.

In summary, this study demonstrates improvement in RV function in the majority of patients with acute PE, independent of baseline RV function. The extent of the RV and LV function recovery related to the severity of RV dysfunction at the time of the acute event. Further investigation is required in larger patient cohorts to study the potential clinical value of cardiac MRI in the clinical follow-up of patients with acute PE.
Chapter 6

References


