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Clinical Research

Right Ventricular Function and Right-Heart Echocardiographic Response to Therapy Predict Long-term Outcome in Patients With Pulmonary Hypertension

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ABSTRACT

Background: Right ventricular (RV) dysfunction in pulmonary hypertension (PH) is linked to adverse outcomes, but this response is considered heterogeneous because it can be associated with multiple factors.

Methods: RV function of 51 PH patients was calculated by averaging peak speckle-tracking longitudinal strain from RV free-wall (RV-free), and the cutoff for RV dysfunction was predefined as RV-free $\leq$ 19%. Right-sided heart remodelling was assessed in terms of RV end-systolic area (RVESA) and right atrial (RA) area (RA-area). Midterm reverse remodelling was defined as a relative decrease in RVESA (ΔRVESA) and RA-area (ΔRA-area) of at least 15% at 5.7 $\pm$ 4.0 months after introduction of pulmonary artery hypertension-specific drugs. Long-term outcome was tracked for 3.0 $\pm$ 2.0 years.

Results: Patients with midterm RV and RA reverse remodelling showed more favourable long-term outcomes than those without

RÉSUMÉ

Introduction : La dysfonction ventriculaire droite (VD) lors d'hypertension pulmonaire est liée à des résultats défavorables, mais cette réponse est diversifiée puisqu'il peut être associé à de multiples facteurs.

Méthodes : La fonction du VD de 51 patients était calculée par la moyenne de la déformation longitudinale maximale en *Speckle-Tracking* (suivi de pixels) de la paroi libre du VD, et la dysfonction VD était prédéfinie comme étant VD-paroi libre $\leq$ 19 %. Le remodelage du cœur droit était évalué en mesurant l'aire du VD en fin de systole (AFSVD) et l'aire de l'oreillette droite (OD; aire-OD). Le remodelage inverse à moyen terme était défini comme étant une diminution relative de l'AFSVD (ΔAFSVD) et de l'aire-OD (Δaire-OD) d'au moins 15 % à 5,7 $\pm$ 4,0 mois après l'introduction de médicaments spécifiques à l'hypertension artérielle pulmonaire. L'évolution à long terme était suivie durant 3,0 $\pm$ 2,0 ans.

Pulmonary hypertension (PH) is a progressive disease that leads to increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR),[1,2] resulting in chronic pressure overload on the right ventricle, and induces a series of right atrial (RA) and right ventricular (RV) functional and morphologic changes and subsequent right-sided heart failure. Although this disease is still characterized by a poor prognosis, several treatment options have become available for patients with various forms of PH, especially pulmonary artery hypertension (PAH)-specific drugs such as prostacyclines, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors, which have shown reduced mortality.[3,4] Baseline RV function is one of the most important determinants of long-term outcomes after the use of PAH-specific drugs,[4-11] because the right ventricle adapts to the increased afterload by increasing its wall thickness and contractility. However, response to these PAH-specific drugs by PH patients is not considered to be homogeneous, because it can be associated with multiple factors including genetic susceptibility, inflammation, or angiogenesis.[12] Therefore, not only assessing baseline RV function, but a more comprehensive approach might result in more accurate prediction of long-term outcome after the initiation of treatment of PH patients with PAH-specific drugs. The appearance of left ventricular (LV) reverse remodelling after medical treatment is generally thought to indicate a favourable prognosis for patients with chronic left-sided heart failure, but it remains unclear whether a similar phenomenon occurs in the right-sided heart of PH patients after treatment with PAH-specific drugs. Accordingly, the objective of this study was to test the hypothesis that

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($P = 0.01$, $P = 0.047$, respectively). Sequential Cox models showed that a model based on hemodynamic parameters ($\chi^2 = 0.3$) was improved by the addition of RV-free ($\chi^2 = 6.4$; $P = 0.01$), and further improved by addition of ΔRVESA and ΔRA-area ($\chi^2 = 28.2$; $P < 0.001$). Furthermore, preservation of baseline RV function and midterm reverse remodelling in right-sided heart was associated with an optimal outcome: a survival rate of 100%. In contrast, absence of midterm reverse remodelling in the right-sided heart of patients with impaired baseline RV function was associated with significantly worse outcome with a survival rate of 33% ($P = 0.01$).

Conclusions: RV function and echocardiographic right-heart reverse remodelling with therapy improves the prediction of long-term outcomes for PH patients over standard hemodynamic indices.

Résultats : Les patients ayant subi un remodelage inverse du VD et de l'OD à moyen terme montraient des résultats cliniques plus favorables à long terme que ceux qui n'en avaient pas eu ($P = 0,01$, $P = 0,047$, respectivement). Les modèles séquentiels de Cox montraient qu'un modèle basé sur les paramètres hémodynamiques ($\chi^2 = 0,3$) était amélioré par l'ajout de la fonction de la paroi libre du VD ($\chi^2 = 6,4$; $P = 0,01$), et davantage amélioré par l'ajout du ΔAFSVD et du Δaire-OD ($\chi^2 = 28,2$; $P < 0,001$). De plus, la préservation de la fonction VD initiale et du et du remodelage inverse à moyen terme dans le cœur droit étaient associés à des résultats optimaux : taux de survie de 100 %. En revanche, l'absence de remodelage inverse à moyen terme dans le cœur gauche des patients souffrant d'une détérioration de la fonction VD initiale était associée à une évolution significativement plus mauvaise avec un taux de survie de 33 % ($P = 0,01$).

Conclusions : La fonction VD et le remodelage inverse du cœur droit mesurées par échocardiographie après traitement améliorent la prédiction des résultats cliniques à long terme des patients HP au-delà des valeurs hémodynamiques standards.

midterm reverse remodelling in right-sided heart failure after the use of PH-specific drugs is linked to long-term outcome for PH patients. We also tested the hypothesis that combining assessment of midterm reverse remodelling in right-sided heart with that of RV function can enhance prediction of long-term outcome.

Methods

Study population

A total of 84 consecutive PH patients who visited the PH clinic in Kobe University Hospital between April 2008 and May 2014 were analyzed retrospectively. PH was defined as resting mean pulmonary artery pressure (mPAP) > 25 mm Hg measured using right-heart catheterization. The patients excluded from the study were those with left-sided heart failure, defined as pulmonary capillary wedge pressure > 15 mm Hg, atrial fibrillation, more than mild aortic and/or mitral valvular heart disease. This protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Echocardiographic examination

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid 7 or E9; GE Vingmed Ultrasound AS, Horten, Norway). Digital routine greyscale 2-dimensional cine loops and tissue Doppler cine loops were obtained from 3 consecutive beats with end-expiratory apnea from standard apical and parasternal views. Frame rates were 48-83 Hz (mean, 67 ± 8 Hz) for greyscale imaging in the RV-focused apical 4-chamber view used for speckle-tracking analysis. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate regardless of heart rate. Standard LV measurements were obtained from the parasternal long-axis view, and LV volumes and ejection fraction were calculated using the biplane Simpson method.[13] Digital data were transferred to dedicated off-line software (EchoPAC version BTO8; GE Vingmed Ultrasound) for subsequent off-line speckle-tracking analysis. All echocardiographic data were analyzed by one observer in a random order, blinded to the clinical characteristics of patients. Midterm follow-up echocardiography was the first routine follow-up echocardiogram, which was performed 5.7 ± 4.0 months after the initial assessment. Midterm follow-up echocardiographic data were analyzed by observers blinded to baseline data.

Assessment of RV function using speckle-tracking strain

The assessment of RV function using 2-dimensional longitudinal speckle-tracking strain from RV free-wall was previously described in detail.[7-10] Briefly, a region of interest was traced on the RV endocardium at end-diastole from the RV-focused apical 4-chamber view. A larger region of interest was then generated and manually adjusted near the epicardium. Next, the RV was divided into 6 standard segments, for which 6 corresponding time-strain curves were generated. RV free-wall longitudinal strain (RV-free) was calculated by averaging each of the 3 regional peak systolic strains along the entire RV free-wall, and was expressed as an absolute value (Fig. 1). On the basis of previously reported findings, the cutoff for RV systolic dysfunction in PH patients was predefined as RV-free of ≤ 19%.[8-10] Acceptable reproducibility of RV-free in our laboratory was previously confirmed.[8,10]

Definition of midterm reverse remodelling in right-sided heart

RV remodelling was assessed in terms of the RV area, which was obtained using planimetric tracing at end-diastole (RVEDA) and end-systole (RVESA) from the annulus, along the free-wall to the apex, and then back to the annulus, and along the interventricular septum from RV-focused apical 4-chamber views (Fig. 2A).[11] Similarly, RA remodelling was assessed in terms of the RA area, which was obtained using planimetric tracing at the end of the ventricular systole from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the RA endocardium, and excluding the inferior and superior vena cava and RA appendage from the RV-focused apical 4-chamber view (Fig. 2B).[11] RV and RA