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Noninvasive Imaging of the Coronary Vasculature Using Ultrafast Ultrasound

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the potential of coronary ultrafast Doppler angiography (CUDA), a novel vascular imaging technique based on ultrafast ultrasound, to image noninvasively with high sensitivity the intramyocardial coronary vasculature and quantify the coronary blood flow dynamics.

BACKGROUND Noninvasive coronary imaging techniques are currently limited to the observation of the epicardial coronary arteries. However, many studies have highlighted the importance of the coronary microcirculation and microvascular disease.

METHODS CUDA was performed in vivo in open-chest procedures in 9 swine. Ultrafast plane-wave imaging at 2,000 frames/s was combined to an adaptive spatiotemporal filtering to achieve ultrahigh-sensitive imaging of the coronary blood flows. Quantification of the flow change was performed during hyperemia after a 30-s left anterior descending (LAD) artery occlusion followed by reperfusion and was compared to gold standard measurements provided by a flowmeter probe placed at a proximal location on the LAD ($n = 5$). Coronary flow reserve was assessed during intravenous perfusion of adenosine. Vascular damages were evaluated during a second set of experiments in which the LAD was occluded for 90 min, followed by 150 min of reperfusion to induce myocardial infarction ($n = 3$). Finally, the transthoracic feasibility of CUDA was assessed on 2 adult and 2 pediatric volunteers.

RESULTS Ultrahigh-sensitive cine loops of venous and arterial intramyocardial blood flows were obtained within 1 cardiac cycle. Quantification of the coronary flow changes during hyperemia was in good agreement with gold standard measurements ($r^2 = 0.89$), as well as the assessment of coronary flow reserve (2.35 ± 0.65 vs. 2.28 ± 0.84; $p = NS$). On the infarcted animals, CUDA images revealed the presence of strong hyperemia and the appearance of abnormal coronary vessel structures in the reperfused LAD territory. Finally, the feasibility of transthoracic coronary vasculature imaging was shown on 4 human volunteers.

CONCLUSIONS Ultrafast Doppler imaging can map the coronary vasculature with high sensitivity and quantify intramural coronary blood flow changes. (J Am Coll Cardiol Img 2017;■:■–■) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Coronary arteries secure the heart supply in blood and oxygen. Any dysfunction or disease of these vessels can lead in turn to adverse clinical outcomes. The coronary vasculature is organized in 3 compartments. The first is made of the epicardial coronary arteries, which run along the heart's surface and exhibit diameters ranging from a few millimeters to 500 μm. The second includes the

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ABBREVIATIONS AND ACRONYMS

CFR = coronary flow reserve

CUDA = coronary ultrafast Doppler angiography

LAD = left anterior descending coronary artery

PVI = power-velocity integral

pre-arterioles, which penetrate the myocardium from the epicardium to the endocardium and exhibit diameters ranging from 500 μm to 100 μm. The third corresponds to the coronary microvasculature, which exhibits vessel diameters below 100 μm (1). To date, the epicardial coronary vasculature is the only compartment that can be imaged in vivo in humans (1) with current angiography techniques such as x-ray, computed tomography (CT) scan, or magnetic resonance imaging (2). As a consequence, cardiology practice has been centered on focal macroscopic coronary artery disease, that is, the functional assessment of epicardial stenoses based on fractional flow reserve and subsequent pharmacological or invasive treatment via percutaneous coronary interventions or surgery (3).

It is now recognized that coronary microvascular dysfunction, that is, including pre-arterioles, is another prognostic marker of myocardial ischemia (1,4). Yet clinical guidelines in the management of stable ischemic heart disease only consider coronary microvascular dysfunction after excluding signs of epicardial disease (5). Therefore, there is a clear role for novel imaging tools capable of imaging and characterizing the pre-arteriolar coronary vasculature.

On the technology front, echocardiography capabilities are being redefined in the advent of ultrafast cardiac ultrasound imaging (6). Relying on plane-wave transmissions, ultrafast ultrasound enables the imaging of the heart at thousands of images per second, that is, 100 times faster than conventional clinical echocardiography (7). The major benefit of this technology lies in the acquisition of spatially synchronous, temporally highly resolved ultrasound datasets. Earlier studies have shown that post-processing of ultrafast ultrasound datasets can lead to a 30-fold increase in power Doppler sensitivity and generate rodent cerebrovascular atlases of 100 μm resolution (8,9).

In the myocardium, 2-mm-thick cryomicrotome projections of swine coronary vasculature (10) reveal that dense vascular networks are being insonified during 2-dimensional echocardiography examinations (3- to 10-mm image slice thickness). In 2012, Osmanski et al. (11) presented a first sparse detection of intramyocardial blood flow in open-chest sheep experiments using directional ultrafast-power Doppler. More recently, we used ultrafast cardiac Doppler imaging to resolve left ventricle hemodynamics with millisecond accuracy (12). These advances exhibited the potential of ultrafast Doppler in mapping cardiac hemodynamics.

In this paper, we report noninvasive ultrasound imaging of the coronary vasculature and assessment of the coronary flow reserve (CFR) using a new technique we call coronary ultrafast Doppler angiography (CUDA). This technique involves acquiring ultrasound images of the beating heart at 2,000 frames per second and processing them adaptively to account for myocardial wall motion and retrieve Doppler signals from tissue clutter throughout the heart cycle. We present ultrasound images of the epicardial and pre-arteriolar (Ø 500 to 100 μm) coronary compartments in a series of in vivo open-chest swine experiments and assess pre-arteriolar CFR using a metric that is proportional to blood flow, referred to as power-velocity integrals (13). Finally, we demonstrate contrast agent–free, transthoracic ultrasound images of the human coronary vasculature.

METHODS

ANIMAL EXPERIMENT PROTOCOL. Eight 2.5-month-old female domestic swine (*Sus scrofa domesticus*) weighing 20 to 25 kg were anesthetized with isoflurane 2%, intubated, and ventilated. After sternotomy, a coronary flow probe (Transonic, Ithaca, New York) was placed around the left anterior descending coronary artery (LAD). During a first set of experiments, the LAD was transiently occluded for 30 s to induce reactive hyperemia (n = 5). Then the swine received intravenous adenosine infusion (0.5 mg/kg/min) to induce major pharmacological coronary artery vasodilation. During a second set of experiments, the LAD was transiently occluded for 90 min, followed by 150 min of reperfusion to induce myocardial infarction (n = 3). After the animals were euthanized, the heart was excised and cut in slices that were incubated with triphenyltetrazolium chloride to reveal infarcted areas in white and viable tissues in red. The animal procedure was approved by the Institutional Animal Care and Use Committee of Ecole Veterinaire de Maison-Alfort (ComEth ANSES-ENVA-UPEC) according to the European Commission guiding principles (2010/63/EU).

HUMAN APPLICATION. In this set of transthoracic experiments in humans, we used the same ultrafast ultrasound scanner and ultrasound probe as in open-chest experiments. A trained sonographer positioned the probe in real time using B-mode imaging. Subsequently, the ultrafast sequence was launched, and ultrafast ultrasound datasets were acquired. The processing was identical to the animal experiments. This study had been approved by the proper ethics committee (Comité de Protection des Personnes-Ile-de-France VI, study identifications: