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Regulation of subcutaneous adipose tissue blood flow during exercise in humans

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¹Turku PET Centre, ²Research Centre of Applied and Preventive Cardiovascular Medicine, and Departments of ³Clinical Physiology and Nuclear Medicine and ⁴Medicine, University of Turku, Turku, Finland; and ⁵Centre for Healthy Aging, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

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Heinonen I, Bucci M, Kempainen J, Knuuti J, Nuutila P, Boushel R, Kalliokoski KK. Regulation of subcutaneous adipose tissue blood flow during exercise in humans. *J Appl Physiol* 112: 1059–1063, 2012. First published January 5, 2012; doi:10.1152/jappphysiol.00732.2011.—Regulation of subcutaneous adipose tissue blood flow (ATBF) remains poorly elucidated in humans, especially during exercise. In the present study we tested the role of adenosine in the regulation of ATBF adjacent to active and inactive thigh muscles during intermittent isometric knee-extension exercise (1 s contraction followed by 2 s rest with workloads of 50, 100, and 150 N) in six healthy young women. ATBF was measured using positron emission tomography (PET) without and with unspecific adenosine receptor inhibitor theophylline infused intravenously. Adipose regions were localized from fused PET and magnetic resonance images. Blood flow in subcutaneous adipose tissue adjacent to active muscle increased from rest (1.0 ± 0.3 ml·100 g⁻¹·min⁻¹) to exercise ($P < 0.001$) and along with increasing exercise intensity (50 N = 4.1 ± 1.4 , 100 N = 5.4 ± 1.8 , and 150 N = 6.9 ± 3.0 ml·100 g⁻¹·min⁻¹, $P = 0.03$ for the increase). In contrast, ATBF adjacent to inactive muscle remained at resting levels with all intensities ($\sim 1.0 \pm 0.5$ ml·100 g⁻¹·min⁻¹). During exercise theophylline prevented the increase in ATBF adjacent to active muscle especially during the highest exercise intensity (50 N = 4.3 ± 1.8 ml·100 g⁻¹·min⁻¹, 100 N = 4.0 ± 1.5 ml·100 g⁻¹·min⁻¹, and 150 N = 4.9 ± 1.8 ml·100 g⁻¹·min⁻¹, $P = 0.06$ for an overall effect) but had no effect on blood flow adjacent to inactive muscle or adipose blood flow in resting contralateral leg. In conclusion, we report in the present study that 1) blood flow in subcutaneous adipose tissue of the leg is increased from rest to exercise in an exercise intensity-dependent manner, but only in the vicinity of working muscle, and 2) adenosine receptor antagonism attenuates this blood flow enhancement at the highest exercise intensities.

adenosine

METABOLIC FUNCTIONS OF SUBCUTANEOUS adipose tissue are closely related to its blood flow, and impaired regulation of adipose tissue blood flow has been linked to metabolic abnormalities in obesity and insulin resistance (5, 12, 13, 18). Adipose tissue blood flow increases during exercise; however, the mechanisms regulating this response in humans remain incompletely elucidated. Although nitric oxide (NO) is strongly implicated in the control of preprandial subcutaneous adipose tissue blood flow (ATBF) and postprandial ATBF is mediated mainly by β -adrenergic mechanisms (1), a recent study suggests that NO does not contribute significantly to physiological increase of adipose blood flow during acute

exercise (9). In addition to hormonally mediated β -adrenergic regulation of ATBF during exercise, locally derived substances such as adenosine could constitute an additional level of regulation to match ATBF to tissue metabolism (lipolysis and subsequent extraction of free-fatty acids). As in skeletal muscle (10), adenosine concentration in subcutaneous adipose tissue increases during exercise (4), but its role in regulating ATBF during exercise in humans remains to be elucidated.

Evidence pointing to local regulation of ATBF comes from a recent study showing that ATBF increases only in a close proximity of the contracting quadriceps muscle and not in the contralateral resting leg (17). The authors speculated that this increase in blood flow was attributable to elevated muscle temperature only in adipose regions adjacent to working muscle. Because it is evident that blood flow can vary even within the different layers of the same adipose tissue wall (2), we sought to ascertain whether ATBF in the vicinity of contracting and noncontracting skeletal muscle increases as a function of exercise intensity. Given that interstitial adenosine increases with exercise intensity in subcutaneous adipose tissue (4), a second aim was to examine the role of adenosine in regulating ATBF during exercise.

In the present study we combined positron emission tomography (PET) and magnetic resonance imaging (MRI) to obtain accurate measures of regional ATBF in the thigh region during intermittent isometric knee-extension exercise. Subcutaneous ATBF was measured adjacent to active and inactive muscle regions with and without intravenous infusion of theophylline. We hypothesized that 1) ATBF increases with exercise intensity adjacent to active, but not adjacent to inactive muscle in the same leg, and that 2) theophylline reduces ATBF adjacent to active, but not adjacent to inactive muscle.

METHODS

Subjects. Six healthy, nonobese, and nonsmoking, yet untrained women were recruited to participate in the study (age 24.0 ± 2.6 yr, height 171.5 ± 2.3 cm, weight 62.1 ± 4.6 kg, body mass index 21.0 ± 1.1 kg/m², $\dot{V}_{O_2 \max}$ 2.4 ± 0.2 l/min). The purpose, nature, and potential risks were explained to the subjects before they gave their written informed consent to participate. The possibility of pregnancy was excluded by a pregnancy test before participation. The subjects were not taking any medication other than possible oral contraceptives. Subjects were studied in the early follicular phase of their menstrual cycle to minimize any confounding effects of reproductive hormones on the control of blood flow. Subjects also fasted overnight and they avoided caffeine-containing beverages such as coffee, tea, and cola drinks for at least 48 h before the experiments. Exhaustive exercise was also avoided 24 h prior to the study. The study was performed

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according to the Declaration of Helsinki and was approved by the Ethical Committee of the Hospital District of South-Western Finland.

Study design. The experiment day started with a MRI study to obtain anatomical references from the femoral region. Thereafter, the PET studies were conducted to measure adipose blood flow. Before the PET experiments, the antecubital vein was cannulated for tracer and theophylline administration. For blood sampling, a radial artery cannula was placed under local anesthesia in the contralateral arm. Subjects were then moved to the PET scanner with the femoral region in the gantry and the left leg was fastened to a dynamometer (Diter Petkin, Oy Diter-Elektronikka Ab, Turku, Finland) at a knee angle of 40 degrees. After a transmission scan, basal blood flow was measured while the subject was lying at rest. Thereafter, the subject was allowed to briefly familiarize with the one-legged intermittent isometric knee-extension exercise model. The exercise model consisted of 1-s isometric contractions of the knee extensors followed by a 2-s pause interval. The subject performed exercise at three different workloads (50, 100, and 150 N) and each load lasted 10 min with 5-min breaks in between. At all three intensities, blood flow was measured after 5 min of exercise. Instructions about maintaining the exercise intensity and rest and exercise periods were provided to the subject by LED lights and also cued by specific sounds from the dynamometer. After the first section of the study, the subjects were removed from the PET scanner and a 90-min rest period followed.

Theophylline was then infused into the antecubital vein and continued for 30 min. The infused dose was 6.9 mg/kg body wt (total dose 422 ± 34 mg, range 382–480 mg), which has been previously shown to decrease muscle blood flow during exercise and thus effectively block adenosine receptors (14). After the cessation of theophylline infusion, the subjects were allowed to rest for another 30 min. Thereafter, the subjects were positioned back into the PET scanner and similar blood flow measurements during three exercise intensities as without theophylline were performed. ECG and heart rate was continuously monitored during the PET measurements, and blood pressure was measured continuously with an automatic apparatus (Omron, M5-1, Omron Healthcare, Europe B.V. Hoofddorf, The Netherlands). Maximal oxygen uptake ($\dot{V}O_{2\max}$) was determined within 3 wk from the PET measurements using an electrically braked cycle ergometer (Ergoline 800 S, Bitz, Germany) with direct respiratory measurements (Medikro 202; Medikro Oy, Kuopio, Finland) using an incremental protocol with 2-min ramps of 25 W starting at 50 W.

Measurements of blood flow. Positron-emitting tracer ($^{15}\text{O}\text{-H}_2\text{O}$) was produced as previously described in detail (16). The ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, TN) was used in 3D mode for image acquisition. Photon attenuation was corrected by 5-min transmission scans performed at both the beginning of the first and second PET study. All data were corrected for dead time, decay, and measured photon attenuation. For the measurement of blood flow, on average 455 ± 34 MBq of $^{15}\text{O}\text{-H}_2\text{O}$ was injected intravenously and blood flow was measured by dynamic scanning for 240 s (48×5 -s frames) for measurements at rest and for 140 s (28×5 s) for measurements during exercise. During exercise, steady-state blood flow measurements began after 5 min of exercise onset. Arterial blood was continuously withdrawn during the PET scans with a pump to determine the blood time-activity curve. The radioactivity concentration in arterial blood was measured using a two-channel online detector system (Scanditronix, Uppsala, Sweden) that was cross-calibrated with an automatic gamma counter (Wizard 1480 3, Wallac, Turku, Finland) and the PET scanner. The delay and dispersion corrected arterial radioactivity was used as an input function. The autoradiographic method and one-compartment model with 200-s (rest measurements) and 90-s (exercise measurements) integration times were applied to calculate blood flow voxel by voxel into parametric blood flow images (6, 8, 11, 15).

Regions of interests. The subcutaneous adipose tissue above exercising QF muscle region of interest (ROI) was drawn into seven

subsequent cross-sectional planes in the upper part of the thigh region. Similar seven ROIs were drawn on the same planes close to inactive posterior hamstring muscles (Fig. 1). The localization of different tissue regions was based on the individual MRI images.

Statistical analysis. Statistical analyses were performed using SAS/STAT statistical software (version 8.2, SAS Institute, Cary, NC). The effects of exercise and theophylline on measured parameters were tested using two-way ANOVA for repeated measurements (exercise intensity and theophylline as factors). If a significant main effect(s) was found, pairwise differences were identified using the Tukey-Kramer post hoc procedure. Results are reported as means \pm SD.

RESULTS

Acute responses of heart rate and blood pressure to exercise and theophylline are shown in Table 1. These, but no other data, have been previously reported (7). Baseline ATBF adjacent to knee extensors (active muscle group during exercise) (1.0 ± 0.3 ml \cdot 100 g $^{-1}\cdot$ min $^{-1}$) and inactive (hamstring) muscles (1.0 ± 0.5 ml \cdot 100 g $^{-1}\cdot$ min $^{-1}$) was similar ($P = 0.9$). One-leg intermittent isometric knee-extension exercise at 50 N increased blood flow four-fold in adipose tissue active muscle ($P < 0.001$), and blood flow was further increased with increase in exercise intensity (Fig. 2; $P = 0.03$ for an overall effect). In contrast, ATBF adjacent to inactive muscle remained essentially similar to rest (Fig. 3). Theophylline reduced ATBF adjacent to active muscle ($P = 0.06$) and most of the reduction was confined to the highest intensity (Fig. 2). In contrast, theophylline did not change ATBF adjacent to inactive muscle ($P = 0.7$; Fig. 3).

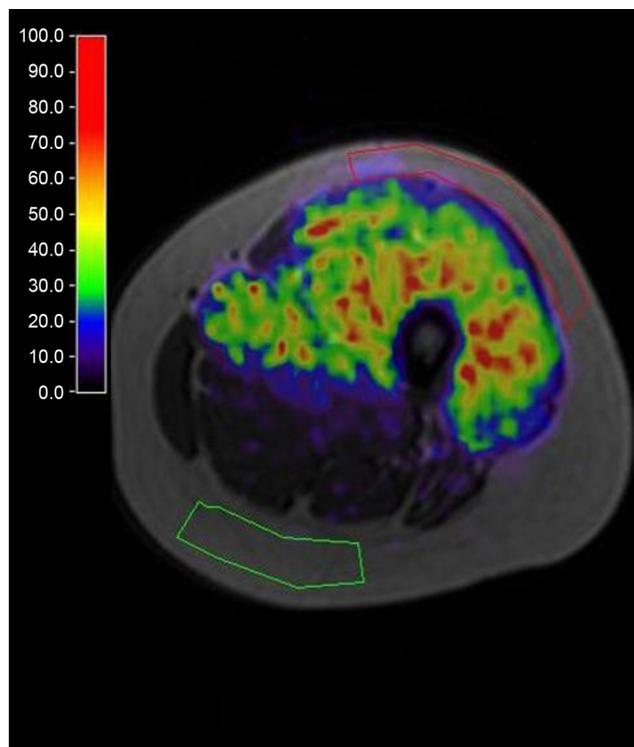


Fig. 1. Fusion image of positron emission tomography (PET) and magnetic resonance imaging (MRI) images from the middle thigh region where regions of interest (ROIs) were drawn. Subcutaneous adipose tissue blood flow during one leg exercise was analyzed adjacent to the working knee extensors in which increased blood flow was also detected as shown in scale and representative colors in the image. Blood flow in adipose tissue adjacent to the inactive posterior hamstring muscles was also analyzed.

Table 1. Heart rate and blood pressure during exercise measurements

	Without Theophylline			With Theophylline		
	EXE1	EXE2	EXE3	EXE1	EXE2	EXE3
HR, beats/min	75 ± 12	81 ± 12*	90 ± 15*	78 ± 18	84 ± 19*	98 ± 26*
MAP, mmHg	94 ± 6	95 ± 7	97 ± 3†	91 ± 8	94 ± 9	100 ± 12†
BPs, mmHg	121 ± 8	123 ± 12	126 ± 12†	120 ± 14	124 ± 15	130 ± 15†
BPd, mmHg	81 ± 5	81 ± 6	82 ± 7†	77 ± 6	80 ± 7	85 ± 13†
RPP, mmHg/(beats/min)	7,163 ± 1,522	7,744 ± 1,794*	8,687 ± 1,512‡	7,246 ± 2,398	8,031 ± 2,656*	9,992 ± 3,807‡

Values are means ± SD. HR, heart rate; MAP, mean arterial pressure; BPs, systolic blood pressure; BPd, diastolic blood pressure; RPP, rate pressure product. * $P < 0.05$ compared with previous exercise intensity, † $P < 0.05$ compared to EXE 1, ‡ $P < 0.01$ compared with EXE 1 and EXE 2.

ATBF in resting contralateral leg both adjacent to knee extensors and hamstring were similar to the respective regions in other leg while subjects were at rest and remained similar to resting values and was not affected by theophylline during all workloads when the other leg was exercising. The ATBF values in the resting leg were as follows: $1.3 \pm 0.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to knee extensors and $1.2 \pm 0.3 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to hamstrings at rest and 1.4 ± 1.0 , 1.3 ± 1.0 , and $1.1 \pm 0.7 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to knee extensors and 1.2 ± 0.7 , 1.4 ± 1.5 , and $1.5 \pm 1.0 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to hamstrings during control exercise at workloads 50, 100, and 150 N and 1.5 ± 1.2 , 1.5 ± 1.4 , and $1.3 \pm 0.8 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to knee extensors and 1.7 ± 1.1 , 1.4 ± 1.3 , and $1.9 \pm 1.7 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ adjacent to hamstrings during respective exercise workloads under the theophylline infusion.

Blood flow in adipose tissue adjacent to active muscle correlated somewhat to muscle blood flow in the resting state ($r = 0.80$, $P = 0.06$). At the two lowest intensities there was no correlation between muscle and adipose tissue blood flow ($r = -0.18$, $P = 0.73$ and $r = 0.00$, $P = 1.00$). However, at highest exercise intensity there was some nonsignificant correlation in blood flow in active muscle and adipose tissue adjacent to active muscle ($r = 0.77$, $P = 0.08$). During theophylline infusion, correlations were poor at all three exercise intensities ($r = 0.47$, $P = 0.35$; $r = 0.00$, $P = 1.00$; and $r = 0.35$, $P = 0.49$).

DISCUSSION

The main findings of the present study are: 1) blood flow in the subcutaneous adipose tissue in the thigh region increases from rest to exercise in an intensity-dependent manner and only in the vicinity of active muscle. 2) Adenosine plays a role in the regulation of ATBF in the vicinity of active muscle at high exercise intensity.

Stallknecht et al. (17) recently reported that blood flow increases only in subcutaneous adipose tissue close to working skeletal muscle from rest to exercise irrespective of exercise intensity, but not in the adipose tissue of contralateral resting leg. Our findings in the present study fit well with these previous results and further extend the findings on two important points. First, we show here that the same pattern of selective increases in ATBF only in the regions of contracting muscle also apply within a single leg. That is, ATBF adjacent to active knee extensor muscles increased during knee-extension exercise, but not adjacent to inactive posterior thigh muscles. An additional observation was that a restraint on ATBF occurs in regions of inactive muscle at all three exercise intensities while blood flow increased in intensity-dependent manner in adipose tissue adjacent to active muscle. Moreover, ATBF in resting contralateral leg in both adjacent to knee extensors and hamstrings remained similar to resting values during all workloads when the other leg was exercising. These findings indicate that metabolic signals classically typical for skeletal muscle may also regulate the blood supply within adjacent adipose tissue (5, 12, 13, 18). However, because of the anatomical organization of blood vessels, it is unlikely that the coupled increase in ATBF in the region of the active muscle

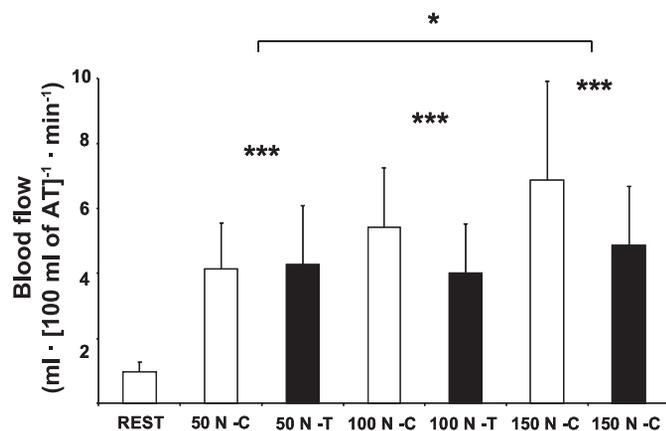


Fig. 2. Subcutaneous adipose tissue (AT) blood flow at rest and during exercise adjacent to the working knee extensor muscle group. Blood flow increased from rest to exercise (***) $P < 0.001$ and further in an intensity-dependent manner (* $P < 0.05$). Adenosine receptor antagonism with theophylline reduced blood flow by 29% during the highest exercise intensity ($P = 0.06$ for the main effect). N, Newton; C, control; T, theophylline.

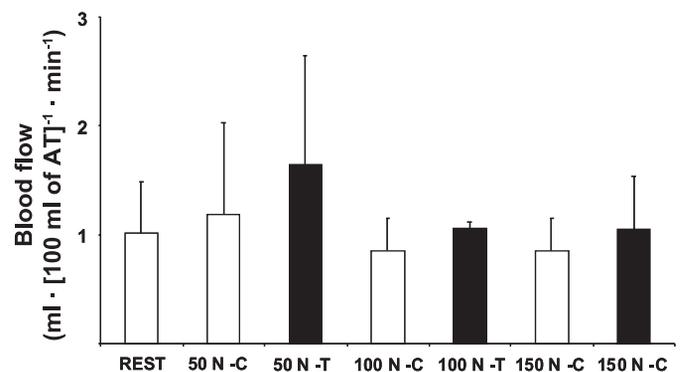


Fig. 3. Subcutaneous AT blood flow at rest and during exercise adjacent to the inactive posterior hamstring muscles. No significant differences were observed either from transition from rest to exercise or between exercise intensities or between control and theophylline administration.

functions ultimately to supply the adjacent muscle with energy substrates or that the increases in blood flow in both tissues are coincident responses to muscle contraction. In addition to this, however, it is likely that if exercise workloads had been increased beyond 150 N, which was the highest exercise intensity in the present study, increase in adipose blood flow would have been leveled off (17), whereas muscle blood flow is well known to increase with increasing exercise intensity up to maximal intensities. Thus exactly similar metabolic regulatory mechanisms that are thought to work in muscle may not directly apply to adipose tissue.

One mechanism that may explain the increase in blood flow only in adipose tissue in close vicinity of the working muscle is conduction of heat from working muscle that may cause blood vessels in the adipose region to vasodilate (17). Another potential explanation may be upstream conductive vasodilation of the arterial tree. It has been shown that vasodilation that is powerfully triggered in the exercising skeletal muscle mainly by the metabolic mechanisms travels upstream by endothelial and smooth muscle cell gap junctions to larger arteries (3). From there the signals may spread also to the arterial vessels that supply adjacent adipose tissue, allowing vasodilation and enhanced adipose blood flow. In the present study we only studied whether metabolic mechanisms that might regulate skeletal muscle blood flow are also involved in the regulation of ATBF.

We recently addressed the possible role of nitric oxide and prostanoids in the regulation of ATBF at rest and during exercise (9). The findings supported the results and view of Ardilouze et al. (1) in that NO seems to be an important regulator of basal preprandial ATBF, but does not have significant role in the regulation of ATBF during local exercise (9). Thus other factors likely play a more important role, and one of these factors may be adenosine. From previous studies it is known that adenosine is formed also in subcutaneous adipose tissue during exercise (4), and there it may stimulate receptors in vascular smooth muscle cells and exert vasodilation. Supporting adenosine's role in the regulation of ATBF during exercise, we found that blood flow in adipose tissue adjacent to active muscle during local knee-extension exercise was attenuated under nonspecific adenosine receptor antagonism by theophylline (by ~30%, $P = 0.06$), whereas ATBF adjacent to hamstrings in exercising leg or in resting contralateral leg in both adjacent to knee extensors and hamstrings was not affected by theophylline from rest to exercise or during any workload when the other leg was exercising. The reduction response was confined mainly to the highest exercise intensity, which may be associated with intensity-related release of adenosine in the adipose tissue.

There could be at least one methodological reason for the increased blood flow in the adipose tissue adjacent to the active muscle. Inherent to the PET method there is a phenomenon called partial volume effect, which means spillover of radioactive activity from highly active areas to less active areas. So in theory PET-derived blood flow could be increased in adipose tissue adjacent to the active muscle because of spillover from active muscle. In that case it could be assumed that there would be correlation between muscle and adipose tissue blood flow values, but we did not find solid evidence for that. There was some (nonsignificant) correlation in only one condition out of six of the measurements during exercise. In the other five

occasions correlation was poor or totally absent, suggesting that blood flow did not increase in the adipose tissue adjacent to the active muscle due to partial volume effect.

In conclusion, we report in the present study that blood flow in subcutaneous adipose tissue of the thigh is increased from rest to exercise in an exercise intensity-dependent manner up to moderate exercise intensities, but only in the vicinity of working knee-extensor muscles. Furthermore, adenosine receptor antagonism attenuates this blood flow increase in subcutaneous adipose tissue adjacent to active muscles. Thus some evidence was found that adenosine may play a role in the regulation of adipose tissue blood flow in humans, and tissues other than muscle must be considered as potential sites of action of adenosine controlling the whole limb blood flow.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: I.H., J. Knuuti, P.N., R.C.B., and K.K.K. conception and design of research; I.H., J. Kempainen, and K.K.K. performed experiments; I.H. and M.B. analyzed data; I.H., M.B., J. Knuuti, P.N., R.C.B., and K.K.K. interpreted results of experiments; I.H. prepared figures; I.H. drafted manuscript; I.H., M.B., J. Kempainen, R.C.B., and K.K.K. edited and revised manuscript; I.H., M.B., J. Kempainen, J. Knuuti, P.N., R.C.B., and K.K.K. approved final version of manuscript.

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