The importance of capillary density–stroke work mismatch for right ventricular adaptation to chronic pressure overload

Pierre-Emmanuel Noly, MD, MSc,[a,b,c] François Haddad, MD,[b,d] Jennifer Arthur-Ataam, MSc,[b,e] Nathaniel Langer, MD,[a,b] Peter Dorfmüller, MD, PhD,[a,b,e,f] Fanny Loisel, MSc,[a,b] Julien Guihaire, MD, MSc,[b,e] Benoit Decante, MSc,[b] Lilia Lamrani, MSc,[b,c] Elie Fadel, MD, PhD,[a,b,c,e] and Olaf Mercier, MD, PhD[a,b,c,e]

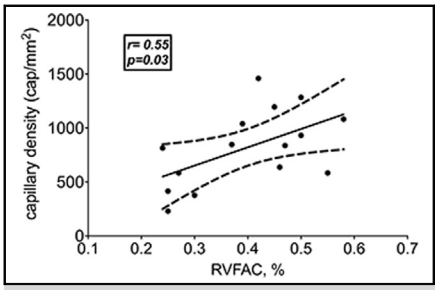
ABSTRACT

Objective: Mechanisms of right ventricular (RV) adaptation to chronic pressure overload are not well understood. We hypothesized that a lower capillary density (CD) to stroke work ratio would be associated with more fibrosis and RV maladaptive remodeling.

Methods: We induced RV chronic pressure overload over a 20-week period in 2 piglet models of pulmonary hypertension; that is, a shunt model (n = 5) and a chronic thromboembolic pulmonary hypertension model (n = 5). We assessed hemodynamic parameters and RV remodeling as well as RV CD, fibrosis, and angiogenic factors expression.

Results: Although RV was similarly hypertrophied in both models, maladapted RV remodeling with impaired systolic function was only seen in chronic thromboembolic pulmonary hypertension group members who had lower CD (484 ± 99 vs 1213 ± 74 cap/mm^2; $P < .01$), lower CD to stroke work ratio (0.29 ± 0.07 vs 0.82 ± 0.16; $P = .02$), higher myocardial fibrosis (15.4% ± 3.8% vs 8.0% ± 2.5%; $P < .01$), as well as a higher angiogenic and fibrosis factors expression.

Conclusions: The RV adaptive response to chronic pressure overload differs between 2 different piglet models of PH. Mismatch between angiogenesis and workload (CD to stroke work ratio) was associated with greater degree of myocardial fibrosis and RV dysfunction and could be a promising index of RV maladaptation. Further studies are needed to understand the underlying mechanisms. (J Thorac Cardiovasc Surg 2017;154:2070-9)



Correlation between capillary density, fibrosis, and right ventricular function in 2 models of right ventricle pressure overload.

Central Message

Mismatch angiogenesis/workload was associated with greater degree of right ventricular dysfunction in animal models. The capillary density to stroke work ratio could be a promising index to assess right ventricular adaptation to pressure overload.

Perspective

Discrepancy between the capillary density and the right ventricular stroke work may help us to understand the inability of end-stage right ventricular pulmonary hypertension to use oxygen correctly despite the metabolic shift. A major clinical implication of our study is that it offers, in a large animal model, support for therapies targeting neovascularization or angiogenesis.

See Editorial Commentary page 2080.

In the modern era, pulmonary hypertension (PH) remains a progressive and often fatal disease despite the use of targeted therapies.[1] Many studies have shown that right ventricular adaptation to pressure overload is the main determinant of survival in patients with chronic pressure overload state (CPOS).[2-5] Some etiologies in PH and CPOS are known to be associated with better right ventricular adaptation and survival. For example, a

From the [a]School of Medicine, Paris-Sud University and Paris-Saclay University, Kremlin-Bicêtre; [b]Research and Innovation Unit, [c]Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation, DHU Thorax Innovation, [e]INSERM UMR-S 999, LabEx LERMIT, and [f]Department of Pathology, Marie Lannelongue Hospital, Le Plessis Robinson, France; and [d]Division of Cardiovascular Medicine, Stanford University, Palo Alto, Calif.

P.-E.N. and F.H. contributed equally to this article.

Received for publication Oct 30, 2016; revisions received May 21, 2017; accepted for publication May 31, 2017; available ahead of print July 13, 2017.

Address for reprints: Olaf Mercier, MD, PhD, Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation, Marie Lannelongue Hospital, 133 ave de la Résistance, 92350 Le Plessis Robinson, France (E-mail: o.mercier@ccml.fr).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2017.05.102

Abbreviations and Acronyms

CD = capillary density
CI = cardiac index
CPOS = chronic pressure overload states
CTEPH = chronic thromboembolic pulmonary hypertension
Ea = pulmonary vascular elastance
Ees = ventricular elastance
ES = Eisenmenger syndrome
mPAP = mean pulmonary arterial pressure
PA = pulmonary artery
PH = pulmonary hypertension
RVFAC = right ventricular fractional area change
SW = stroke work
VEGF = vascular endothelium growth factor
VEGF-type A = vascular endothelium growth factor type A

Scanning this QR code will take you to a supplemental video for this article.

recent prospective multicenter study has shown that the survival of patients with idiopathic, postembolic, or anorexigen-induced PH is 58% at 3-year follow-up[1] compared with 58% at 10-year follow-up for patients with congenital heart disease-associated PH and Eisenmenger syndrome (ES).[6] In these patients, the main cause of death remains right ventricular failure (36%).[1]

Although adaptive remodeling is often contrasted with maladaptive remodeling, the mechanisms underlying this transition are not well understood. Preclinical animal models suggested that a mismatch between right ventricular hypertrophy and right ventricular angiogenesis as well as altered metabolism could induce myocardial ischemia and promote the development of right heart failure.[7-11] We hypothesize that a mismatch between hypertrophy and angiogenesis, and workload of the right ventricle could be associated with an impairment of right ventricular function. However, limited data are available from studies comparing right ventricular capillary density (CD) of ES and non-ES patients. In this context, we performed an experimental study using 2 different models of chronic right ventricular pressure overload in piglets. In the first model, the increase in pulmonary artery (PA) pressure was obtained using a systemic-to-pulmonary shunt (Blalock-Taussig procedure).[12] In the second model, we performed a ligation of the left PA followed by 5 embolizations of the right lower PA to increase PA pressure[13,14] (chronic thromboembolic pulmonary hypertension [CTEPH] model). We aimed to study the right ventricle in these 2 different pig models of CPOS to determine whether mismatch between angiogenesis and workload would be associated with a greater degree of myocardial fibrosis and right ventricular dysfunction.

METHODS

Experimental Study

Fifteen large white piglets were randomly allocated to 3 groups (Figure 1). All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (publication No. 86-23, revised 1996) and the guidelines from directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes. All animals were studied at baseline and at 20-weeks' follow-up.

Approval for the study was granted by our institutional ethics review board. All animal experiments were performed under general anesthesia with the following protocol. After prophylactic cefotaxime and premedication with ketamine, induction of anesthesia was performed with 1% propofol (3 mg/kg) and cisatracurium allowing endotracheal intubation. General anesthesia was maintained with isoflurane in 21% oxygen (Clarys 2000; TAEMA, Air Liquid, Paris, France) during surgery as well as during hemodynamic and echographic assessments. At the end of the experiment, anesthesia and paralysis were interrupted and the animals were weaned from mechanical ventilation. Postoperative analgesia was provided with subcutaneous nalbuphine as required for 4 days. Animals were killed at the end of the last experiment by administration of a lethal dose of sodium thiopental followed by exsanguination.

Induction of CPOS. CPOS was induced either by a systemic-to-pulmonary shunt[12] (shunt group, n = 5) or by a progressive obstruction of the pulmonary vascular bed (CTEPH group, n = 5). These 2 CPOS groups were compared with sham-operated animals (sham group, n = 5).

Shunt model. In shunted animals, a modified Blalock-Taussig procedure was performed by left inominate artery to pulmonary trunk transposition mimicking a patent ductus arteriosus. Through a left small thoracotomy, the left inominate artery was dissected and harvested after systemic heparinization (intravenous heparin sulfate 3000 UI). Using this vascular autograft (10 mm diameter), we performed a bypass between the thoracic aorta (usually the aortic arch) and the pulmonary trunk. The patency of the shunt was assessed by Doppler ultrasound intraoperatively, and by auscultation (thrill) or by echocardiography during the postoperative period. This procedure achieves an extracardiac systemic-to-pulmonary shunt without right ventricular volume overload, because the pulmonary valve is competent. The overflow in the pulmonary vascular bed induces remodeling of the small PAs and led to an increase of pulmonary pressures and resistances after 12 weeks.[15]

CTEPH model. The CTEPH model is described elsewhere.[13,14] Briefly, CPOS was induced after ligation of the left PA and weekly embolization of the right lower lobe PA with n-butyl-2-cyanoacrylate (Histoacryl; B. Braun Medical S.A., Diegem, Belgium) during 5 weeks to progressively occlude the pulmonary vascular bed. Pulmonary pressures increase progressively and the model is mature after 6 to 7 weeks of evolution.

Right heart hemodynamic assessment. Mean systemic blood pressure, heart rate, and peripheral oxygen saturation were monitored during the procedures. In addition, right heart catheterization was performed percutaneously via the right internal jugular vein using a Swan-