Standard and Strain Measurements by Echocardiography Detect Early Overloaded Right Ventricular Dysfunction: Validation against Hemodynamic and Myocyte Contractility Changes in a Large Animal Model

Amir Hodzic, MD, Pierre Bobin, PhD, Delphine Mika, PhD, Mohamed Ly, MD, Florence Lefebvre, BSc, Patrick Lechêne, BSc, Emmanuel Le Bret, MD, PhD, Elodie Gouadon, PhD, Mathieu Coblence, MD, Grégoire Vandecasteele, PhD, André Capderou, MD, PhD, Jérôme Leroy, PhD, Catherine Rucker-Martin, PhD, and Virginie Lambert, MD, PhD, *Le Plessis-Robinson and Châtenay-Malabry, France*

Background: Early detection of right ventricular (RV) failure is required to improve the management of patients with congenital heart diseases. The aim of this study was to validate echocardiography for the early detection of overloaded RV dysfunction, compared with hemodynamic and myocyte contractility assessment.

Methods: Using a porcine model reproducing repaired tetralogy of Fallot, RV function was evaluated over 4 months using standard echocardiography and speckle-tracking compared with hemodynamic parameters (conductance catheter). Sarcomere shortening and calcium transients were recorded in RV isolated myocytes. Contractile reserve (ΔE_{max}) was assessed by β-adrenergic stimulation in vivo (dobutamine 5 μg/kg) and ex vivo (isoproterenol 100 nM).

Results: Six operated animals were compared with four age- and sex-matched controls. In the operated group, hemodynamic RV efficient ejection fraction was significantly decreased (29.7% [26.2%–34%] vs 42.9% [40.7%–48.6%], $P < .01$), and inotropic responses to dobutamine were attenuated (ΔE_{max} was 51% vs 193%, $P < .05$). Echocardiographic measurements of fraction of area change, tricuspid annular plane systolic excursion, tricuspid annular peak systolic velocity (S′) and RV free wall longitudinal systolic strain and strain rate were significantly decreased. Strain rate, S′, and tricuspid annular plane systolic excursion were correlated with ΔE_{max} ($r = 0.75$, $r = 0.78$, and $r = 0.65$, respectively, $P < .05$). These alterations were associated in RV isolated myocytes with the decrease of sarcomere shortening in response to isoproterenol and perturbations of calcium homeostasis assessed by the increase of spontaneous calcium waves.

Conclusions: In this porcine model, both standard and strain echocardiographic parameters detected early impairments of RV function and cardiac reserve, which were associated with cardiomyocyte excitation-contraction coupling alterations. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Tetralogy of Fallot, Right ventricular function, Echocardiography, Speckle-tracking, Excitation-contraction coupling, Animal model

Right ventricular (RV) performance is a major factor in the long-term survival of patients with congenital heart diseases. A reliable noninvasive technique for RV evaluation is essential in managing these patients. Among congenital heart diseases that result in long-term RV dysfunction, repaired tetralogy of Fallot (TOF) is one of the most frequent. Although cardiac magnetic resonance imaging (CMR) provides a good estimation of RV volumes and geometry, CMR could not accurately assess clinical status impairment in adult patients

From the UMR-S 999, Inserm, Hôpital Marie Lannelongue, Université Paris-Sud, Université Paris-Saclay, Le Plessis-Robinson (A.H., E.G., A.C., C.R.-M, V.L.); UMR-S 1180, Inserm, Université Paris-Sud, Université Paris-Saclay, Châtenay-Malabry (P.B., D.M., F.L., P.L., G.V., J.L.); and Pôle des Cardiopathies Congénitales, Hôpital Marie Lannelongue (M.L., E.L.B.), and Laboratoire de Recherche Chirurgicale, Hôpital Marie Lannelongue, Université Paris-Sud, Université Paris-Saclay (M.C.), Le Plessis Robinson, France.

This work was supported by Fédération Française de Cardiologie (to A.H.), the CORDDIM program of Région Ile-de-France (to P.B. and D.M.), Fondation pour la Recherche Médicale (FDT20140931029 to P.B.), Département Hospitalo-Universitaire Thorax Innovation, and Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique.

Drs. Hodzic and Bobin contributed equally to this work.

Conflicts of Interest: None.

Reprint requests: Amir Hodzic, MD, Centre Hospitalier Régional et Universitaire de Caen, Service de Cardiologie, Avenue de la Côte de Nacre, 14033 Caen Cedex 9, France (E-mail: *hodzic-a@chu-caen.fr*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2017.07.003

Abbreviations

β-AR = β-adrenergic receptor

CMR = Cardiac magnetic resonance imaging

eEF = Efficient ejection fraction

FAC = Fractional area change

FW = Free wall

GLS = Global longitudinal strain

GLSR = Global longitudinal strain rate

ICC = Intraclass correlation coefficient

Iso = Isoproterenol

LV = Left ventricular

RV = Right ventricular

SR-Ca^{2+} = Sarcoplasmic reticulum calcium content

TAPSE = Tricuspid annular plane systolic excursion

TOF = Tetralogy of Fallot

with TOF repair.[1] These observations highlighted the need for more sensitive parameters to detect an early decrease in RV performance to initiate treatments that can affect the progression of RV dysfunction and prevent the development of decompensated RV failure.

In clinical practice, echocardiography is the modality of choice for RV assessment and screening. Developments in echocardiographic techniques with speckle-tracking imaging that assesses strain and strain rate may potentially provide a more sensitive detection of RV dysfunction.[2] Although speckle-tracking has demonstrated its clinical utility for the assessment of left ventricular (LV) dysfunction at an early stage,[3,4] the accuracy for RV evaluation in pathologic conditions remains questionable. Considering the characteristics of the right ventricle in terms of geometry and mode of contraction, speckle-tracking measurements cannot be achieved with the same level of confidence for the right ventricle as for the left ventricle. The complexity of RV morphology, including geometry and numerous trabeculations, makes it challenging to accurately define endocardial borders for the application of the speckle-tracking algorithm. In recent clinical studies, patients with repaired TOF had decreased RV myocardial deformation, which seemed to be independently associated with CMR-derived RV ejection fraction.[5-7] These authors have defined thresholds of longitudinal strain for predicting low RV ejection fraction in pediatric and adult populations with TOF repair.[6,7] Furthermore, speckle-tracking may be helpful to identify the optimal timing for pulmonary valve replacement in patients with TOF repair, which should be performed early to increase the likelihood of complete recovery.[8] To date, speckle-derived parameters assessing RV systolic function have not been validated using the conductance catheter. The conductance technique is the gold-standard method for the evaluation of RV myocardial contractility and function. This was previously demonstrated in experimental models of RV chronic volume and pressure overload[9,10] and for patients with TOF repair.[11]

To establish correlations between speckle-tracking echocardiography and hemodynamic parameters, an animal model of RV dysfunction is required. Our group validated a porcine model of repaired TOF that presented with early RV dysfunction by chronic combined overload.[12] We used this model to evaluate the accuracy of echocardiographic standard and strain parameters in the detection of early alterations of RV myocardial performance.[13,14] Because echocardiographic evaluation of RV function is influenced by load conditions, we investigated functional (myocyte contractility and calcium homeostasis) changes at the cardiomyocyte level to support the validity of these echocardiographic parameters to detect myocardial alteration at a subclinical stage.

The objective of this study was to validate echocardiographic standard and strain parameters against hemodynamic and cellular contractility changes for detection of early overloaded RV dysfunction.

METHODS

Experimental Design

A surgical procedure mimicking repaired TOF was performed on six Landrace piglets (operated group) that were between 50 and 67 days of age. Six age-matched animals were used as controls (control group). Control animals did not undergo sham surgery. All animals were male to avoid bias related to hormonal variations. Echocardiographic and hemodynamic assessment of RV function were performed at baseline just before the surgical procedure and 4 months later. Clinical status was evaluated daily during the study. After completing the 4-month follow-up period, animals were euthanized for a cellular study on isolated RV myocytes. All experiments were carried out according to the European Community guiding principles on the care and use of animals (2010/63/UE, September 22, 2010), the local ethics committee (CEEA26 CAPSud) guidelines, and French decree 2013-118 on the protection of animals used for scientific purposes (JORF 0032, February 7, 2013, p. 2199, text no. 24). Authorization to perform animal experiments according to this decree was obtained from Ministère Français de l'Agriculture, de l'Agroalimentaire et de la Forêt (agreement B92-019-01).

Experimental Model of Combined RV Overload

As previously described by our group,[12] after premedication with ketamine hydrochloride (15 mg/kg intramuscularly), general anesthesia was induced with propofol 1% and cisatracurium (0.3 mg/kg every 2 hours), allowing endotracheal intubation, which was maintained with isoflurane in 100% oxygen (Servo 900; Siemens-Elema, Solna, Sweden). Through a left thoracotomy approach, a side-biting vascular clamp was longitudinally placed across the pulmonary valve annulus without obstruction of the RV outflow tract. A pulmonary valve leaflet was excised and the pulmonary infundibulum, annulus, and trunk were enlarged by a 2-cm-long, elliptically shaped polytetrafluoroethylene patch to ensure the loss of valve integrity. This chronic pulmonary valve regurgitation led to RV volume overload. Branch pulmonary arterial obstruction is not uncommon after surgical correction of TOF related to native hypoplasia or surgical complications and is known to increase pulmonary valve regurgitation.[15] In our model, RV pressure overload was achieved by pulmonary artery banding, made of umbilical tape, placed around the artery truncus and secured for a final diameter of approximately 1 cm to ensure progressive pulmonary stenosis with animal maturation.

Echocardiographic Analysis

Echocardiography was performed on closed-chest animals under general anesthesia in the dorsal decubitus position. We used a commercially available Vivid E9 ultrasound machine (GE Medical Systems, Milwaukee, WI) equipped with a 2.5-MHz transducer. The values of all echocardiographic parameters were obtained as the average value of three consecutive cardiac cycles during transient apnea and were analyzed on a comprehensive workstation