

Capillary density and myocardiofibrosis in adaptation of the right ventricular function to pulmonary hypertension insight an animal and human study.

Pierre-Emmanuel Noly, Olaf Mercier, François Haddad, Julien Guihaire, Matthieu Glorion, Peter Dorfmueller, Florence Lecerf, Benoit Decante, Bruno Baudet, Frederic, Saadia Eddahibi, Philippe Darteville, Elie Fadel

Department of Thoracic Surgery, Marie Lannelongue Hospital, Le Plessis Robinson, France

Background:

Mechanisms of right ventricular adaptation to pulmonary hypertension are not well understood yet. We hypothesized that better matched myocardial angiogenesis contributes to delay the transition to RV failure in pulmonary hypertension.

Methods:

In a first time, we induced chronic PH over a 20 weeks period in a Shunt group (n=5) by creating an aorto-to-pulmonary shunt and in a chronic thromboembolic PH (CTEPH group, n=5) by ligating the left pulmonary artery (PA) followed by weekly embolizations to progressively occlude the segmental arteries of the right lower lobe. In the Sham group (n=5), the pigs were studied 20 weeks after a left PA dissection. We assessed hemodynamics using right heart catheterization and RV structural and functional remodeling using echocardiography and pressure-volume loops measurement. Myocardial angiogenesis of the RV was studied by measuring capillary density (CD), VEGF-A and HIF-1 α expression

We performed a human study in a second time. We retrospectively studied capillary density in right ventricles from 14 Eisenmenger syndrome patients and 14 patients with idiopathic PH who underwent heart-lung transplantation for severe PH and heart failure.

Results: At 20 weeks, mean PA pressure (26.8 \pm 1.4 mm Hg vs. 22.8 \pm 0.9 mm Hg, p=NS) and RV stroke work (SW) (2192 \pm 255 mmHg/ml vs. 2110 \pm 211 mmHg/ml, p=NS) were significantly elevated in the SHUNT and the CETPH groups when compared to the Sham group (14.8 \pm 0.8 mm Hg and 1124 \pm 44 mmHg/ml, respectively; p<0.01). Although RV was similarly hypertrophied in both PH groups when compared to Sham, the RV systolic function was impaired only in CETPH group. The TAPSE and RVFAC values were decreased and the ventriculo-arterial coupling was decreased only in the CETPH group. Although the cardiomyocyte diameter was similarly increased in both P groups (p<0.05), the CD was only increased in the SHUNT group (p<0.05). HIF-1 α and VEGF-A expression remained no different between the three groups.

The diagnosis-transplantation delay, MPAP and PVR were higher in the Eisenmenger syndrome patients. The capillary density of the right ventricle was no different between the 2 groups (1345 \pm 70.55 capillary.mm⁻² and 1242 \pm 93.02 capillary.mm⁻² in Eisenmenger and in idiopathic PH patients respectively; p>0,05).

Conclusion: In our translational study, capillary density elevation in the right ventricle under pulmonary hypertension was associated with preserved right ventricular function. Further studies are needed to describe the angiogenesis pathways involved in RV adaptation and identify new target for angiogenic therapy.