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● *Original Contribution*

20-MHZ ULTRASOUND FOR MEASUREMENTS OF FLOW-MEDIATED DILATION AND SHEAR RATE IN THE RADIAL ARTERY

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Abstract—A high-frequency scanning system consisting of a 20-MHz linear array transducer combined with a 20-MHz pulsed Doppler probe was introduced to evaluate the degree of radial artery flow-mediated dilation (FMD [%]) in two groups of patients after 5 min of controlled forearm ischemia followed by reactive hyperemia. In group I, comprising 27 healthy volunteers, FMD (mean ± standard deviation) was 15.26 ± 4.90% (95% confidence interval [CI]: 13.32%–17.20%); in group II, comprising 17 patients with chronic coronary artery disease, FMD was significantly less at 4.53 ± 4.11% (95% CI: 2.42%–6.64%). Specifically, the ratio FMD/SR (mean ± standard deviation), was equal to $5.36 \times 10^{-4} \pm 4.64 \times 10^{-4}$ (95% CI: 3.54×10^{-4} to 7.18×10^{-4}) in group I and $1.38 \times 10^{-4} \pm 0.89 \times 10^{-4}$ (95% CI: 0.70×10^{-4} to 2.06×10^{-4}) in group II. Statistically significant differences between the two groups were confirmed by a Wilcoxon–Mann–Whitney test for both FMD and FMD/SR ($p < 0.01$). Areas under receiver operating characteristic curves for FMD and FMD/SR were greater than 0.9. The results confirm the usefulness of the proposed measurements of radial artery FMD and SR in differentiation of normal patients from those with chronic coronary artery disease. (E-mail: anowicki@ippt.gov.pl) © 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **Flow-mediated vasodilation, Radial artery, Shear rate, Reactive hyperemia, Endothelium, Pulsed doppler, Ultrasonography.**

INTRODUCTION

The process of development of atherosclerosis is preceded by endothelial dysfunction of blood vessels and the development of a local inflammatory process. The endothelium is involved in the regulation of vessel tone, blood cell adhesion to vessel walls and the formation of blood thrombi.

Dysfunction of vascular endothelium leads to hypertension (Brandes 2014) and cardiovascular disease (Cahill and Redmond 2016; Deanfield et al. 2007; Deshko et al. 2011; Lehoux and Jones 2016). Early and accurate assessment of endothelial function may help in understanding the etiology of these diseases and in determining the effectiveness of treatment of vascular diseases.

It is established that flow-mediated dilation (FMD) of the vessel correlates with the release of nitric oxide (NO) (Balletshofer et al. 2003; Joannides et al. 1995; Laurent et al. 1990). NO is considered the main mediator of vasodilation (Corson et al. 1996; Forstermann and Munzel 2006; Furchgott and Zawadzki 1980; Govers and Rabelink 2001). During an FMD test, vasodilation occurs after an acute increase in blood flow, typically induced *via* circulatory arrest in the arm and typically lasting 5 min. The increase in blood flow that follows circulatory arrest, a process known as hyperemia, increases shear stress on the vessel wall, resulting in smooth muscle relaxation and vasodilation. The percentage change in FMD is determined by comparing the diameter of the vasodilated vessel after reactive hyperemia with the baseline diameter before vessel occlusion.

Celermajer et al. (1992) reported a new FMD measurement technique using ultrasound as a non-invasive

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method for assessing endothelial function. Since that time, ultrasonic evaluation of FMD in response to a few minutes of ischemia, induced by occlusion of the artery with a pressure cuff placed on the forearm, followed by reactive hyperemia after release of the pressure cuff, has been well known in the literature. Corretti et al. (2002) published preliminary guidelines for assessing FMD of the brachial artery using ultrasound, adjusting the original methodology introduced by Celermajer to clinical measurement conditions. Corretti et al. (2002) suggested that brachial FMD could provide a bioassay for *in vivo* endothelial function; they were supported by many laboratories that conducted ultrasonic assessment of the endothelial function. It was reported that increased blood flow was not affected by brachial artery dilation after removal of the endothelial lining (Pohl et al. 1986). Early articles by Anderson et al. (1995) and Takase et al. (1998) reported a correlation between brachial FMD and invasive measurements of endothelial function in the coronary arteries. It was found that a change in the magnitude of FMD not only reflects endothelial function, but also depends on the value of the applied shear stress stimulus resulting from reactive hyperemia and different flow velocity gradients in the vicinity of the endothelial lining (Harris and Padilla 2007; Harris et al. 2010; Padilla et al. 2008; Pyke and Tschakovsky 2007; Pyke et al. 2004).

Although blood flow velocity usually peaks within the first 15 s, Black et al. (2008) have clearly illustrated that the time course of FMD after cuff deflation differs significantly between younger and older as well as between fit and sedentary patients, from 30 s to more than 140 s, and it was suggested that FMD should be recorded for 3 min after cuff release (Eskurza et al. 2006; Parker et al. 2006). The total value of the stimulus corresponds to the area under the shear stress curve or approximately to the shear rate curve (Berry et al. 2000; Corretti et al. 2002; Joannides et al. 1997; Leeson et al. 1997; Mitchell et al. 2004; Pyke et al. 2004).

Most of the previously reported FMD measurements were made in the brachial artery according to a strictly standardized protocol (Charakida et al. 2016; Harris et al. 2010). Radial artery FMD was rarely studied, though it was reported that FMD was greater using the radial artery compared with the brachial artery, suggesting that the radial artery may be a useful way to assess FMD in future clinical studies (Agewall et al. 2001; Mitchell et al. 2016).

The accuracy of the arterial diameter assessment and the calculation of FMD directly depend on the axial resolution of the applied US scanner. The greater the frequency, the better is the accuracy of the vessel diameter measurements. The axial resolution of standard US scanners working at 7.5–12 MHz, used in the articles cited earlier, is limited to about 0.3 mm, which is close to the expected dilation of the brachial or radial artery and, thus, potentially biases the results. The brachial artery is located at an average depth of more than 1 cm below the skin surface, and because of the attenuation, no higher sounding frequency can be used for imaging. The radial artery is located 3 to 5 mm below the skin surface, and its shallow location allows increasing the scanning frequency to 20 MHz with superior axial resolution close to 0.1 mm. The accuracy of shear rate measurements is dependent on the quality of the pulse Doppler. In a series of experiments, we found that the pulse Doppler modality incorporated into commercially available linear array transducers had insufficient sensitivity to record precisely the blood flow velocity in the radial artery, especially the slow flow in the diastolic phase. In 7- to 12-MHz probes, the Doppler mode operates at 6 or 7 MHz, being the lower end of the available bandwidth. In the 20-MHz Ultrasonix SonixTouch (Analogic, Peabody, MA, USA) linear array transducer, the Doppler operates at about 10 MHz. The signal backscattered on red blood cells increases roughly with the fourth power of the scanning frequency. Thus, by doubling the Doppler transmitted frequency from 10 to 20 MHz, we can expect a significant improvement in Doppler signal-to-noise ratio, resulting in a more accurate measurement of blood flow velocity, and can determine the shear rate on this basis. For this reason, we introduced to FMD and SR measurements a 20-MHz linear array probe combined with a single-element 20-MHz pulse Doppler.

The aim of our study was to illustrate that measurement of FMD and SR in the radial artery with the designed 20-MHz scanning/Doppler system is feasible. The efficiency and usefulness of the system were confirmed in the pilot study of the group of 27 healthy volunteers and 17 patients with chronic coronary artery disease.

METHODS

Our pilot study involved two groups: Group I consisted of 27 healthy volunteers, 15 men and 12 women (20–71 y old), and group II consisted of 17 patients, 14 men and 3 women (36–77 y old), with chronic coronary artery disease (CAD). We used following criteria for the healthy group: no history of hypertension and a normal blood pressure at the time of examination; no history of diabetes mellitus, hyperlipidemia, cardiovascular disease or chronic kidney disease; and no history of cardiac medication use. The diagnosis of chronic CAD was based on the presence of symptoms of stable angina or a positive myocardial ischemia stress test (confirmed >50% epicardial coronary stenosis in one or more epicardial coronary arteries). Patients presenting with unstable angina and myocardial infarct were excluded.

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by