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Early View

Research letter

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Magnetic resonance imaging of pulmonary arterial compliance after pulmonary endarterectomy

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Short title: Pulmonary arterial compliance after PEA

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Pulmonary endarterectomy (PEA) is the treatment of choice of chronic thromboembolic pulmonary hypertension (CTEPH) (1). However, successfully operated patients may continue to suffer from dyspnea and limitation of exercise capacity despite improvement or even normalization of pulmonary artery pressure (PAP), cardiac output (CO) and pulmonary vascular resistance (PVR) (2). This absence of complete symptomatic recovery has been explained by a decreased right ventricular (RV) function reserve due to persistent increased afterload (3,4), related to decreased pulmonary arterial compliance (PCa) more than to mildly increased PVR (5,6). There is therefore interest in assessing PCa in patients during the follow-up of PEA.

Estimation of PCa commonly relies on the invasively measured ratio of stroke volume (SV) and pulse pressure (PP). This approach is limited by the fact that pulmonary circulation is not a closed system and blood leaves through the pulmonary resistive vessels, therefore SV/PP ratio over-estimates PCa considerably (7). This problem can be addressed by the pulse pressure method (PPM), which calculates PCa from the instantaneous PA flow and a two-element windkessel model with an initial value of SV/PP and PVR (8). Another approach is to estimate PCa using systolic and diastolic cross sectional area or flow imaging of SV by cardiac magnetic resonance (CMR) in combination or not with the right heart catheterization (RHC) assessment of PP (9,10).

We wondered whether CMR imaging of the PA could be a clinically useful addition to RHC determination of PCa for the evaluation of CTEPH patients in the follow-up of a successful PEA. We also compared patients with proximal vs distal lesions to better understand the role of anatomical location of the disease in the assessment of PCa.

The present study was a retrospective evaluation of a consecutive cohort of patients who underwent PEA at our institution (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy) and in whom CMR, RHC and a Bruce test were successively performed during the same day, before PEA and 12 months after surgery. All patients signed an informed consent agreement, approved by the institutional review board of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) for longitudinal, nonpharmacological, non-sponsored studies, which complies with the Italian legislation (Codex on Privacy, D. Lgs. 30 giugno 2003, n. 196).

The anaesthesiological and the surgical methods used have been reported previously (11). RHC was performed as recommended in the guidelines of the European Respiratory and Cardiology societies (12). The response variable was exercise capacity assessed using the modified Bruce protocol and expressed in distance achieved in meters. CMR was performed using a 1.5 T scanner (Siemens Synphony, Erlangen, Germany) with a phased array cardiac coil and electrocardiogram gating.

RHC PCa was calculated as SV/PP divided by 1.76 + 0.1 in conformance to the PPM model (8). CMR-derived estimates included: relative cross-sectional relative area change (RAC) of the PA (RAC = [(maxA – minA)/minA]*100, area compliance calculated as absolute change in lumen area for a given change in pressure [(maxA – minA)/PP], area distensibility calculated as the ratio of RAC and PP, vessel wall stiffness (β) calculated as [ln (PAPs/PAPd)]/(2 RAC) and CMR compliance as the ratio of CMR flow imaging SV (SV_{CMR}) and PP.

Data were described as mean (standard deviation) and compared between the groups (proximal-mid vs distal disease) with the Student t-test. Hemodynamic and CMR parameters before and after surgery, were compared within individual subjects, by fitting a mixed model for repeated measure, response was defined as total distance at Bruce test. Time (surgery) effect was explored between the groups (proximal vs distal CTEPH) by including the group and interaction term time * group in the model; other covariates were included into the model to assess independent predictive impact on response. Post-hoc comparisons were adjusted by the Tukey honest significant difference correction, a 2-sided probability value ≤0.05 was considered significant. Data were analyzed in R version 3.5.3.

The study included 86 patients, aged 61 ± 13 (mean ± SD) years, 46 with proximal and 41 with distal CTEPH, with a WHO functional class III or IV in 60 of them. PEA was associated with improvement in the Bruce test distance from 181 ± 201 to 544 ± 286 m.

At RHC, cardiac index improved after PEA from 2.3 ± 0.7 to 2.7 ± 0.5 $l/min/m^2$, mean PAP from 42 ± 12 to 19 ± 6 mmHg, PVR from 776 ± 378 to 216 ± 105 $dyne/s/cm^{-5}$ and SV/PP from 1.2 ± 0.7 to 3.1 ± 1.1 ml/mmHg (all p<001). The time constant PVR x PCa remained unchanged in both proximal and distal CTEPH patients. At CMR, area compliance increased after PEA from 4.0 ± 3.6 to 6.8 ± 4.4 mm^2/mmHg, SV_{CMR}/PP from 1.3 ± 0.6 to 3.2 ± 1.2 ml/mmHg, RAC from 23 ± 18to 25 ± 17% and RAC/PP from 0.5 ± 0.5 to 1.2 ± 0.91 %/mmHg while vessel wall stiffness decreased from 703 ± 1832 to 167 ± 214 arbitrary units (all p< 0.001, except for vessel wall stiffness p=0.18 and RAC p=0.24). All the RHC and CMR changes after PEA were similar and not significantly different in patients with proximal or distal lesions. This is illustrated by PEA-related changes in PCa and Bruce test in Figure 1.

PCa was the only independent hemodynamic parameter associated with improvement in exercise capacity by Bruce exercise test before/after PEA at multivariable model (p=0.018), while mean PAP and PVR were nonsignificant predictors (p=0.692 and 0.095 respectively). When CMR based indices of PA structure and function were incorporated in a multivariable model, only SV_{CMR}/PP independently predicted exercise capacity but with borderline significance (p=0.051). However, RHC-derived assessment of PCa but not SV_{CMR}/PP was independently associated with improvement in exercise capacity when both were included in a bivariable model (p<0.001 and p=0.588, respectively).

The observation that the anatomical location of vascular obstruction and relief by PEA surgery did not affect the time constant of the pulmonary circulation is in keeping with previous demonstration (13). RV afterload is determined by a dynamic interplay between pulmonary vascular resistance, compliance and wave reflection (14). Therefore the present results suggest a negligible contribution of wave reflection as PCa is tightly related to PVR and thus RV hydraulic load essentially predicted by PCa and PVR only - with a hyperbolic relationship so that PCa predominates in the presence of normal or only mildly increased PAP (15). On the other hand, CMR imaging of PA stiffness is necessarily limited to the proximal part of the pulmonary arterial tree, so that proximal PA compliance contributes to no more than 20% of the total compliance of the pulmonary vascular bed (13). This explains why CMR imaging of PA stiffness did not predict exercise capacity in the present study.

In conclusion, the present results show that CMR imaging PA dimensions cannot replace RHC and is of no added value to RHC for the determination of PCa before and after successful PEA in CTEPH patients with either proximal or distal thrombotic lesions.

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Author contributions: Stefano Ghio has made substantial contributions to conception and to the design of the study and to interpretation of data; has drafted the submitted article; and has provided final approval of the version to be published. Gabriele Crimi, Stefania Guida, Adele Valentini, Anna Celentano, Maurizio Pin, Claudia Raineri, Annalisa Turco, Luigi Oltrona Visconti, Robert Naeije, Andrea Maria D’Armini have made substantial contributions to conception of the study, to interpretation of data; have revised the manuscript critically for important intellectual content and

has provided final approval of the version to be published; Gabriele Crimi has also analysed the data.

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Figure legend

Changes in PCa calculated at right heart catheterization (A) and in meters walked at Bruce test (B) from baseline to post surgery in patients with Jamieson type 1-2 disease (red line and circles) and in patients with Jamieson type 3 disease (green line and circles). Post PEA Jamieson type 1-2 vs distal Jamieson type 3 casts are illustrated in the upper part of the figure. Data were analysed in a mixed multivariable model for repeated measure, class effect, time(surgery) effect and the interaction between class and time were included as covariates.

Statistical significance as follows:

1A: Jamieson_class effect p=0.193; time effect p<0.001; Jamieson class*time p=0.018)

1B: Jamieson_class effect p=0.710; time effect p<0.001; Jamieson class*time p=0.050)