Effect of Peripheral Artery Sympathetic Denervation on Muscle Microperfusion and Macroperfusion in an Animal Peripheral Artery Disease Model Using Contrast-Enhanced Ultrasound and Doppler Flow Measurement

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ABSTRACT

Purpose: To determine the effects of catheter-based peripheral sympathetic denervation (CPSD) on peripheral artery sympathetic tone and peripheral microperfusion (PMP).

Materials and Methods: The effects of bilateral CPSD in common iliac arteries on PMP of the biceps femoris were determined in pigs using contrast-enhanced ultrasound, and mean transit time (mTT) and wash-in rate (WiR) were calculated during steady-state infusion of INN-sulfur-hexafluoride. Measurements were performed bilaterally at rest and during infusion of adenosine 70 μg/kg/min after unilateral moderate left external iliac artery stenosis.

Results: Before CPSD, PMP decreased significantly ($P < .05$) under adenosine stress compared with resting conditions, with right mTT of 7.5 seconds ± 3.6 versus 16.9 seconds ± 11.9 and WiR of 63.1 arbitrary units (AU) ± 49.0 versus 25.0 AU ± 17.5 and left mTT of 29.2 seconds ± 18.0 versus 56.3 seconds ± 38.7 and WiR of 13.6 AU ± 8.4 versus 6.0 AU ± 4.1. After CPSD, PMP did not differ significantly ($P > .05$) between conditions of adenosine stress and rest, with right mTT of 19.9 seconds ± 24.7 versus 23.2 seconds ± 21.0 and WiR of 16.2 AU ± 25.0 versus 20.5 AU ± 19.7 and left mTT of 23.3 seconds ± 23.1 versus 25.8 seconds ± 21.7 and WiR of 12.5 AU ± 6.2 versus 20.0 AU ± 12.1.

Conclusions: CPSD reduced peripheral artery sympathetic tone and may be an alternative to surgical or computed tomography–guided sympathectomy for the treatment of end-stage peripheral artery disease and Raynaud phenomenon.

ABBREVIATIONS

AU = arbitrary units, CPSD = catheter-based peripheral sympathetic denervation, DF = Doppler flow, mTT = mean transit time, PAD = peripheral artery disease, PI = perfusion index, PMP = peripheral microperfusion, WiR = wash-in rate

Renal sympathetic denervation has gained considerable attention more recently as a treatment for drug-resistant arterial hypertension (1). The effects of renal sympathetic denervation have also been investigated for other diseases of generalized sympathetic overactivity, such as sleep apnea, insulin resistance (2), and left ventricular hypertrophy (3). However, sympathetic denervation in arteries other than renal arteries has been examined in only one previous study (4), and it has not been assessed in the context of peripheral artery disease (PAD) and Raynaud phenomenon, despite being a well-established treatment option for these diseases. End-stage PAD occurs in 1%–2% of all PAD patients and significantly impairs quality of life and increases health care costs (5). Similarly, Raynaud phenomenon occurs in

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6%–20% of women and 3%–12.5% of men (6) and significantly compromises quality of life (7). However, surgical as well as computed tomography–guided lumbar sympathectomy has substantial complication rates in patients with upper extremity Raynaud syndrome (6), warranting consideration of minimally invasive peripheral artery sympathetic denervation as a treatment alternative. The present study evaluates the effects of catheter-based peripheral sympathetic denervation (CPSD) on vascular tone and peripheral perfusion using an animal model of PAD.

MATERIALS AND METHODS

This work is in part based on a previous study (8), at the end of which the baseline measurements before CPSD were performed.

Experimental Protocol

The experimental protocol (Fig 1) was approved by the state animal care committee, and experiments were performed using 10 pigs (4 male and 6 female; mean weight, 37.3 kg ± 3.9). Animal perfusion measurements were initially taken at rest and then under adenosine stress. Subsequently, CPSD was performed, rest and stress measurements were repeated, and the animals were euthanized.

Animal Preparation

All examinations were performed under general anesthesia using isoflurane inhalation and fentanyl infusions. Anesthesia was initiated by intravenous injections of midazolam (5 mg/mL; ratiopharm GmbH, Ulm, Germany) and fentanyl (0.05 mg/mL; Janssen-Cilag GmbH, Neuss, Germany), and animals were intubated and mechanically ventilated (Julian; Draeger, Luebeck, Germany) throughout the procedure. To minimize the risk of allergic reactions to the contrast agent, animals received 15 mg acetylsalicylic acid per kg body weight. A 6-F sheath was placed in the left common carotid artery to monitor invasive blood pressure and to provide catheter and guide wire access. Venous access was obtained via the left internal jugular vein for administration of fluid, drugs, and ultrasound (US) contrast agent. To prevent blood clotting and thrombus formation, 5,000 IU heparin was administered after central venous and arterial access had been established. Subsequently, deep femoral arteries were ligated bilaterally to exclude collateral flow. A stenosis was created at the left distal external iliac artery using a 5-mm-wide Dacron graft (Vascutek, Hamburg, Germany), and the target mean arterial pressure gradient of 10–20 mm Hg (75%–80% narrowing (9)) was achieved. Mean arterial pressure gradients (before vs after stenosis) were determined using a 2-F microcatheter. To measure distal external femoral arterial blood flow, a cutdown was performed on both sides, and Doppler probes were inserted.

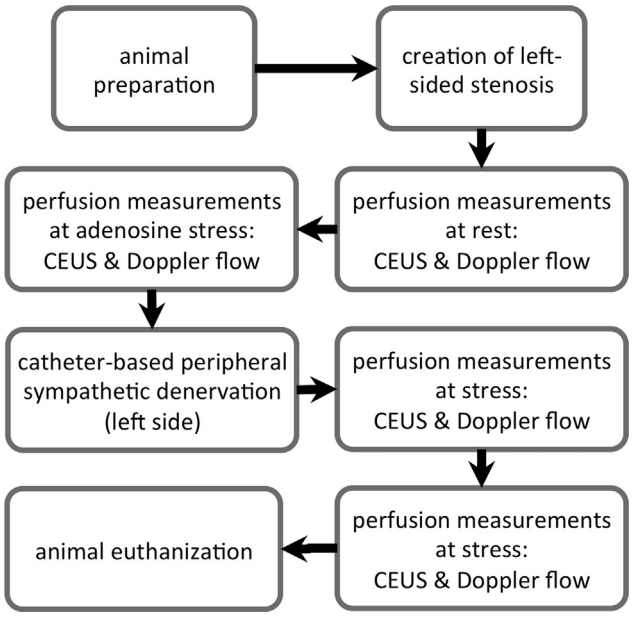

Figure 1. Experimental protocol. CEUS = contrast-enhanced ultrasound.

Contrast-Enhanced US

Contrast-enhanced US imaging of the lateral thigh (biceps femoris muscle) was performed using an 8-MHz linear US transducer (GE Healthcare, Solingen, Germany) during infusion of INN-sulfur hexafluoride (SonoVue; Bracco Suisse SA, Geneva, Switzerland) with a dedicated rotating power injector (VueJECT; Bracco Suisse SA) at a rate of 2 mL/min (8). Gain was held constant during the entire examination after initial optimization, the mechanical index was set to 0.11, and compression was set to 60. After reaching a contrast steady state, cineloops of the replenishment kinetics were recorded and digitally stored, and measurements were repeated under adenosine stress. Cineloops were digitally transferred to a computer, and image analyses were performed using dedicated commercially available software (ViewBox; Bracco Suisse SA). Microperfusion rates were evaluated by calculating mean transit time (mTT), wash-in rate (WiR), relative blood volume, and perfusion index (PI) using the aforementioned software (10). Flow reserve was calculated as PI_{stress}/PI_{rest} (11).

Femoral Artery Blood Flow

Femoral artery blood flow (in mL/s) was measured using an US flowmeter (VeriQ VQ4122; Medistim, Oslo, Norway) and calibrated Doppler flow (DF) probes (QuickFit; Medistim). To ensure measurement accuracy, the Doppler probe size was chosen according to the vessel diameter.