Assessment of peripheral skeletal muscle microperfusion in a porcine model of peripheral arterial stenosis by steady-state contrast-enhanced ultrasound and Doppler flow measurement

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Objective: **Noninvasive measurement of peripheral muscle microperfusion could potentially improve diagnosis, management, and treatment of peripheral arterial disease (PAD) and thus improve patient care. Contrast-enhanced ultrasound (CEUS) as a noninvasive diagnostic tool allows quantification of muscle perfusion. Increasing data on bolus technique CEUS reflecting microperfusion are becoming available, but only limited data on steady-state CEUS for assessment of muscle microperfusion are available. Therefore, the aim of this study was to evaluate steady-state CEUS for assessment of peripheral muscle microperfusion in a PAD animal model.**

Methods: **In a porcine animal model, peripheral muscle microperfusion was quantified by steady-state CEUS replenishment kinetics (mean transit time [mTT] and wash-in rate [WiR]) of the biceps femoris muscle during intravenous steady-state infusion of INN−sulfur hexafluoride (SonoVue; Bracco, Geneva, Switzerland). In addition, macroperfusion was quantified at the external femoral artery with a Doppler flow probe. Peripheral muscle microperfusion and Doppler flow measurements were performed bilaterally at rest and under adenosine stress (70 μg/kg body weight) before and after unilateral creation of a moderate external iliac artery stenosis.**

Results: **All measurements could be performed completely in 10 pigs. Compared with baseline measurements, peripheral muscle microperfusion decreased significantly during adenosine stress (rest vs adenosine stress: mTT, 7.8 ± 3.3 vs 21.2 ± 17.8 s, $P = .0006$; WiR, 58.4 ± 38.1 vs 25.3 ± 15.6 arbitrary units [a.u.]/s, $P < .0001$; Doppler flow, 122.3 ± 31.4 vs 83.6 ± 28.1 mL/min, $P = .0067$) and after stenosis creation (no stenosis vs stenosis: mTT, 8.1 ± 3.1 vs 29.2 ± 18.0 s, $P = .0469$; WiR, 53.0 ± 22.7 vs 13.6 ± 8.4 a.u./s, $P = .0156$; Doppler flow, 124.2 ± 41.8 vs 65.9 ± 40.0 mL/min, $P = .0313$). After stenosis creation, adenosine stress led to a further significant decrease of peripheral muscle microperfusion but had no effect on macroperfusion (mTT, 29.2 ± 18.0 vs 56.3 ± 38.7 s, $P = .0078$; WiR, 13.6 ± 8.4 vs 6.0 ± 4.1 a.u./s, $P = .0078$; Doppler flow, 65.9 ± 40.0 vs 79.2 ± 29.6 mL/min, $P = .8125$). Receiver operating characteristic curves for the presence of inflow stenosis showed an excellent area under the curve of 0.93 for mTT at rest and 0.86 for Doppler flow.**

Conclusions: **Peripheral muscle microperfusion measurement by steady-state CEUS with replenishment kinetics is feasible and allows detection of muscle microperfusion changes caused by vasodilative stress alone or in combination with a moderate inflow stenosis. Steady-state CEUS offers superior diagnostic performance compared with Doppler flow measurements. Therefore, steady-state CEUS may prove to be a useful tool in diagnosis of PAD and for evaluation of new therapies. (J Vasc Surg 2015;61:1312-20.)**

Clinical Relevance: **Noninvasive imaging modalities currently used for the diagnosis of peripheral arterial disease (eg, Doppler ultrasound, magnetic resonance angiography, invasive angiography) cannot provide information on nutrient blood flow, limiting their ability to evaluate the influence of collateral perfusion in diffuse and small-vessel disease. Measurement of peripheral muscle microperfusion by contrast-enhanced ultrasound with replenishment kinetics is feasible and allows detection of microperfusion changes caused by vasodilative stress alone or a moderate inflow stenosis. In this regard, contrast-enhanced ultrasound may prove to be superior to Doppler flow measurements and therefore may evolve into a useful tool in diagnosis and therapy monitoring of peripheral arterial disease.**

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Author conflict of interest: C.P.N. is a consultant to Medtronic, Minneapolis, Minn.

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To date, peripheral arterial disease (PAD) is routinely diagnosed clinically first, followed by noninvasive or invasive imaging. Imaging modalities such as Doppler ultrasound, magnetic resonance angiography, computed tomography angiography, and invasive angiography not only have specific disadvantages but ultimately also fail to measure nutrient blood flow. This limits their ability to evaluate diffuse and small-vessel disease and the influence of collateral perfusion. Despite these disadvantages, ultrasound is widely used in clinical routine to assess macroperfusion. Other noninvasive imaging modalities (eg, magnetic resonance imaging with contrast enhancement or arterial spin labeling

and positron emission tomography–computed tomography) are available to evaluate peripheral perfusion while taking collateral perfusion into account.[1-3] However, their usefulness in a routine clinical setting is limited for various reasons (eg, their limited portability, contraindications, and use of ionizing radiation, among others). Therefore, a noninvasive imaging method for assessment of peripheral muscle microperfusion is desirable for two reasons. First, in a laboratory setting, a noninvasive imaging method for assessment of skeletal muscle microperfusion may allow evaluation of new therapies before use in humans. Second, in a clinical setting, a noninvasive imaging method could potentially improve the management of patients with PAD by providing information on the physiologic impact of the disease and by allowing monitoring of the disease (eg, follow-up examinations under therapy).

Contrast-enhanced ultrasound (CEUS) may become helpful not only by overcoming many of these limitations but also by providing the possibility to measure peripheral microperfusion.

In microperfusion CEUS, all contrast bubbles within the imaged region are first destroyed (flash) after a steady state of the contrast agent is reached, followed by nondestructive imaging (ie, use of a low mechanical index) of bubble replenishment.[4] By use of this technique, PAD impact on nutritive microvascular flow, which can originate from stem artery inflow, collateral vessels, or redistribution from other regions, can directly be measured and quantified.[5,6] Current experience with steady-state CEUS-based muscle microperfusion quantification in an animal model is limited to one publication using laboratory dogs.[7] However, the number of laboratory dogs has constantly decreased during the last year,[8,9] underlining the need for an alternative PAD animal model.

Therefore, the purpose of this study was to assess peripheral skeletal muscle microperfusion by means of state-of-the-art steady-state CEUS at rest and during stress under vasodilator administration in a porcine model of peripheral arterial stenosis.

METHODS

Experimental protocol and measurements. A flow chart of the experimental protocol is given in Fig 1. First, animals were prepared as described next (animal preparation). CEUS measurements and Doppler flow measurements were performed bilaterally at rest and under adenosine stress without stenosis and on the left side only after creation of the stenosis. For vasodilative adenosine stress measurements, intravenous infusion of adenosine (70 μg/kg body weight) was started 5 minutes before infusion of the ultrasound contrast agent and continued until stress measurements were completed. After stress measurements, a moderate stenosis with a mean arterial pressure gradient of 10 to 20 mm Hg of the distal left external iliac artery was created and measurements were repeated on that side (Fig 2). This pressure gradient reflects an approximate area narrowing of 75% to 80%.[6,10]

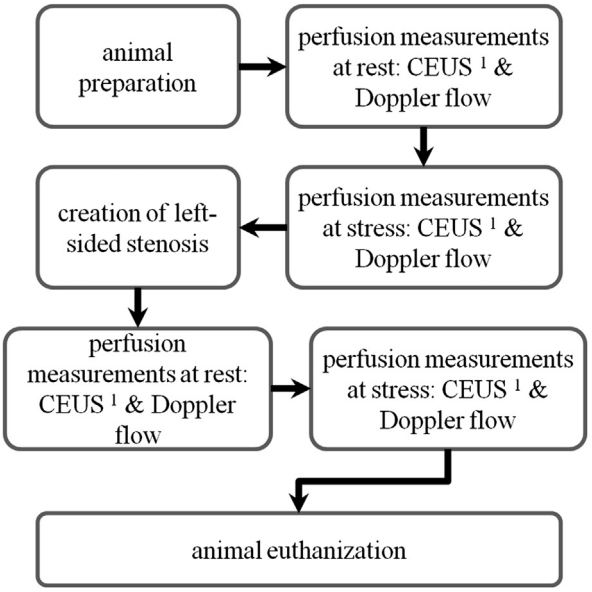

Fig 1. Experimental protocol. *CEUS*, Contrast-enhanced ultrasound.

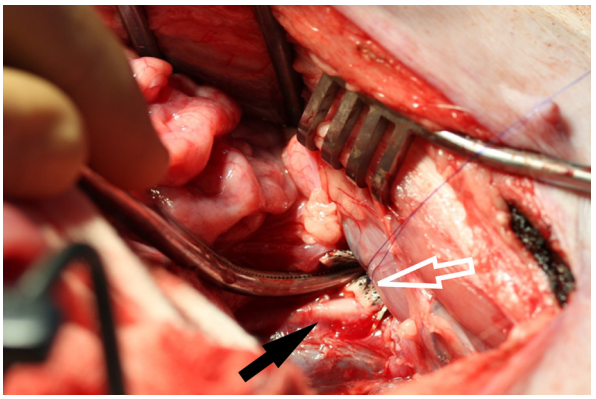

Fig 2. Stenosis creation. A 5-mm-wide graft (*open arrow*) is wrapped around the external iliac artery (*black arrow*) and then gradually tightened with sutures through the graft (*open arrow*) until the target pressure gradient is reached.

Animal preparation. Ten domestic pigs (Deutsche Landrasse) were included in this study after approval from the state animal care committee. All examinations were performed under general anesthesia. After intramuscular premedication with 0.02 mg/kg body weight atropine (Atropin Sulfat 0.5 mg/mL; WDT, Garbsen, Germany), 2 mg/kg body weight xylazine (Xylazin 2%; Riemser Arzneimittel AG, Greifswald, Germany), and 20 mg/kg body weight ketamine (Ketamin 10%; Medistar Arzneimittelvertrieb GmbH, Ascheberg, Germany), anesthesia was started by intravenous injection of 0.5 mg/kg body weight midazolam (Midazolam 5 mg/mL; Ratiopharm GmbH, Ulm, Germany) and 0.01 mg/kg body weight fentanyl (Fentanyl 0.05 mg/mL; Janssen-Cilag GmbH, Neuss, Germany). Animals were orotracheally

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