Unveiling the Vascular Mechanisms Behind Long-Term Effects of Coarctation Treatment Using Pulse Wave Dynamics

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The current issue of the *Journal of the American Heart Association* (*JAHA*) includes, 2 articles that focus on the effects of aortic coarctation treatment on the cardiovascular system several years after the treatment has been performed.[1,2] Even though different techniques for the treatment of a coarctation of the aorta have been successfully used for many years now, these patients have premature morbidity and mortality.[3] The complications are manifold: hypertension is common among these patients in adulthood, followed or accompanied by additional morbidities such as increased left ventricular mass, impaired systolic or diastolic function, or coronary artery and cerebrovascular disease. Importantly, the risk of stroke also is increased.[1,2,4,5] The articles of Martins et al[1] and Kowalski et al[2] investigate the mechanisms behind the long-term effects of aortic coarctation and its repair.

The starting point for both studies is the fact that coarctation of the aorta has lifelong consequences even after successful treatment. In both studies, subjects were examined in early adulthood, thus several years after coarctation treatment was performed. This corresponds to an intermediate stage between repair and a manifestation of organ damage later in life. Potentially, changes in cardiovascular structure and hemodynamics are present already at this stage, and suitable techniques to quantify such alterations are needed. The ultimate goal behind both studies is to optimize treatment for these patients, thus minimizing these consequences. However, the approaches to gather new pieces of evidence on the way to this goal are different and complement one another. Based on the 2 specific research questions, a major difference in the settings of the studies lies in the selection of patient groups. While Martins et al compare coarctation repair patients grouped by 3 treatment modalities (surgery, balloon dilation, and stent implantation), Kowalski et al compare a group of coarctation repair patients with a group of controls. Both studies apply a variety of advanced techniques, among them central pressure, measures for local and regional arterial stiffness, and methods of pulse wave analysis to quantify wave reflection and transmission. These study designs are based on the expectation that such methods will enable insights beyond traditional hemodynamic risk markers, such as brachial blood pressure.

The aim of the study by Martins et al was to determine whether the choice of treatment modality impacts vascular function later in life.[1] While they found that the majority of cardiovascular indices did not differ between the treatment groups, some significant differences using advanced techniques indicate preferable results for the balloon dilation technique. One favorable characteristic is the lowest stiffness measured locally in the ascending aorta among the 3 groups. Another aspect is the favorable dipping behavior of blood pressure during the night obtained with an ambulatory blood pressure measurement. Both effects would have been overlooked, if solely office blood pressure and office regional pulse wave velocity (carotid–femoral pulse wave velocity) were applied.

The main aim of the study of Kowalski et al was to investigate whether an increased wave transmission from the aorta to the carotid artery occurs after coarctation repair.[2] This would be a potential link to cerebrovascular diseases and stroke in these patients. They used wave intensity and wave power as primary methods for their study. While wave intensity is using pressure and velocity signals for analysis and was introduced almost 3 decades ago,[6] wave power uses pressure and volume flow signals and was introduced only a few years ago by Mynard and Smolich.[7] Since wave power is a conserved quantity under most circumstances in contrast to wave intensity, it allows wave transmission between distinct

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locations in the vascular system to be studied.[7] In the current study, wave intensity and wave power were calculated in the aortic arch and in the left common carotid artery. Blood pressure as well as local stiffness (characteristic impedance) were elevated for coarctation patients, but no differences in wave reflection deduced from wave intensity were found in both sites between coarctation patients and controls. However, wave power analysis revealed an increased transmission of wave power from the aorta to the carotid artery for coarctation patients. Again, effects would have been overlooked with the established techniques and parameters, in this case differences in pulse wave morphology related to pulse wave transmission.

We can learn a couple of things from the 2 studies. The physiological findings are comprehensively discussed in both articles and we refrain from repeating them in detail; we refer the readers to the articles for a closer look. The articles contain 2 excellent examples for applying advanced techniques that are not routinely used either in clinical practice or in clinical research, but that provide the essential insights. The measurement of local aortic stiffness seems to be crucial for patients with coarctation repair. In general, methods combining pressure and flow signals for the determination of pulse wave transmission and reflection can bring advantages in accuracy and sensitivity compared with pressure-only methods. However, the measurement of time-synchronized pressure and flow signals is demanding and currently not feasible in daily practice.[8]

Martins et al used pressure measurements under exercise and under ambulatory conditions to assess the influence of postural and diurnal changes,[1] whereas Kowalski et al combined pressure and flow to tackle their research question.[2] In another article recently published in *JAHA*, Chirinos et al chose a combination of both of these approaches to study patients with heart failure with preserved ejection fraction.[9] They showed that forward and backward

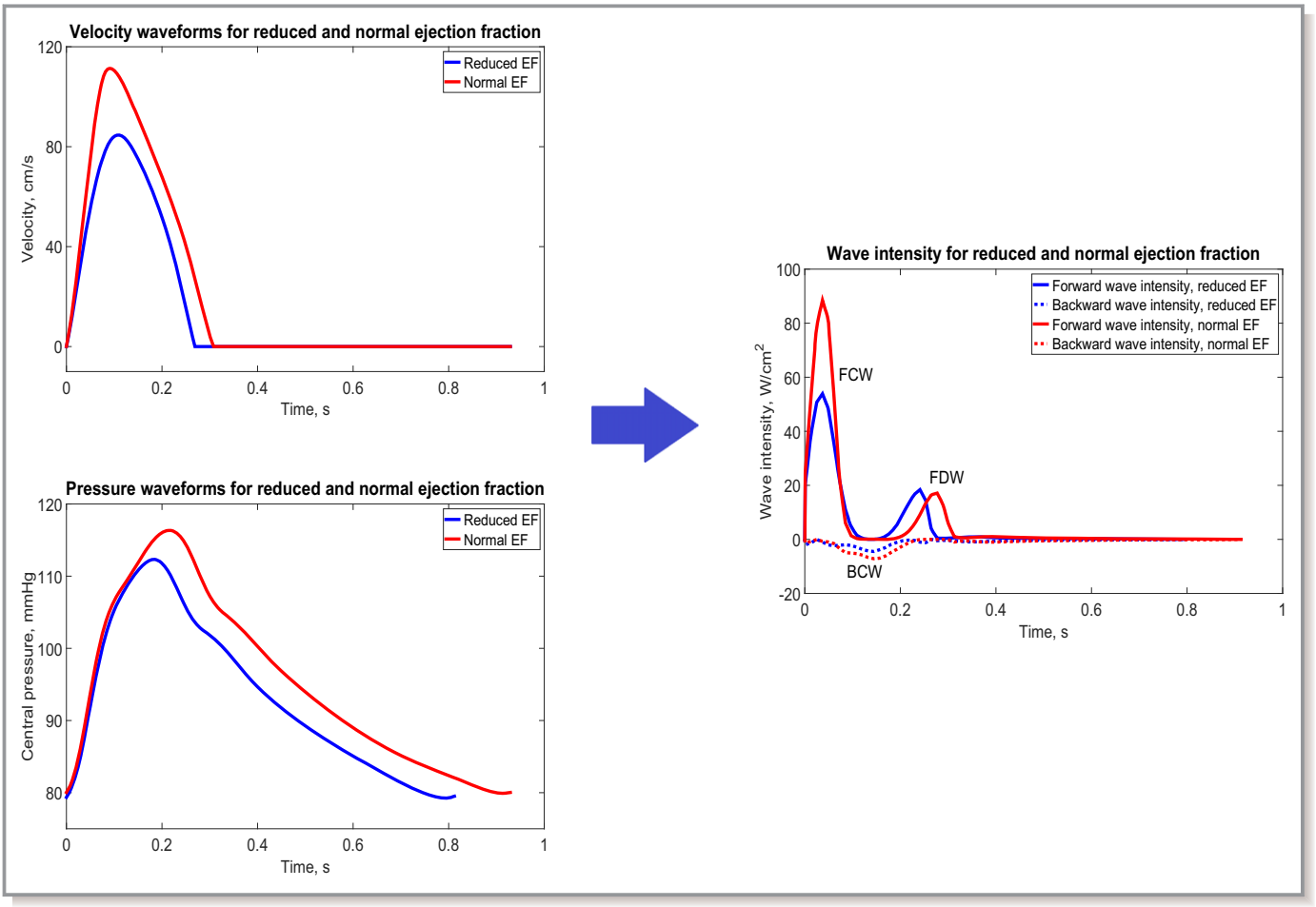

Figure. Averaged pressure and velocity waveforms for patients with HFrEF and controls[10] as well as corresponding forward and backward wave intensity signals obtained from these averaged waveforms. BCW/FCW peak ratio is 0.08 for both groups. FCW/FDW peak ratio is 2.9 for the HFrEF group waveform and 5.2 for the control group waveform. BCW indicates backward compression wave; FCW, forward compression wave; FDW, forward decompression wave; HFrEF, heart failure with reduced ejection fraction.

wave amplitudes, assessed over 24 hours with wave separation based on oscillometric pressure measurements and a modeled flow, differ between patients with heart failure with preserved ejection fraction with and without diabetes mellitus. Since the cardiovascular system is not in a full steady state but is continuously changing its characteristics, such repeated measurements, not only for blood pressure but also for parameters obtained from pulse wave analysis, can provide additional information. In the context of the studies of Martin et al and Kowalski et al, this is also relevant beyond a methodological point of view, since systolic and diastolic dysfunction is one of the major morbidities linked to coarctation repair besides stroke.[4,5]

In a previous study, we have investigated the relationship between heart failure with reduced ejection fraction and wave reflection parameters. After adjustment for heart rate and ejection duration, no significant differences were found.[10] However, wave intensity analysis revealed significant differences in waveforms.[11] When the peak value of the forward compression wave (FCW, or S-wave) was divided by the peak value of the forward decompression wave (FDW, or D-wave), this ratio was significantly lower in patients with heart failure with reduced ejection fraction. To illustrate these effects, we have plotted in the Figure averaged pressure and velocity waveforms for the group of patients with heart failure with reduced ejection fraction and the group of controls,[10] as well as the resulting forward and backward wave intensity. The main differences can be found in the FCW. Presumably, these changes occur because of altered ejection dynamics of the ventricle, leading to a reduced wave intensity of the FCW. Similar findings were obtained in a study by Ntsinjana et al in children and adolescents with heart failure with preserved ejection fraction.[12]

Having these findings in mind, a closer look should be taken at the results of Kowalski et al.[2] Unfortunately, they do not report the FCW/FDW ratio explicitly, but we can calculate it from the mean values of FCW and FDW that have been reported. For example, we find for the cumulative wave intensity in the aorta FCW/FDW ratios of about 4.6 for the coarctation group and 6.5 for the control group, which seems to be a noteworthy difference. In contrast to the abovementioned studies in patients with heart failure, this is mainly because of an increased FDW. Whether these changes in the FCW/FDW ratio can be interpreted currently as precursors of heart disease is subject to speculation at this stage. Regardless, the triangle of aortic stiffness (in this case because of coarctation repair), stroke, and heart failure warrant further investigations based on methods such as wave intensity and wave power analysis.

Luckily, we have an increasing number of options for the assessment of cardiovascular properties, but eventually, with confusion from all these measurement possibilities one might ask: Which technique should be used for the measurement of arterial stiffness? Which technique should be used for the quantification of pulse wave transmission and reflection? Unfortunately, there is no simple answer. For widespread use, such as patient screening or therapy monitoring, one would rather opt for a user-friendly approach, in the best case operator-independent and usable in an ambulatory setting. For a specialized clinical study, more complicated but also more sensitive methods could be the right choice. In any case, several options for guidance are available. One could look into expert consensus documents.[13] A typical approach would be to set up a pilot trial to test the potential of a method. Alternatively, in-silico studies are becoming increasingly feasible. Here, properties of a specific disorder can be simulated based on mathematical models and methods can be tested on these artificial patient data.[14] But probably the best way is to be inspired by excellent studies, 2 of which can be found in this issue.[1,2]

Disclosures

None.

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