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Exercise Training Improves Microvascular Function in Burn Injury Survivors

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Abstract

Introduction.—Vasodilator function is impaired in individuals with well-healed burn injuries, but therapeutic interventions that lessen or reverse this maladaptation are lacking. The purpose of this study was to test the hypothesis that a 6-month community-based exercise training program would increase microvascular dilator function in individuals with well healed burn injuries irrespective of the magnitude of the injured body surface area. Further, we hypothesize that macrovascular dilator function would remain unchanged post-training.

Methods.—Microvascular function, (forearm reactive hyperemia), macrovascular function (brachial artery flow-mediated dilation), and the maximal vasodilatory response following ischemic handgrip exercise (an estimate of microvascular remodeling) were assessed before and after exercise training in non-burned control subjects ($N = 11$) and individuals with burn injuries covering a moderate body surface area ($26 \pm 7\%$; $N = 13$) and a high body surface area ($59 \pm 15\%$; $N = 19$).

Results.—Peak vascular conductance and area under the curve during post-occlusive reactive hyperemia increased from pre- to post-training in control and burn injury groups (both $P < 0.05$), the magnitude of which did not differ between groups (both $P = 0.6$). Likewise, the maximal vasodilatory response following ischemic handgrip exercise increased in all groups after exercise training ($P < 0.05$). Macrovascular dilator function did not differ across time or between groups ($P = 0.8$).

Conclusion.—These data suggest that a community-based exercise training program improves microvascular function in individuals with well-healed burn injuries, which may be due in part to vascular remodeling.

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Author contributions

CGC conceived the research project. SAR, GM, MFJ, MH, REE, MNC, and CGC performed acquisition, analysis or interpretation of data. SAR drafted the manuscript. SAR, GM, MFJ, MH, REE, MNC, and CGC revised it critically for important intellectual content. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation, and statement that results of the present study do not constitute endorsement by ACSM.

Disclosures

The authors have no competing interests to declare.

Keywords

reactive hyperemia; vascular conductance; ischemic handgrip exercise; flow-mediated dilation

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Introduction

Numerous pathophysiological changes are present in individuals following a severe burn injury. While some of the changes resolve acutely after the injury, others may persist well beyond the initial recovery period. These maladaptations include, but are not limited to, impaired temperature regulation, decreased cutaneous sensation, decreased aerobic capacity, and functional impairments that together increase the likelihood of rehospitalization and mortality (1–7).

Arterial vascular control and function are substantially altered immediately following a burn injury (8–10), an effect that may be worsened by prolonged bedrest that can last for 6 months or more. Interestingly, these vascular changes appear to persist well beyond the recovery period. Indeed, we recently demonstrated that microvascular and macrovascular dilator function is impaired years following a burn injury (11). Moreover, this vascular dysfunction is present in individuals with as little as 20% of their body surface area having sustained a burn injury, to individuals with burn injuries covering 90% of their body surface area. While the mechanisms mediating the impairment in vasodilator function remain uncertain, it is clear that therapeutic interventions are needed to prevent and/or reverse this long-term phenotypic maladaptation within the arterial vasculature.

Exercise training remains an effective therapeutic intervention to improve the health and well-being of individuals with burn injuries. Indeed, exercise training initiated acutely after the injury or even years later can improve cardio-metabolic function (12–18). Given the high incidence cardiovascular disease and/or mortality in individuals with burn injuries (19, 20), beneficial adaptations to exercise training would likely translate to lowered long-term risk. Importantly, the effect of aerobic exercise training on vascular function in individuals with burn injuries is unknown. Investigating the impact of exercise training on vascular health could provide a holistic assessment of risk factor modification (21) and serve as a proxy for long term cardiovascular health for individuals with burn injuries. Therefore, the purpose of this study was to examine the effect of a 6-month community-based exercise training program on vascular health. To that end, we tested the hypothesis that a 6-month community-based exercise training program would reduce arterial stiffness and increase microvascular dilator function, whereas macrovascular dilator function would remain unchanged in both control subjects and individuals with well healed burn injuries irrespective of the magnitude of injured body surface area.

Methods

Subjects

This study was conducted in parallel with a larger study examining the effect of a progressive exercise training program on cardio-metabolic function in individuals with well-

healed burned injuries. Some of the results reported herein have been published previously (18).

Subject physical characteristics are shown in Table 1. Written informed consent was obtained from all subjects subsequent to a verbal and written briefing of all experimental procedures. This study and informed consent were approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas and the study was performed in accordance with the principles outlined in the Declaration of Helsinki. Individuals with burn injuries were grouped based on whether the magnitude of the initial burn injury was greater than or less than 40% of their body surface area, as previously performed by our group (11, 18, 22–24). This criterion value was determined in part by the 2007 US Army guideline (AR 40–501) indicating that individuals with burn injuries covering 40% or more of their body surface area cannot serve in the US Army. All burned subjects were studied at least 2 years post-injury. All subjects (including non-burned controls) were sedentary and had not participated in a consistent/structured exercise training regimen at any time over the prior 12 months. Medication use did not change across each subject's study duration.

Exercise Training

All subjects participated in a community-based (i.e., unsupervised) 6-month progressive exercise training program based upon the Training Impulse approach outlined by Banister, et al. (25). The exercising training protocol is described in detail elsewhere (18). Briefly, the frequency, intensity, and duration of exercise bouts gradually increased across the 6-month training period. Each bout of exercise was preceded with a warm-up period and concluded with a cool down period. Subjects chose to exercise via cycling, walking/jogging, and/or elliptical training, as long as they were able to achieve the prescribed heart rate with the employed exercise mode(s). Training intensity was individualized based each subject's heart rate responses at ventilatory threshold and maximal heart rate, both identified during a graded exercise test. Exercise intensity was increased as needed throughout the exercise training program to ensure that heart rate remained within the specified zone. Heart rate was monitored for each subject using a heart rate monitor (Polar® Vantage XL (model 145900, Polar Electro, Inc., Woodbury, NY), providing date and time stamps for onset and completion of each exercise bout, which was downloaded remotely to the investigators. Thus, heart rate responses to every exercise bout were obtained. Progressive strength training, focusing on large muscle groups, began in month 2 of the program using fitness center-based devices (both machines and free weights, as preferred by the subject). All subjects exercised in temperature controlled facilities, thereby controlling for potentially confounding influences of seasonal acclimatization in differing climates, as well as providing an increased measure of safety for thermally intolerant subjects.

Pre- and Post-exercise Training Measurements

On the day of the vascular assessments, subjects reported to the laboratory at ~8:00 AM. All testing was performed in a temperature controlled laboratory (~22 °C) and subjects were required to abstain from caffeine, nutritional supplements, alcohol, and physical activity (aside from exercise testing performed the prior day, see reference (18)) for 24 h prior the

study. Subjects were also required to abstain from over-the-counter medications, but were allowed to take prescription medications as needed and prescribed.

Blood pressure and heart rate.—Arterial blood pressure was measured from the upper arm using an automated sphygmomanometer (Tango+, SunTech Medical, Raleigh, NC, USA). Heart rate was monitored via electrocardiogram (Solar 8000i, GE Healthcare, Milwaukee, WI, USA) interfaced with a cardiometer (CWE, Ardmore, PA, USA).

Pulse-wave velocity.—Electrocardiogram and Doppler waveforms (MD6 Doppler System, Hokanson, Bellevue, WA, USA) were collected simultaneously at 50 Hz using commercially available software (Biopac MP150, Santa Barbara, CA, USA). Pulse-wave velocity, an index of arterial stiffness, was performed in accordance with established guidelines (26).

Vasodilator function.—Macrovascular dilator function was assessed via endothelial-dependent flow-mediated dilation of the brachial artery in accordance with recent guidelines (27), whereas endothelial-independent dilation was assessed via glyceryl trinitrate (GTN) mediated dilation. Microvascular dilator function was assessed simultaneously during flow-mediated dilation via post-occlusive reactive hyperemia. A pneumatic cuff (SC5D, Hokanson, Bellevue WA, USA) was placed on the forearm, immediately distal to the antecubital fossa. Arterial inflow to the forearm was occluded by rapidly inflating the cuff to 220 mmHg for 5 min (E20 Rapid Cuff Inflator, Hokanson, Bellevue WA, USA). Prior to cuff inflation, brachial artery diameter and blood velocity were recorded during a 1 min baseline period and resumed 20 s prior to cuff deflation and continued for 3 min thereafter. Subsequent to a 30 min rest period, maximal macro- and micro-vascular dilatory responses were assessed following ischemic handgrip exercise (28, 29). Intermittent isometric handgrip exercise was performed using a 3-kg load and a duty cycle of 1-s contraction and 1-s relaxation (30 contractions/min) from min 1 – 4 of 5 min forearm ischemia (as described above). Prior to ischemic handgrip exercise, brachial artery diameter and blood velocity were recorded during a 1 min baseline period and resumed 20 s prior to cuff deflation and continued for 3 min thereafter.

Brachial artery blood velocity and diameter were measured simultaneously via duplex ultrasonography. Velocity and diameter measurements were made proximal to the brachial artery bifurcation. All velocity measurements were made using a linear-array transducer (11 MHz, Phillips iE33, Andover, MA, USA) operating with an insonation angle of 60° and a Doppler sample volume that encompassed the entire vessel lumen. The ultrasound system was interfaced with a computer running custom audio-recording software (DUC²) to capture blood velocity (30). Additionally, an outline of the ultrasound transducer was marked on the skin to ensure consistent placement across time.

Data and Statistical Analyses

For pulse-wave velocity, the average transit time was calculated between a minimum of 10 R-waves and associated Doppler waveforms. Transit times from the right common carotid artery to the right femoral artery were used to determine central pulse-wave velocity.

Peripheral pulse-wave velocity was determined using transit times from right common carotid artery to the right radial artery. The distance between sampling sites was measured as a straight line and applied in conjunction with the measured transit time to the following equation: pulse-wave velocity = distance/transit time. The distance from the carotid site to the suprasternal notch was subtracted from the total distance between the suprasternal notch and the femoral site as previously recommended (31).

Blood velocities were determined from the Doppler ultrasound audio recordings using a custom intensity-weighted algorithm (DUC²), subsequent to demodulation of forward and reverse Doppler frequencies (11). Brachial artery diameter was determined using custom edge-detection and wall-tracking software (32). Blood flow was calculated as the cross-sectional area of the imaged artery multiplied by mean blood velocity and reported in ml min⁻¹. Vascular conductance was calculated by dividing blood flow by mean arterial pressure and expressed as ml min⁻¹ mmHg⁻¹. Shear rate was calculated by multiplying 8 by the quotient of blood velocity and vessel diameter and expressed as s⁻¹. Peak diameter measured during flow-mediated dilation and GTN-mediated dilation was determined using an algorithm previously described by Black and colleagues (32). Post-occlusive reactive hyperemia area under the curve was determined by averaging blood flow (determined via simultaneously acquired diameter and velocity) across 4 s bins for the initial 20 s subsequent to release of arterial occlusion and averaged across 10 s bins thereafter as previously performed in our laboratory (11). Vascular conductance was then determined for each bin to account for differences in perfusion pressure and then used to calculate peak reactive hyperemia and area under the curve by summing the product of each bin multiplied by its duration in minutes and normalized for baseline conductance.

Our primary outcome variables were analyzed using a two-way (group × time) mixed model analysis of variance with repeated measures (JMP Pro 12; SAS Institute Inc., Cary, NC, USA). Follow-up tests were performed using Tukey's post hoc procedure. Flow-mediated dilatation was assessed using the allometric modeling solution proposed by Atkinson *et al.* (33), subsequent to the determination of inadequate scaling by examining the slope of the relation between logarithmically transformed baseline and peak diameter. Shear rate area under the curve summed through peak diameter was also entered into the model as a covariate to account for changes in shear stimulus. Data are reported as mean ± SE unless stated otherwise.

Results

Exercise Compliance and Training Impulse Scores

Compliance to the prescribed exercise training bouts did not differ between groups (control, 91 ± 2 %; moderate burn injury, 88 ± 3 %; high burn injury, 88 ± 3 %; $P = 0.7$). Exercise training stimulus was quantified by calculating the total "training impulse" scores across the entire training period (25). Training impulse scores increased over the course of the 6-month exercise training program for all groups ($P < 0.05$, main effect of time). Total training impulse scores were greater for the control group (4901 ± 451 a.u.) when compared with the moderate (3442 ± 439 a.u.; $P < 0.05$) and high (3498 ± 334 a.u.; $P < 0.05$) burn injury groups.

Pulse-wave Velocity

Prior to exercise training, central pulse-wave velocity did not differ between control ($7.1 \pm 0.5 \text{ m s}^{-1}$), moderate ($7.7 \pm 1.4 \text{ m s}^{-1}$) and high ($7.2 \pm 0.6 \text{ m s}^{-1}$) burn injury groups ($P = 0.8$), nor did it differ from pre- to post-training for all three groups (control, $7.7 \pm 0.3 \text{ m s}^{-1}$; moderate burn injury, $6.5 \pm 0.3 \text{ m s}^{-1}$; high burn injury, $7.1 \pm 0.5 \text{ m s}^{-1}$; $P = 0.1$). Prior to exercise training, peripheral pulse-wave velocity did not differ between control ($7.8 \pm 0.2 \text{ m s}^{-1}$), moderate ($8.3 \pm 0.8 \text{ m s}^{-1}$) and high ($8.1 \pm 0.3 \text{ m s}^{-1}$) burn injury groups ($P = 0.8$), and was also unaffected by exercise training ($P = 0.1$).

Vasodilator Function

Brachial artery hemodynamics during the assessment of macrovascular dilator function are presented in Table 2. ANCOVA-corrected flow-mediated dilation did not differ between control or burn injury groups from pre- to post-training ($P = 0.8$). Likewise, GTN-mediated dilation of the brachial artery did not differ between groups or across time ($P = 0.9$). The maximal dilator response of the brachial artery following ischemic handgrip exercise did not differ from pre- to post-exercise training ($P = 0.9$ for interaction) for control (pre-exercise, $11.6 \pm 1.5 \%$ vs. post-exercise, $12.1 \pm 1.4 \%$), moderate (pre-exercise, $14.1 \pm 1.6 \%$ vs. post-exercise, $15.3 \pm 1.8 \%$) and high (pre-exercise, $9.0 \pm 2.1 \%$ vs. post-exercise, $10.1 \pm 1.9 \%$) burn injury groups. Microvascular dilator function, assessed as peak vascular conductance and area under the curve during post-occlusive reactive hyperemia, is shown in Figure 1. Exercise training increased peak reactive hyperemia ($P < 0.05$ for main effect of exercise), an effect that did not differ between groups ($P = 0.9$ for interaction). Likewise, exercise training increased reactive hyperemia area under the curve ($P < 0.05$ for main effect of exercise), but did not differ between groups ($P = 0.8$ for interaction). The maximal microvascular dilator response assessed as peak vascular conductance following ischemic handgrip exercise is shown in Figure 2. Exercise training increased maximal microvascular dilator capacity across all three groups ($P < 0.05$ for main effect of exercise), with the magnitude of these increases not different between groups ($P = 0.6$ for interaction).

Discussion

The purpose of this study was to test the hypothesis that a 6-month community-based exercise training program would reduce pulse-wave velocity (i.e. reduce arterial stiffness) and increase microvascular dilator function, whereas macrovascular dilator function would remain unchanged in individuals with well healed burn injuries irrespective of the magnitude of body surface area having sustained an injury. In partial support of our hypothesis, exercise training increased microvascular dilator function, an effect that appears to be mediated in part by microvascular remodeling given the increase in the maximal vasodilatory response following ischemic handgrip exercise. Neither macrovascular dilator function nor pulse-wave velocity differed from pre- to post-training for any group.

Exercise Training and Vasodilator Function

Vascular health is dependent on structural and functional characteristics that are influenced by central neural and local vascular mechanisms that regulate moment-by-moment vascular tone, but perhaps more importantly, contribute to the long term phenotypic maladaptations

associated with disease conditions (34). However, these vascular maladaptations can be slowed or even reversed by therapeutic interventions. The peripheral vascular system adapts exquisitely to exercise training via functional and structural changes (34). This “vascular conditioning” provides a unique window into the cardioprotective effects of exercise training, but independently can serve as a highly sensitive risk factor for future cardiovascular disease/events (21, 35).

Until recently, our understanding of the vascular responses associated with burn injuries was based largely on investigations focused on the acute recovery period (i.e. weeks to months after injury) or extrapolated based on simulated recovery conditions (i.e. bed rest) (36–38). However, we recently demonstrated that microvascular and macrovascular dilator function was impaired in a cohort of individuals with well-healed burn injuries. Importantly, this impairment in vasodilator function was present despite the assessment being performed years following the burn injury. The causal link between the initial burn injury and the long-term maladaptation in vasodilator function is unknown. Nevertheless, there is a clear therapeutic need to prevent and/or reverse this phenotypic maladaptation within the arterial vasculature.

We recently demonstrated that a community-based 6-month progressive exercise training program improves cardio-metabolic function in individuals with well-healed burn injuries (18). The current findings suggest that the benefits afforded by this training program extend to the peripheral microvasculature. Indeed, exercise training induced both functional (augmented post-occlusive reactive hyperemia) and structural (maximal vasodilation) adaptations, suggesting that the vascular phenotype can be conditioned in individuals with well-healed burn injuries.

Macrovascular dilator function measured via flow-mediated dilation of the brachial artery did not differ from pre- to post-exercise training in any group. Similarly, brachial artery vascular smooth function assessed via GTN-mediated dilation was unchanged from pre- to post-training. These findings should not be interpreted as a lack of adaptation at the level of the conduit vessel, but more likely reflects the timing of pre- and post-training measurements. As originally proposed by Laughlin (39), conduit vessel vasodilator function is augmented early in the adaptive response to exercise training, but will normalize subsequent to arterial remodeling (40). Thus, it is possible that we failed to capture the early adaptive response given that pre/post testing was separated by 6 months and given the absence of measurements during exercise training, which were simply not feasible in this current study given that most of the participants were not local and thus travelled to our laboratory from all over North America. Interestingly, estimates of macrovascular remodeling, baseline brachial artery diameter, and the estimated maximal brachial artery dilatory response to ischemic handgrip exercise did not differ from pre- to post-exercise training, which suggests that vascular remodeling is absent. However, these results should be interpreted judiciously as factors independent of remodeling (e.g., sympathetic control) can alter these responses. Alternatively, the lack of improvement in macrovascular dilator function, coupled with no change in resting brachial artery diameter, or the maximal brachial artery dilatory response to ischemic handgrip exercise, perhaps suggests that the exercise training stimulus was not sufficient to induce macrovascular adaptations.

Arterial Stiffness

We utilized pulse-wave velocity as a surrogate for arterial stiffness. While numerous studies have demonstrated that exercise training reduces arterial stiffness in a variety of clinical populations, we were unable to replicate this finding. It is unclear why our findings differ from prior reports, but could be related to the observation that the efficacy of exercise training to reduce arterial stiffness is influenced by the magnitude of stiffness present at the start of exercise training and is influenced by the type of training program (aerobic, weight training, combined) (41). That is, exercise training is less efficacious in individuals with relatively compliant arteries when compared to those with stiffer arteries. This is particularly important given that arterial stiffness was relatively low ($\sim 8.1 \text{ m s}^{-1}$) in both non-burn control subjects and individuals with burn injuries. Additionally, we employed an exercise training program that incorporated aerobic exercise and resistance-based strength training (18). Such combination exercise training programs appear to be less effective at reducing arterial stiffness relative to pure aerobic exercise training programs (41, 42).

Experimental Considerations

Several experimental considerations should be noted. Second, vasodilator function did not differ between non-burned control and burn injury groups prior to exercise training. This likely reflects a selection bias, in that individuals with burn injuries who were willing to enter and complete a 6-month exercise training program are generally healthier than those individuals with burn injuries who are unwilling to participate in a long-term training regimen; the latter of which tend to be on the opposite end of the health spectrum. That is, individuals with burn injuries who are willing and able to travel for testing and complete a six-month exercise training program are, in our experience, on the healthier end of the health spectrum relative to those individuals with burn injuries who are unable and unwilling to complete such an intense research study. The lack of baseline vasodilator differences between groups may also be related to non-burn control subjects being sedentary relative to the general population (as required by the study inclusion criteria to match activity levels between control subjects and burn survivors), whereas non-burn control subjects in our prior publication were recreationally active (11). Finally, in performing a post-hoc one-way ANOVA, we found that microvascular function (peak reactive hyperemia) was indeed reduced for individuals with burn injuries compared with non-injured control subjects ($P < 0.05$). This finding suggests that we are likely underpowered to detect pre-training group differences with the current data set upon including results from the training regimen. Second, as noted previously, given the challenges associated with coordinating multiple laboratory visits by participants from all over North America and recruiting challenges associated with such a unique population, we were unable to perform assessments during exercise training nor did we include a non-exercise control group. Third, we were unable to control for menstrual cycle phase or prescription medication use in our subjects, both of which have the potential to alter vascular function. Finally, vasodilator function was assessed only in the upper limb (forearm) and may not accurately represent other vascular beds such as those within the legs, which are exposed to dramatically different conditions during exercise.

Perspectives and Significance

Burn injury is a traumatic event that significantly challenges cardiovascular homeostasis. To date, research efforts have focused primarily on the acute cardiovascular changes following the initial burn injury. As a result, our understanding of the long-term cardiovascular effects of a severe burn injury is incomplete. However, recent work has advanced our understanding of the long-term maladaptations associated in burn injuries, which allows clinicians to implement proper rehabilitation therapy. In addition to its use as a novel risk factor for cardiovascular disease, peripheral vasculature function is highly responsive to aerobic exercise training and can therefore be utilized as a tool to assess vascular specific and overall cardiovascular health in individuals with well-healed burn injuries. Importantly, given the close association between microvascular function and adverse cardiovascular outcomes (35), implementing exercise training as standard rehabilitation tool for individuals with well-healed burn injuries will greatly reduce the risk for future cardiovascular morbidity and mortality.

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Figure 1.

Microvascular dilator function as assessed by peak (top panel) vascular conductance and area under the curve (bottom panel) during post-occlusive reactive hyperemia. Open bar, pre-training; black bar, post-training. * $P < 0.05$ vs. pre-training

Figure 2. Maximal microvascular dilatory capacity assessed as the peak reactive hyperemic response following 5 min of forearm ischemia combined with handgrip. Open bar, pre-training; black bar, post-training. * P < 0.05 vs. pre-training

Table 1.**Subject Characteristics**

	Control	Moderate Burn Injury	High Burn Injury
Men/women	6/5	7/6	11/8
Age (yrs)	33 ± 8	35 ± 14	42 ± 11
Height (cm)	173 ± 8	168 ± 10	170 ± 8
Heart rate (b min ⁻¹)	59 ± 4	61 ± 2	54 ± 2
Mean arterial pressure (mmHg)	85 ± 2	88 ± 3	94 ± 2 [†]
Body Mass (kg)	83 ± 24	77 ± 17	84 ± 17
Body surface area burned (%)	-	26 ± 7	59 ± 15
Years from burn injury	-	16 ± 10	17 ± 13
Medication groups, (n)			
Hypertension	1	2	1
Hypercholesterolemia	1	1	1
Hypothyroidism	2	1	1
Stimulants	2	0	0
Pain	0	3	2
Anti-inflammatory	0	1	1
Medical marijuana	0	3	2
Sedatives	0	1	1
Multivitamin	6	5	2
Antidepressant	0	2	2
Contraceptive	0	2	2
Allergy	0	3	1

Non-medication values are mean ± SD.

[†], $P = 0.07$ vs. control group

Table 2.

Brachial Artery Hemodynamics during the Assessment of Vasodilator Function

	Control		Moderate Burn		High Burn	
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training
Forearm Blood Flow (ml min^{-1})	46 $\pm$ 7	50 $\pm$ 7	44 $\pm$ 6	50 $\pm$ 13	48 $\pm$ 10	36 $\pm$ 5
Forearm Vascular Conductance ($\text{ml min}^{-1} \text{ mmHg}^{-1}$)	0.54 $\pm$ 0.08	0.61 $\pm$ 0.09	0.49 $\pm$ 0.07	0.57 $\pm$ 0.14	0.52 $\pm$ 0.11	0.41 $\pm$ 0.06
Baseline Diameter (cm)	0.405 $\pm$ 0.024	0.396 $\pm$ 0.021	0.373 $\pm$ 0.018	0.393 $\pm$ 0.022	0.394 $\pm$ 0.029	0.391 $\pm$ 0.028
Peak Diameter (cm)	0.426 $\pm$ 0.022	0.421 $\pm$ 0.020	0.395 $\pm$ 0.018	0.416 $\pm$ 0.021	0.412 $\pm$ 0.030	0.411 $\pm$ 0.029
Diameter (cm)	0.021 $\pm$ 0.003	0.025 $\pm$ 0.003	0.022 $\pm$ 0.003	0.023 $\pm$ 0.002	0.018 $\pm$ 0.004	0.020 $\pm$ 0.003
Time to peak diameter (s)	48 $\pm$ 8	43 $\pm$ 5	43 $\pm$ 4	42 $\pm$ 4	47 $\pm$ 4	52 $\pm$ 7
Shear Rate AUC	32097 $\pm$ 2624	36055 $\pm$ 2888	38767 $\pm$ 3471	38092 $\pm$ 4052	34686 $\pm$ 6156	36425 $\pm$ 3013
Flow-mediated Dilatation (%)	5.3 $\pm$ 0.7	6.2 $\pm$ 0.6	5.7 $\pm$ 0.6	5.8 $\pm$ 0.7	4.7 $\pm$ 0.6	5.0 $\pm$ 0.6
GTN-mediated Dilatation (%)	21.5 $\pm$ 1.1	20.9 $\pm$ 1.2	24.6 $\pm$ 1.4	23.1 $\pm$ 2.7	22.4 $\pm$ 1.5	20.8 $\pm$ 1.3

Values are mean $\pm$ SE. Shear Rate AUC, shear rate area under the curve through peak diameter; GTN, glyceryl trinitrate.