Assessing structural and functional response of murine vasculature to acute β-adrenergic stimulation in vivo during hypothermic and hyperthermic conditions

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ABSTRACT

Background: Because of the importance of adrenoreceptors in regulating the cardiovascular (CV) system and the role of the CV system in thermoregulation, understanding the response to these two stressors is of interest. The purpose of this study was to assess changes of arterial geometry and function in vivo during thermal and β-adrenergic stress induced in mice and quantified by MRI.

Methods: Male mice were anesthetized and imaged at 7 T. Anatomical and functional data were acquired from the neck (carotid artery), torso (suprarenal and infrarenal aorta and iliac artery) and periphery (femoral artery). Intravenous dobutamine (tail vein catheter, 40 μg/kg/min, 0.12 mL/h) was used as β-adrenergic stressor. Baseline and dobutamine data were acquired at minimally hypothermic (35°C) and minimally hyperthermic (38°C) core temperatures. Cross-sectional vessel area and maximum cyclic strain were measured across the cardiac cycle.

Results: Vascular response varied by location and by core temperature. For minimally hypothermic conditions (35°C), average, maximum and minimum areas decreased with dobutamine only at the suprarenal aorta (avg: −17.9%, max: −13.5%, min: −21.4%). For minimally hyperthermic conditions (38°C), vessel areas decreased between baseline and dobutamine at the carotid (avg: −19.6%, max: −15.5%, min: −19.3%) and suprarenal aorta (avg: −24.2%, max: −17.4%, min: −17.3%); whereas, only the minimum vessel area decreased for the iliac artery (min: −14.4%). Maximum cyclic strain increased between baseline and dobutamine at the iliac artery for both conditions and at the suprarenal aorta at hyperthermic conditions.

Conclusions: At hypothermic conditions, the vessel area response to dobutamine is diminished compared to hyperthermic conditions where the vessel area response mimics normothermic dobutamine conditions. The varied response emphasizes the need to monitor and control body temperature during medical conditions or treatments that may be accompanied by hypothermia, especially when vasoactive agents are used.

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Introduction

The cardiovascular (CV) system plays a vital role in the human body’s ability to thermoregulate to withstand physiological states [1–3]. Various pathological conditions and treatments, including sepsis [4] and the treatment of cardiogenic shock [5], can cause core body temperature to deviate from normothermia. Clinically, dobutamine is used in critical care for acute treatment of congestive heart failure, cardiogenic and septic shock, and as a pharmacological surrogate to exercise for stress tests [6–8]. There is an interest in better understanding the combined effects of temperature and dobutamine because of the detrimental consequences of decreased peripheral resistance after dobutamine administration in hypothermic patients [9,10].

The primary mechanism of a racemic mixture of dobutamine is direct stimulation of β1-adrenergic receptors in the heart to increase cardiac contractility and output. However, one enantiomer is a β2-agonist and α1-antagonist while the other is an α1-agonist, which often leads to vasodilation [11]. Conversely, temperature elicits a full-body autonomic response to maintain core body temperature. With increasing core temperature, regional changes in cerebral blood flow [12–14], increased cardiac output [15,16] and decreased total peripheral resistance due to vasodilation [15,17] have been observed.

To improve parameterization and validation of mathematical and computational models [18], recent work has used magnetic resonance imaging (MRI) to quantify geometric (cross-sectional area) and functional (Green-Lagrange circumferential strain) changes in core arteries and veins due to increases in core temperature [19,20]. Previous work by Crouch et al. [20] showed that under hypothermic conditions
(35°C) the average area was significantly smaller in the infra-
renal aorta and femoral artery by −12% and −72%, respect-
ively, and larger for hyperthermic conditions (38°C) by 1.3
and 6.0%, respectively, compared to normothermic condi-
tions (37°C). While cross-sectional area tended to increase
with temperature, with larger changes occurring inferiorly,
previous work in well-controlled and nearly identical condi-
tions, Castle et al. [21] showed that cross-sectional area at
normothermic conditions decreased with the administration
of dobutamine for the carotid, suprarenal and infra renal
aorta and iliac artery by −19%, −16%, −14% and −12%,
respectively, with larger changes occurring superiorly in the
body. For either increases in core temperature or dobut-
amine administration, the end-diastolic/minimum areas expe-
tenced larger changes than the peak-systolic/maximum areas,
resulting in changes in maximum cyclic strain. Temperature’s
effect on strain varied by location with a gen-
eral overall decrease in strain from 35 to 38°C [19,20],
whereas dobutamine caused an increase in maximum cyclic
strain for all vessels [21]. Combining these two cardiac stres-
sors is of interest because of the differential response of core
vasculature to changing temperature or administration of
dobutamine alone.

Preclinical animal models play a vital role in the advance-
mment of therapeutic development and optimization of cur-
tent treatment paradigms. It is important to understand the
results of cardiac stressors in the healthy murine condition
before studying their effects in preclinical CV disease models.
With MRI, core vasculature geometry and function can be
investigated noninvasively due to high spatial and temporal
resolution. The purpose of this study was to assess physio-
logical changes of arterial geometry and function in vivo dur-
ing thermal and β-adrenergic stress via dobutamine using
murine models and MRI. MRI data were acquired under
hypothermic (35°C) and hyperthermic (38°C) conditions at
the carotid artery, suprarenal and infrarenal aorta, iliac artery
and femoral artery of C57BL/6 male mice, prior to and during
dobutamine infusion.

We hypothesized that: (1) at hypothermic conditions
(35°C), dobutamine would not elicit changes in cross-
sectional area and strain, due to temperature-induced
vasoconstriction; and (2) at hyperthermic conditions (38°C)
cross-sectional area would decrease and strain would
increase, mirroring dobutamine responses at normothermic
conditions (37°C). To our knowledge, these data are the first
to empirically quantify the spatially and temporally resolved
response of core vasculature to dobutamine at hypo- and
hyper-thermic conditions in vivo from head-to-toe.

Methods

All experiments were carried out with local Institutional
Animal Care and Use Committee approval. Animals were
housed in a room with temperature (22 °C ± 2 °C) and humidity
(−27%) control with an alternate 12-h light/dark cycle.
Healthy adult male (13–15 weeks old, ~20 human years
[22]) C57BL/6 mice, purchased from Charles River Laboratories,
were used in this study. Male mice were chosen in this initial
study combining hypo- and hyper-thermic states with dobut-
amine stimulation because this sex showed the smallest
response to increases in core temperature in the aorta in
previous work (male: 0.019 mm²/°C vs. female: 0.024 mm²/°C,
[19]). A dobutamine dosage of 40 μg/kg of body weight
(Hospira, Inc., Lake Forest, IL) was prescribed at an infusion
rate of 2 μL/min (Cole Parmer, Vernon Hills, IL) and pre-mixed
assuming an average murine body weight of 25 g (actual
mean and SEM of animals was 26.4 ± 0.7 g). Prior to imaging,
a tail vein catheter was placed using a 30 gauge needle, con-
necte to an ~5 cm length of PE10 tubing prefilled with saline,
followed by the dobutamine solution [21]. Mice were
anesthetized with 1.25–2% isoflurane in 1 L/min of oxygen
[23]. Animals were imaged in the supine position at 7 T field
strength using a Direct Drive console (Agilent Technologies,
Santa Clara, CA) and a 40 mm inner diameter transmit-receive
volume coil (Morris Instruments, Ontario, Canada).

Figure 1 illustrates the locations investigated in this study
and a protocol timeline. CINE data were acquired in the neck
(carotid artery), torso (suprarenal and infrarenal aorta, iliac
artery) and periphery (femoral artery). The two target core
temperatures were minimally hypothermic (35°C) and minim-
ally hyperthermic (38°C), controlled within ±0.2°C using
forced convection [19]. The forced convection system
includes a rectal temperature probe (core temperature), a
heater blowing air through the bore of the magnet and over
the animal, and a custom-built proportional-integral-deriva-
tive (PID) controller (Labview, National Instruments, Austin,
TX). These temperatures were selected to avoid pathological
changes [24,25]. Baseline and dobutamine data were
acquired at all five locations for a given animal in two separate
imaging sessions, corresponding to the two target core
temperatures. Heart rate (HR) and respiration were moni-
tored (SA Instruments, Stony Brook, NY). After acquiring
baseline data at all five locations for the given target core
temperature, dobutamine infusion was initiated. After a plate-
eau in increased HR was achieved, slices planned at each of
the five locations were acquired a second time during the
infusion of dobutamine (referred to as ‘dobutamine’ in this
paper). The total imaging time for each animal was approxi-
ately 90 min with approximately 60 min of dobutamine
infusion (~120 μL infused). Time to reach maximum HR plat-
eau was 12 min of dobutamine infusion for hypothermic
state compared to 19 min for hyperthermic state.

Sagittal 2D and axial 3D acquisitions were used to plan
slices perpendicular to the carotid artery. Coronal 2D and
sagittal 3D acquisitions were used to plan slices perpendicu-
lar to the aorta, iliac and femoral arteries. A cardiac-gated
and velocity compensated 2D CINE sequence with 16 frames
was used to acquire data at each location. Parameters were
TR/TE 120/4 ms, flip angle (α) 60°, field of view (20 mm)²,
matrix 256² zero-filled to 512², zero-filled in-plane resolution
(39 μm)², slice thickness 1 mm, NEX 6.

The CINE images were analyzed for vessel cross-sectional
area and circumferential cyclic strain using an in-house semi-
automated process previously described [19,21,26]. Circumferen-
tial cyclic strain is a measurement of the repeti-
tive mechanical deformation of the vessel wall as it expands
and constricts with the cardiac cycle. Green-Lagrange circumferential cyclic strain was calculated using the following equation:

\[ E_i = \frac{1}{2} \left( \frac{P_i}{P_{\text{dias}}} \right)^2 - 1 \times 100\% \text{ with } i \rightarrow 1 - 16 \quad (1) \]

where \( P_i \) is the perimeter at a given time frame and \( P_{\text{dias}} \) is the perimeter of the vessel at end-diastole.

**Statistical analysis**

Data are reported and plotted as mean ± standard error (SEM). To test if areas (average, maximum and minimum) and maximum cyclic strain differed significantly between baseline and dobutamine at a given target core temperature and location, a two-tailed paired t-test was used. To test if the response to dobutamine \( (\text{average}_{\text{area}}_{\text{dobutamine}} - \text{average}_{\text{area}}_{\text{baseline}}) \) differed between the two temperatures for a given location, a two-tailed paired t-test was used. Two methods were used to compare the response at different locations. The response at different locations was compared using two-way ANOVA with Tukey’s post hoc test. The relative response \( (\text{average}_{\text{area}}_{\text{dobutamine}} - \text{average}_{\text{area}}_{\text{baseline}}) / \text{average}_{\text{area}}_{\text{baseline}} \) was calculated to account for size-differences between vessels and was compared between locations using two-way ANOVA with Tukey’s post hoc test. Significance was set at \( p < .05 \).

**Results**

A summary of the main results is presented in Table 1.

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**Table 1.**

| Animal Prepped | Baseline MRI | Dobutamine Infusion/HR Plateau | Dobutamine MRI |
|----------------|--------------|--------------------------------|----------------|
| Hypothermia (35°C) | - Animal anesthetized* | - Animal core temperature controlled to 35 °C using air | - Core temperature maintained at 35 °C |
| - Eye lubricant applied | - Tail vein catheter placed | - Slice planning MRI | - Core temperature infused (rate 2 µL/min) |
| - Animal positioned in RF coil | - Area and cyclic strain data acquired | - ~12 minutes of infusion before HR plateau | - Area and cyclic strain data acquired using same slice planning and parameters from baseline |

Hyperthermia (38°C)

- Animal anesthetized* | - Animal core temperature controlled to 38 °C using air | - Core temperature maintained at 38 °C |
- Eye lubricant applied | - Tail vein catheter placed | - Dobutamine infused (rate 2 µL/min) |
- Animal positioned in RF coil | - Area and cyclic strain data acquired | - ~19 minutes of infusion before HR plateau |

*two separate imaging sessions/days with order of hypo- and hyper-thermia randomized
Table 1. Summary of main findings of arterial vascular response to adrenergic and thermal stress by in vivo MRI investigation.

| Heart rate (HR) | Dobutamine resulted in an elevated HR in all mice at 35 °C (baseline: 419 ± 6 to dobutamine: 541 ± 5 beats per minute, p < .0001) and at 38 °C (baseline: 482 ± 20 to dobutamine: 594 ± 9 beats per minute, p = .0003). HR was higher at 38 °C compared to 35 °C for both baseline (p = .002) and dobutamine (p = .007). | Comparison of the response during hypothermic vs. hyperthermic conditions | The response (dobutamine-baseline) at 35 °C was compared to the response at 38 °C for vessel areas and strain. The change in areas for all locations at 35 and 38 °C is shown from head-to-toe in Figure 4. The response to dobutamine as measured by area varied between the temperatures. Statistically significant differences were seen at the carotid artery and suprarenal aorta. The change in carotid average area at 35 °C was an increase of 0.01 ± 0.01 mm² compared to a decrease of −0.04 ± 0.01 mm² (p = .005) at 38 °C. The change in carotid maximum area at 35 °C was an increase of 0.02 ± 0.01 mm² compared to a decrease of −0.04 ± 0.01 mm² (p = .004) at 38 °C. The change in suprarenal aorta minimum area at 35 °C was a decrease of −0.16 ± 0.04 mm² compared to a decrease of −0.25 ± 0.03 mm² (p = .03) at 38 °C.

Effect of dobutamine at different core temperatures, within a location | Baseline vs. dobutamine during hypothermic or hyperthermic conditions | The first comparison was baseline versus dobutamine for vessel area (average, maximum and minimum) and maximum cyclic strain. Statistically significant results for the cross-sectional area across the cardiac cycle at baseline and during dobutamine for 35 and 38 °C are shown in Figure 2. For the hypothermic condition (35 °C), dobutamine resulted in a decrease in vessel area in the suprarenal aorta by 17.9 ± 1.8% (p < .0001), 13.5 ± 3.3% (p = .005) and 21.4 ± 5.2% (p = .006) for average, maximum and minimum areas, respectively. For the hyperthermic condition (38 °C), dobutamine resulted in a decrease in vessel area in the carotid by 19.4 ± 5.7% (p = .006), 15.5 ± 6.7% (p = .04) and 19.6 ± 4.2% (p < 0.01) for average, maximum and minimum areas, respectively. In the suprarenal aorta, the vessel area decreased by 24.2 ± 2.8% (p = .0002), 17.4 ± 4.4% (p = .005) and 33.6 ± 2.2% (p < .0001) for average, maximum and minimum areas, respectively. In the iliac artery, the vessel area decreased by 14.4 ± 5.2% (p = .03) for the minimum area. 

Statistically significant results for maximum cyclic strain at baseline and during dobutamine for 35 and 38 °C are shown in Figure 3. For the hypothermic condition (35 °C), maximum cyclic strain increased with dobutamine in the iliac artery 20.3 ± 4.5% (p = .003). For the hyperthermic condition (38 °C), maximum cyclic strain increased with dobutamine in the suprarenal aorta by 21.0 ± 3.6% (p = .0006) and in the iliac artery by 17.3 ± 5.5% (p = .02). The maximum cyclic strain response at 35 °C was a decrease of −0.04 ± 0.01 mm² (p = .005) at 38 °C. The change in carotid maximum area at 35 °C was an increase of 0.02 ± 0.01 mm² compared to a decrease of −0.04 ± 0.01 mm² (p = .004) at 38 °C. The change in suprarenal aorta minimum area at 35 °C was a decrease of −0.16 ± 0.04 mm² compared to a decrease of −0.25 ± 0.03 mm² (p = .03) at 38 °C. | Effect of dobutamine at different core temperatures and across locations | To determine the effect of location on overall response, two comparisons were made: absolute response and relative response. For the absolute difference in response (Figure 4), changes in area were dependent on location for average (p = .0001/0.005; location/temp), maximum (p = .0001/NS) and minimum (p = .0001/0.007) areas. For the hypothermic condition (35 °C), pairwise comparisons were significantly different (p < .0001, all) between the suprarenal aorta (avg: −0.17 ± 0.02, max: −0.15 ± 0.04, min: −0.16 ± 0.04 mm²) and the carotid (0.01 ± 0.01, 0.02 ± 0.01, −0.001 ± 0.01 mm²), infrarenal aorta (−0.005 ± 0.02, 0.005 ± 0.03 and −0.02 ± 0.02 mm²), iliac artery (0.006 ± 0.01, 0.03 ± 0.01 and −0.01 ± 0.01 mm²) and femoral artery (0.006 ± 0.004, 0.007 ± 0.005 and −0.002 ± 0.003 mm²). For the hyperthermic condition (38 °C), pairwise comparisons were also significantly different (p < .001, all) between the suprarenal aorta (avg: −0.23 ± 0.03, max: −0.19 ± 0.04 and min:
and the carotid (−0.04 ± 0.01, −0.04 ± 0.01 and −0.03 ± 0.01 mm²), infrarenal aorta (−0.023 ± 0.01, −0.02 ± 0.01 and −0.02 ± 0.01 mm²), iliac artery (−0.008 ± 0.006, 0.01 ± 0.01 and −0.02 ± 0.006 mm²) and femoral artery (−0.005 ± 0.009, −0.002 ± 0.01 and −0.006 ± 0.008 mm²).

Strain responses were not dependent on location (Figure 5). However, the vessels varied in the magnitude of the change between 35 and 38 °C. For example, the carotid, suprarenal aorta and femoral artery had a larger increase during hyperthermic conditions, while the infrarenal aorta and iliac artery had a smaller increase.

Size-differences between the vessels were accounted for by calculating the relative response. The relative changes for average, maximum and minimum areas for all locations at 35 and 38 °C are shown in Figure 6. All relative changes in area were dependent on location and temperature for average (p = .004/.003; location/temp), maximum (p = .02/.009) and minimum (p = .004/.01) areas. For average area, pairwise comparisons were significantly different at 35 °C between the suprarenal aorta and iliac artery (−0.18 vs. 0.07, p = .03) and the suprarenal aorta and femoral artery (−0.18 vs. −0.09, p = .003). For minimum area, significant differences occurred at 35 °C between the suprarenal aorta and iliac artery (−0.21 vs. 0.14, p = .02). For maximum area, significant differences occurred at 35 °C between the suprarenal aorta and iliac artery (−0.14 vs. 0.17, p = .03).

Discussion

Two CV stressors, deviations from normothermia and dobutamine administration, have been combined in this study. Because of the importance of adrenoreceptors in regulating the CV system and the role of the CV system in thermoregulation, understanding the response to these two stressors is of interest. To our knowledge, these data are the first to empirically quantify the spatially and temporally resolved
response of arterial vasculature to a pharmacological stressor at different core body temperatures. The response to dobutamine, as measured by changes in vessel area, was diminished during hypothermic conditions while the response during hyperthermic conditions mimicked normothermia [21]. For both temperature conditions, dobutamine resulted in elevated HR consistent with previous findings [27,28]. The hypothermic condition resulted in a slightly larger increase in HR of 29% compared to an increase of 23% in the hyperthermic condition, likely due to an increase in baseline HR at 38°C [19,29]. Although not statistically significant for all vessels, dobutamine-induced decreases in area were more consistent across location during hyperthermic conditions. The suprarenal aorta exhibited distinct and greater decreases during both hypothermic and hyperthermic states. The unique response of the suprarenal aorta may be due to its position as the most superior vessel located below the heart. Another factor that may be influencing results at the suprarenal aorta is the influence of the gut. Interest in the brain-gut connection has grown after research has revealed that the enteric nervous system, coined the ‘second brain’, controls more than just digestion [30,31]. Due to the large nervous network, this location may be more susceptible to

Figure 3. Maximum cyclic strain across the cardiac cycle for suprarenal aorta (left) and iliac artery (right) at baseline and dobutamine for two core body temperatures 35 and 38°C (n = 8 adult male mice). Strain increases from baseline to dobutamine for the iliac at 35°C and both vessels at 38°C. Significance set at p < .05. Comparing baseline to dobutamine at a given location and temperature (*).

Figure 4. The response to dobutamine (dobutamine – baseline) for average, minimum and maximum areas at 35°C (left) and 38°C (right) (n = 8 adult male mice). Comparing response between 35 and 38°C at a given location, e.g., compare response at 35 to response at 38 for the suprarenal aorta (A). For a given temperature, the three responses at all other locations were significantly different from the corresponding values at the suprarenal aorta (#). Significance set at p < .05.
dobutamine. Further studies in the connection of the enteric nervous system and thermoregulation and dobutamine could provide interesting results.

Data presented here show that the vessel area response to dobutamine during minimally hyperthermic conditions mimics previously published data acquired during normothermic conditions. For the carotid artery, the relative area response was nearly identical (−20% at 38°C vs. −19% at 37°C, respectively). At the suprarenal location, the relative area response was larger during hyperthermic conditions (−24% vs. −16%, at 38 and 37°C, respectively). For the infrarenal and iliac locations, the relative area response was smaller (infrarenal: −7% at 38°C vs. −14% at 37°C; iliac: −6% at 38°C vs. −12% at 37°C). Dobutamine-induced decreases in the average cross-sectional area of the core arteries during normothermic conditions are consistent with redistribution of blood to the skin/periphery due to dobutamine’s vasodilatory effects [9,21]. Conversely, cross-sectional area of the core arteries increases with increasing temperature, paralleling hyperthermia-induced vasodilation known to occur in the skin/periphery [19,20]. Comparing these recently published results with data presented here, one can begin to estimate the seemingly opposing factors of changes in core temperature and dobutamine administration on core arteries. For example, Crouch et al. [20] quantified an ~4%, 1% and 6% increase in area for the carotid artery, infrarenal aorta and femoral artery, respectively, when core temperature is increased from 37 to 38°C. Here, for hyperthermia with dobutamine relative to hyperthermia alone we show a ~20%, 7% and 5% decrease in area for the same vessels, respectively. This implies that the vasodilatory effects of dobutamine on downstream vasculature outweigh the local effects of temperature. This balance becomes less evident in the more superficial vessels (i.e., the femoral artery), which could be related to fewer vessels downstream to be dilated by dobutamine and/or the fact that these vessels, themselves, play a larger role in heat exchange with the environment.

Dobutamine administration during hypothermia resulted in smaller or no decreases in area for the carotid, suprarenal and infrarenal aorta compared to hyperthermic conditions.

![Figure 5](image1.png)

Figure 5. The response to dobutamine (dobutamine – baseline) for maximum cyclic strain at 35 and 38°C (n = 8 adult male mice). Strain tended to increase from baseline to dobutamine. Comparing response between 35 and 38°C at a given location (NS); comparing response at 35 or 38°C between locations (NS). Significance set at p < .05. NS: not significant.

![Figure 6](image2.png)

Figure 6. The relative response to dobutamine for average, minimum and maximum areas at 35°C (left) and 38°C (right) (n = 8 adult male mice). For a given temperature, comparing the relative response of the suprarenal aorta to corresponding values at other locations (#). Significance set at p < .05.
Crouch et al. [20] also demonstrated that the cross-sectional area of some core arteries decreases due to decreases in temperature, paralleling hypothermia-induced vasoconstriction known to occur in the skin/periphery. For example, while there was a 7% increase for the carotid artery at 35°C compared to 37°C, conversely, the areas of the infrarenal aorta and femoral artery decreased by 11% and 72%, respectively. Here, we show a 5% increase in area at the carotid, no change at the infrarenal aorta and a 13% increase in the femoral artery when dobutamine is applied at 35°C. This suggests that reductions in area of the core arteries due to hypothermia are mitigated by the application of dobutamine. Similarly, Oung et al. [10] showed an increase in vaso-dilation from dobutamine during hypothermic conditions compared to normothermic conditions. Focusing on the femoral artery, the difference between a large reduction in area due to hypothermia, to minimize heat loss to the environment [15,17,19], and an enlargement when dobutamine [9] is applied during hypothermia would be hypothesized to cause further decreases in core temperature due to increased heat exchange with the environment. However, these structural changes are not necessarily indicative of blood flow changes. In addition to blood pressure measurements, laser Doppler imaging and phase contrast MRI could be used to determine whether changes in subcutaneous perfusion and blood flow velocity and volume, respectively, are accompanying geometric alterations.

Circumferential cyclic strain is a calculation of vessel deformation across the cardiac cycle [32]. Reductions in strain can accompany the onset of pathology [33–35]. Consistent with previous work [20], baseline strain was qualitatively larger during hypothermic conditions compared to hyperthermic conditions. Like normothermia [21], maximum cyclic strain increased with dobutamine during both hypothermic and hyperthermic conditions, reaching significance for some core arteries. Notably, the elastic arteries (carotid artery, aorta and iliac artery), which act to dampen the pulsatility of flow from the heart through expansion and elastic recoil [36], had qualitatively greater increases in maximum cyclic strain (1.5–6 fold larger) compared to the only muscular artery studied in this work (femoral artery).

The adenosine A1 receptors which are involved in the regulation of body temperature, HR and locomotion activity [37] are likely interacting with the adrenergic receptors stimulated by dobutamine in this work [38] causing a varied vascular response during the hypo- and hyper- thermal conditions as well as differences across locations. Previous in vitro studies using isoproterenol, a β-adrenoreceptor specific agonist, show a vasodilatory effect in the core vessels. However, studies using isolated vessels cannot account for blood flow redistribution due to changes in downstream resistance resulting from vasodilation [39]. Changes in downstream resistance may be caused by the response of the microcirculatory system to the administration of dobutamine, leading to increased pressure gradients/drops within the arterial system. Chruscinski et al. [39] did show that the distribution of β1 and β2 receptors varied by location, and this could partially explain the location-dependent response seen in this study and may also affect microcirculatory flow. In future studies, the noninvasive methods established in this work can be combined with more specific reagents to determine the contribution of receptors and control mechanisms for both thermoregulation and β-adrenergic stimulation.

While hypo- and hyper-thermia have been used as therapeutic treatments, in relation to surgery, hypothermia due to anesthesia has been associated with increases in surgical site infection, transfusions, and length of hospital stays, as well as delayed wound healing [40,41]. A thorough review of more successfully managing body temperature intra- and peri-operatively during abdominal surgery revealed improved outcomes [42]. However, there are no guidelines on when, where on the body, or how to monitor and control body temperature intraoperatively [43]. Critical care treatment may require the use of anesthesia and/or dobutamine when the patient already has an altered core temperature. Here, our data suggest that the addition of vasoactive agents when the patient is already hypothermic likely compromises the ability of the patient to achieve normothermia due to the role the CV system plays in thermoregulation. Put more simplistically, a hypothermic patient given dobutamine will drop further into hypothermia, potentially exacerbating poor outcomes. Under such circumstances, core temperature monitoring is even more important and likely necessitates prolonged monitoring and supplementary temperature control.

Although we did not have saline control in this study; previous studies administering similar volumes of saline demonstrated minimal effect in the heart [44] or the vasculature [21] as compared to dobutamine. Regarding potential effects of isoflurane on vasculature, Crouch et al. [20] showed minimal changes in vasculature or HR after a two-hour anesthesia exposure. Maximizing the number of anatomical locations, while minimizing blood volume increases due to infusion and time under anesthesia, necessitated the foci on hypo- and hyper-thermic conditions. Hence, normothermic data were not included in this study. However, the metrics of our study have been shown to be reproducible in the arteries of small-animal preclinical models during normothermic baseline conditions, even across laboratories, field strengths and modalities [14,31]. Dobutamine response also varies between mice and humans, particularly in the heart, with human studies showing stroke volume changes [11] whereas these changes are not seen in the mouse [27]. Human studies would be necessary to determine if dobutamine response in the vasculature is consistent across species.

In conclusion, this study provides quantitative insight into CV responses to two clinically relevant stressors, administration of dobutamine and variation of core temperature, while illustrating an innovative noninvasive approach using MRI. To our knowledge, these data are the first to empirically quantify the spatially and temporally resolved response of core vasculature to dobutamine at hypo- and hyper-thermic conditions in vivo from head-to-toe. The study was performed in healthy male mice and not a specific disease model. However, stressing the CV system can reveal deficits that otherwise remain undetectable at rest. Therefore, these initial
data for healthy animals subjected to two cardiac stressors can be used to compare future measurements from disease models, such as cardiac failure or sepsis, to quantify early deficits, thereby helping to improve our understanding of how changes in core temperature interact with a clinical standard of treatment. Our data show that the response in core vasculature depends on anatomical location and varies for hypothermic and hyperthermic conditions. The results presented here also provide foundational data (geometry of the vessels) to begin coupling empirical values of the physiological response to temperature and dobutamine with computational fluid dynamics modeling to better understand how the CV system responds to stress. A better understanding of how the CV system responds to these two stressors, independently and combined, could provide motivation for further clinical studies on the effects of temperature and adrenergic stress on core vasculature.

Ethics approval and consent to participate
All experiments were carried out with University of Michigan Institutional Animal Care and Use Committee approval.

Availability of data and material
The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Disclosure statement
The authors report no conflicts of interest.

Author contributions
ACC and PEC conceived and designed the study; ACC, PEC, LNF collected and analyzed data; ACC and PSC performed statistical analysis and interpreted the data; ACC and JMG wrote the paper; ACC, PEC, UMS, and JMG critically revised the paper; all authors gave final approval of the paper.

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