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Transthoracic Doppler echocardiography compared with positron emission tomography for assessment of coronary microvascular dysfunction: The iPOWER study☆,☆☆

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ABSTRACT

Background: Coronary microvascular function can be assessed by transthoracic Doppler echocardiography as a coronary flow velocity reserve (TTDE CFVR) and by positron emission tomography as a myocardial blood flow reserve (PET MBFR). PET MBFR is regarded the noninvasive reference standard for measuring coronary microvascular function but has limited availability. We compared TTDE CFVR with PET MBFR in women with angina pectoris and no obstructive coronary artery disease and assessed repeatability of TTDE CFVR.

Methods: From a cohort of women with angina and no obstructive coronary artery stenosis at invasive coronary angiography, TTDE CFVR by dipyridamole induced stress and MBFR by rubidium-82 PET with adenosine was successfully measured in 107 subjects. Repeatability of TTDE CFVR was assessed in 10 symptomatic women and in 10 healthy individuals.

Results: MBFR was systematically higher than CFVR. Median MBFR (interquartile range, IQR) was 2.68 (2.29–3.10) and CFVR (IQR) was 2.31 (1.89–2.72). Pearson's correlation coefficient was 0.36 ($p < 0.01$). Limits of agreement (2·standard deviation) assessed by the Bland–Altman (confidence interval, CI) method was 1.49 (1.29;1.69) and unaffected by time-interval between examinations. Results were similar when adjusting for rate pressure product or focusing on perfusion of the left anterior descending artery region. Limits of agreement (CI) for repeated CFVR in 10 healthy individuals and in 10 women with angina was 0.44 (0.21;0.68) and 0.48 (0.22; 0.74), respectively.

Conclusion: CFVR had a good repeatability, but the agreement between CFVR and MBFR was modest. Divergence could be due to methodology differences; TTDE estimates flow velocities whereas PET estimates myocardial blood flow.

1. Introduction

Coronary microvascular dysfunction (CMD) is gaining interest as a cause of angina-like chest pain. CMD could be an early sign of vascular pathology progressing to atherosclerosis and therefore cause an increased risk of future obstructive coronary artery disease (CAD) [1]. Moreover, the microvasculature is a major determinant of vascular resistance and therefore of myocardial blood flow, tissue oxygenation, and metabolism [2]. Therefore, it is important to assess CMD in patients with symptoms suggestive of angina and no obstructive CAD at invasive coronary angiography (CAG). However,

Abbreviations: TTDE, Transthoracic Doppler echocardiography; CFVR, Coronary flow velocity reserve; PET, Positron emission tomography; MBFR, Myocardial blood flow reserve; CMD, Coronary microvascular dysfunction; CAD, Coronary artery disease; CAG, Coronary angiography; LAD, Left anterior descending artery; MBF, Myocardial blood flow; CFV, coronary flow velocity.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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the CMD diagnosis is challenging, partly due to lack of valid, noninvasive, accessible techniques [3].

Endothelial-independent coronary microvascular function in the absence of obstructive CAD is assessed as the ratio between coronary blood flow or flow velocity during maximal myocardial hyperaemia (usually induced by pharmacological stress) and coronary flow at rest [4]. Transthoracic Doppler echocardiography (TTDE) of the left anterior descending artery (LAD) is a method to assess the coronary flow velocity reserve (CFVR). This method is noninvasive, easily accessible, low-cost, and free of radiation [5] and has shown good repeatability [6,7,12]. CFVR shows excellent agreement with invasively measured CFVR assessed with an intracoronary Doppler wire [6,8–11]. Positron emission tomography (PET) measured myocardial blood flow reserve (MBFR) is regarded as a noninvasive reference standard for CMD assessment. One small study in 10 healthy men and a study in obese patients with stable CAD compared TTDE CFVR with PET MBFR and found the two methods to have modest to acceptable agreement [7,12]. Importantly, both reduced MBFR and CFVR identify patients with a poor cardiovascular prognosis, suggesting that both methods are valuable tools in the detection of CMD at an early stage [1,13,14].

In view of the limited evidence available on comparison studies between TTDE and PET assessed coronary microvascular function, we investigated the agreement between CFVR and MBFR in women with angina-like chest pain and no obstructive CAD. Furthermore, we examined the CFVR repeatability in healthy volunteers and in symptomatic women with no obstructive CAD.

2. Methods

2.1. Study population

Women with angina-like chest pain and no significant obstructive CAD (<50% coronary artery stenosis) assessed by invasive CAG and with a successful TTDE CFVR examination were randomly selected from the iPOWER study cohort [15,16], based on availability of PET timeslot, participants' willingness to participate, and minimising time interval between the TTDE and PET examination. Participants had no previous history of myocardial infarction, valvular or congenital heart disease, a left ventricular ejection fraction above 45%, and no severe pulmonary disease (FEV_1 < 50% or uncontrolled asthma). Baseline assessment included clinical and demographic data from interview, charts, and the regional CAG database. To assess CFVR repeatability, 10 healthy individuals were recruited from the hospital staff along with 10 women with angina and no obstructive CAD from the iPOWER study cohort. The women all had an initial TTDE CFVR measurement of good quality [17].

2.2. MBFR and CFVR measurements

Participants underwent examination with both TTDE and PET. For the CFVR examination, coronary flow velocities were measured at rest and at maximal vasodilation induced by intravenous dipyridamole infusion (0.84 mg/kg) over 6 min. After the examination, theophylline (maximum dose 220 mg) was given to relieve potential side effects to dipyridamole. MBFR was obtained by measuring myocardial blood flow per unit myocardial tissue mass at rest and during a 6-min equipotent intravenous adenosine infusion (0.84 mg/kg). Blood pressure and heart rate were measured every 3 min during the TTDE examination and in the PET study before the scan, 2 min after initiation of the adenosine infusion and after the Rubidium-82-tracer infusion. For both examinations, participants were instructed to be abstinent from caffeine and food containing significant amount of methylxanthine (coffee, tea, chocolate, cola, and banana) for 24 h. Medication containing dipyridamole was paused for 48 h, anti-ischemic agents (long-lasting nitroglycerin, beta-blockers, calcium antagonist, ivabradine etc.), anti-hypertensive medication, and diuretics for 24 h and short-lasting nitroglycerin 1 h before the examination. Before the examinations, abstinence of the abovementioned foods and medication was confirmed.

Rate pressure product, a measure of myocardial demand, was calculated as heart rate multiplied by systolic blood pressure. Both CFVR and MBFR were corrected for rate pressure product by dividing coronary flow velocity (TTDE) and myocardial blood flow (PET) at rest by the rate pressure product and multiplying by 10,000 [18,19].

For assessment of repeatability of CFVR, the same experienced echocardiographer performed repeat CFVR examinations. Time intervals between examinations were 3–4 days in healthy individuals and 7–20 days in symptomatic women with no obstructive CAD.

2.3. TTDE examination

Echocardiographic examinations were performed using GE Healthcare Vivid E9 cardiovascular ultrasound system (GE Healthcare, Horten, Norway) with a 1.3–4.0 Mhz transducer (GE Vivid 5S probe) for the standard echocardiography and a 2.7–8 MHz transducer (GE Vivid 6S probe) for the CFVR examination. Participants were examined in the left lateral decubitus position. Three experienced echocardiographers performed the examinations in the same settings.

For the CFVR measurement, the octave was set at 3.1/6.2 MHz, frequency at 8 MHz for B-mode (2D), while a baseline colour scale between 1.00 and 2.50 KHz (velocity range ± 10–24 cm/s) was chosen according to low or high flow velocities, respectively. Colour gain was adjusted to provide optimal 2D image quality. LAD was visualised by colour Doppler in an apical modified foreshortened 2- or 4-chamber view or in a modified short-axis view of the left ventricle. Coronary flow velocities were measured by pulsed-wave Doppler as a laminar flow signal directed towards the transducer. Probe position was adjusted to align the ultrasound beam direction as parallel to the LAD flow as possible. In case of difficulty with visualisation of the LAD, ultrasound contrast (SonoVue®, Bracco Imaging) was used. The probe was kept in the same position during recording of 2D colour Doppler and pulse wave images. Acquisitions of coronary flow velocities during dipyridamole infusion were obtained throughout the infusion or up to 3 min after the infusion had terminated until flow had reached peak velocity. Images were stored for off-line analysis (GE EchoPac v.112, Horten, Norway).

Coronary flow velocities were assessed as diastolic peak flow velocities at rest and at peak hyperaemia and CFVR calculated as the ratio between the two (Fig. 1). Every CFVR examination was read by two experts independently, who were blinded to participant data and results of the PET examination or the previous CFVR examination. The first reading was used except in case of discrepancies (CFVR difference > 0.2) in which case the examination was re-evaluated by the two analysers and agreement was reached. Using a classic 2- and 4-chamber view, left ventricular ejection fraction was analysed by an automated biplane calculation (Auto-EF tool, GE EchoPac v.112, Horten, Norway).

2.4. PET examination

PET scans were performed using a Siemens Biograph Computer Tomography (CT)/PET 128-slice scanner (Siemens Healthcare, Knoxville, Tennessee, USA). Participants underwent

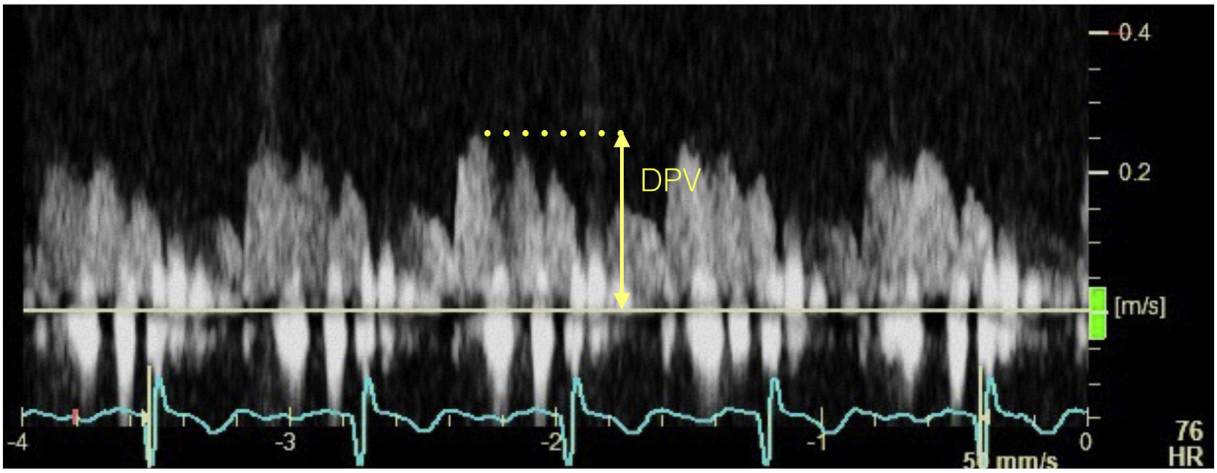

Fig. 1. Measurement of diastolic peak flow velocity (DPV).