

University Medical Center Groningen

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Dear Members of the Council on Basic Cardiovascular Science,

I would like to sincerely thank the ESC Council on Basic Cardiovascular Science for selecting me to receive an ESC First Contact Initiative Grant. The support of the grant enabled me to visit the Vascular Tissue Biomechanics Laboratory at the Department of Biomedical Engineering, College of Engineering, University of Wisconsin-Madison in the United States. The visit took place from October 1, 2018 through December 31, 2018. This visit has made it possible for me to learn essential techniques that will in future enable me to study the role and prognostic value of pulmonary arterial stiffening in pulmonary arterial hypertension and congenital heart diseases. Furthermore, it has helped me to establish more permanent contacts with Professor Naomi Chesler and her team that has aroused mutual interest for future research collaboration.

Pulmonary arterial hypertension is a progressive pulmonary vascular disease, eventually leading to right ventricular failure and death. Despite the introduction of specific PAH-targeted drug therapy, children with PAH still have a detrimental prognosis. We are seeking to improve paediatric treatment strategies in order to improve survival of children with PAH.

Despite the emerging data on determinants of outcome for paediatric PAH, it is still difficult to evaluate disease progression, prognosis and treatment effects in children with the disease. Consequently, studies focused on establishing the beneficial effect of new treatment strategies are hampered, due to a lack of clinical endpoints. Moreover, evaluation of treatment effects in daily patient care is still difficult, impeding the adjustment of therapy to the individual patient's disease progression and treatment effect.

In PAH, pulmonary vascular remodelling directly results in an increased right ventricular afterload. Therefore, parameters that characterize right ventricular afterload are especially suitable to be used to evaluate disease progression. Currently in PAH patients, only steady components of the right ventricular afterload are evaluated (mean pulmonary arterial pressure and pulmonary vascular resistance). The pulsatile components such as pulmonary arterial compliance and pressure reflections, which are both determined by pulmonary arterial stiffness, are currently overlooked. Measuring the pulmonary arterial stiffness would therefore improve the characterization of the right ventricular afterload and with that may help to better evaluate disease progression in children with PAH.

In our animal model for PAH, we want to investigate the extent and potential reversibility of pulmonary arterial stiffening (measured both in vivo and ex vivo) for increasing severity of pulmonary vascular disease, as well as the underlying pathobiological vascular changes. In addition, we are seeking to measure pulmonary arterial stiffness in patients (children) to study the prognostic abilities of pulmonary arterial stiffness measurements in pediatric PAH.

In order to conduct these studies, we need to develop measuring techniques that are able to measure pulsatile right ventricular afterload and pulmonary arterial stiffness in both laboratory animals and patients. With the support of the European Society of Cardiology First Contact Initiative Grant, I have visited the laboratory of Professor Naomi Chesler to learn such techniques

At the Vascular Tissue Biomechanics Laboratory of the University of Wisconsin-Madison, the research group of Professor Naomi Chesler has taught me how to measure pulmonary arterial impedance in both rodents and human subjects. Pulmonary arterial (or input) impedance is regarded to be the pulsatile resistance of the pulmonary arterial vascular bed that represents the entire right ventricular afterload. It is calculated using continuous or single beat pulmonary arterial flow and pressure waves. The pressure waves are measured invasively during cardiac catheterization. The flow waves are reconstructed from phase-contrast MRI (humans) or pulsed wave doppler echocardiography (rodents and human subjects). Both signals are transformed to the frequency spectrum using a Fourier transformation, decomposing the waves into the frequencies that make up the original waves. Thereafter, the ratio between pressure and flow is calculated for these individual frequencies leading to a spectrum pulmonary arterial impedance. The impedance at zero frequency (Z_0) then represents the pulmonary vascular resistance, the lower frequency impedance represents distal pulmonary arterial stiffness and reflected pressure waves, whereas higher frequency impedance represents proximal pulmonary arterial stiffness. I have learned to perform and post-process these measurements in rodents. Furthermore, the research group at Madison has taught me how to write Matlab software that can perform this complex analysis using flow and pressure data from human subjects. This will enable me to write the necessary analyses software for future experiments back home at the University Medical Center Groningen.

Secondly, during my visit in Madison I have learned ex-vivo methods that can be used to validate in vivo impedance and pulmonary arterial stiffness measurements. The Vascular Tissue Biomechanics Laboratory at Madison has several ex-vivo techniques that can determine the ex-vivo proximal pulmonary arterial stiffness in isolated pulmonary arteries and pulmonary arterial impedance in isolated lungs from laboratory animals. These techniques will enable the ex-vivo validation of in vivo pulmonary arterial stiffness measurements, which may prove to be pivotal in our future animal and human studies.

In conclusion, the European Society of Cardiology First Contact Initiative Grant has enabled me to visit the University of Wisconsin-Madison, where I learned complex measurement techniques that are essential for my future research at the University Medical Center Groningen. The visit has helped me to further develop my professional network and has paved the way for future collaboration with the hosting research group of Professor Chesler. I again like to express my sincere gratitude to the ESC Council on Basic Cardiovascular Science for making this possible.

Sincerely

Menno Douwes, MD, PhD.