Lidocaine Does Not Affect Conducted Vasodilation in Humans

Jacey Tuura[1], Sushant Ranadive[2,3], Timothy Curry[3], Michael Joyner[3]

[1]Biology, Winona State University, [2]Kinesiology, University of Maryland, [3]Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA

Introduction

Rapid vasodilation is studied extensively in skeletal muscle contractions, and vasodilation responses resulting from the action of muscle contractions can be conducted via the microcirculation starting in the small arterioles close to the capillaries and ascending into upstream feed arteries[1,2,3]. There are no current pharmacological tools that dependably block or attenuate vascular conducted responses in humans, but there is some evidence that propagated dilation was blocked by the local anesthetic lidocaine in animal studies[4]. If lidocaine can successfully block conducted dilation in humans, it could be used to address many issues related to skeletal muscle blood flow and metabolic control during exercise. This is significant because the mechanisms for skeletal muscle blood flow in response to exercise are poorly understood[5]. **The aim of the study was to determine if lidocaine administration alters the vasodilator response to a brief forearm contraction**. Three different doses of lidocaine at 1, 2, and 5 μg/100dL/min were infused into the brachial artery via a 20 ga catheter. A single muscle contraction (SMC) at 40% of maximum voluntary contraction (MVC) was performed and forearm blood flow (FBF) was determined from brachial artery diameter and mean blood velocity measured using Doppler ultrasound. Forearm vascular conductance (FVC) was calculated from blood flow (ml/min) and blood pressure (mmHg). Total vasodilator responses with and without lidocaine did not show any significant differences at any dose. Change (Δ) in FVC with saline vs. 5 μg/100mL lidocaine infusion values (206 ± 33, 210 ± 27 mL·min^{-1}·100mmHg^{-1}, respectively) suggests that there was no significant change between differing drug doses.

Experimental Timeline

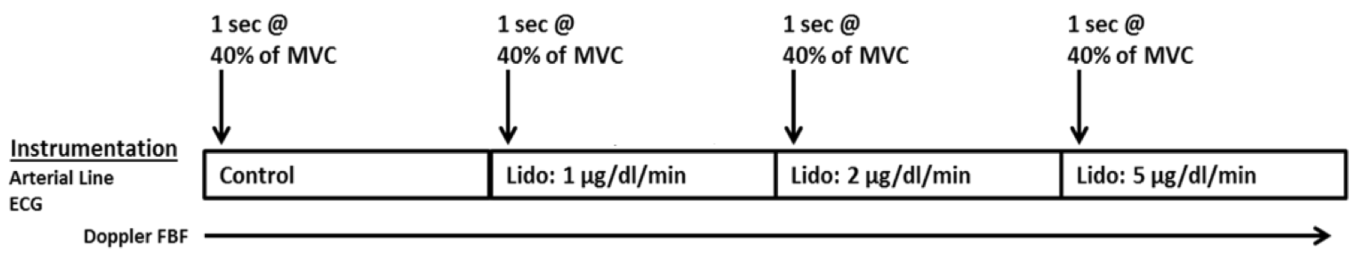


Figure 1. Timeline for experimental protocol. The participant was instructed to perform a 1s contraction at 40% of MVC, followed by 5 minutes of recovery. Doses were increased after each 5 minute session and repeated SMC.

References

1. Jensen LJ, Holstein-Rathlou NH, The vascular conducted response in cerebral blood flow regulation. Journal of Cerebral Blood Flow & Metabolism, 2013. 33: 649-656.
2. Sinkler SY, Seal SS, Rapid *versus* slow ascending vasodilation: intercellular conduction *versus* flow-mediated signaling with tetanic *versus* rhythmic muscle contractions. J Physiol, 2017. 23: 7149-7165.
3. Joyner MJ, Casey DP, Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. Physiol Rev, 2015. 95: 549-601.
4. Duling BR, Berne RM, Propagated vasodilation in the microcirculation of the hamster cheek pouch. Circ Res, 1970. 26: 163-170.
5. Casey DP, Walker BG, Ranadive SM, Taylor JL, Joyner MJ, Contribution of nitric oxide in the contraction-induced rapid vasodilation in young and older adults. J Appl Physiol, 2015. 115(4): 446-455.

Methods

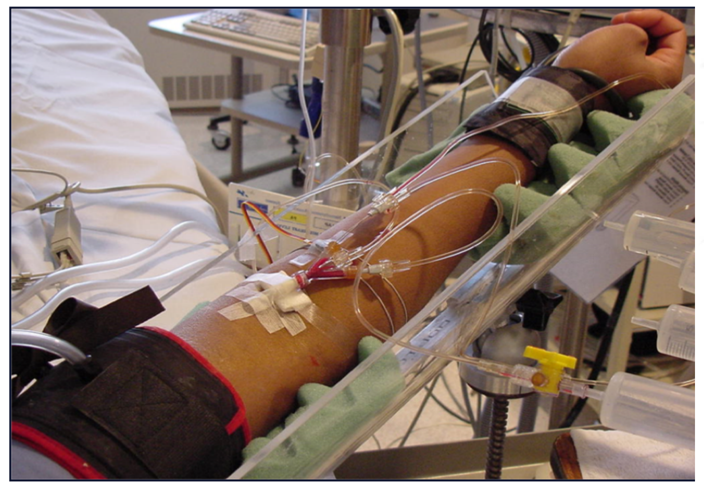


Figure 2. Standard instrumentation setup for brachial arterial catheter placement in a human subject. A strain gauge was placed around the forearm for measurement of volume changes following saline (baseline) and lidocaine infusion.

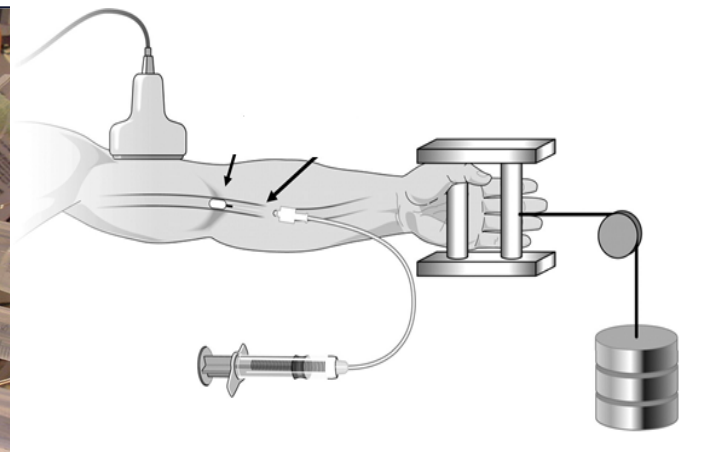


Figure 3. Flow-mediated dilation technique using Doppler ultrasound and a handgrip device set to 40% of MVC. The participant was infused with saline and the respective dose of lidocaine with ultrasound guidance to view brachial artery responses.

- 10 healthy human participants between the ages of 18-40 years old who fasted for 4 hours prior to the study were instrumented with a 3-lead ECG to measure heart rate. A 20 ga catheter was placed in the brachial artery under aseptic conditions for beat-by-beat blood arterial monitoring and drug infusions.
- A Doppler ultrasound image was taken of the brachial artery in the subjects' arms. Forearm volume was also measured via volume displacement and a maximum voluntary contraction was performed using a handgrip dynamometer.
- FBF was determined by measurements of brachial artery mean blood velocity (MBV) and vessel diameter. The echo-Doppler, a hand-held 10.5 MHz linear probe operating in B-mode, was positioned over the brachial artery and blood flow was calculated as FBF = MBV x r^2, where r is the vessel radius. FVC was then calculated as FVC = FBF/MAP x 100, expressed in mL/min/100mmHg.
- Forearm tissue volume (FAV) was used to determine the rate for drug infusion for saline and lidocaine. Subjects performed a single 1 second contraction at 40% of MVC three times over the study period with 5 minutes of rest between the respective lidocaine infusions of 1, 2, and 5 μg/100mL (Figure 1).

Hemodynamic Responses

	Saline (μg/dL)	Lidocaine 1 (μg/dL)	Lidocaine 2 (μg/dL)	Lidocaine 5 (μg/dL)
Baseline	52.09 ± 9.57	40.00 ± 4.58	45.83 ± 3.97	43.02 ± 3.41
Peak	258.1 ± 41.59	223.0 ± 25.67	269.6 ± 37.37	252.9 ± 28.02
ΔFVC	206.0 ± 33.49	183.0	223.8 ± 34.5	209.8 ± 26.57
Area under the Curve (AUC)	5820 ± 1110	4933 ± 580	6116 ± 1055	4821 ± 512

Table 1. Values are means ± SEM for all 10 subjects. Lidocaine administration had no statistically significant effects on FVC or FBF during exercise.

Change in Vasodilatory Responses

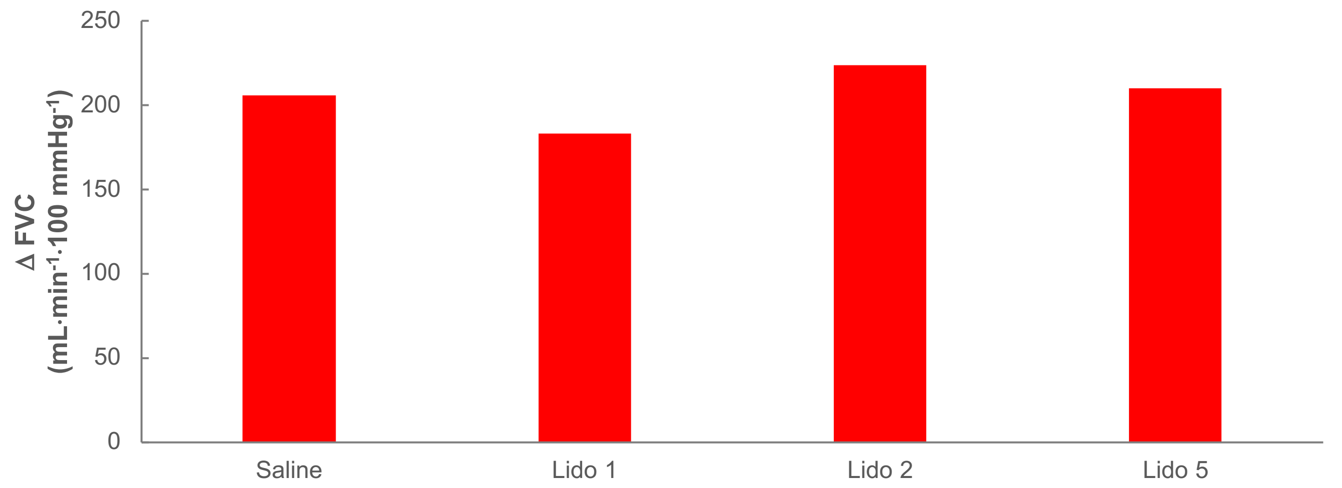


Figure 4. Change in FVC after a brief SMC during sustained drug infusion was not significantly different between saline and lidocaine doses. Deltas were calculated by subtracting resting baseline FVC from post-contraction FVC.

40% MVC Single Contraction

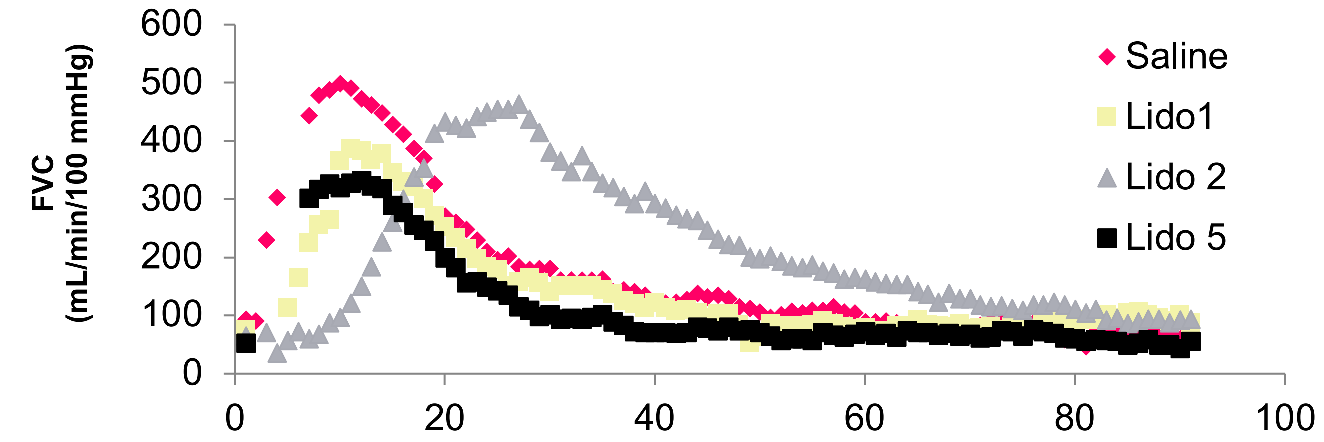


Figure 5. Representative response of one subject: FVC and cardiac cycle post-single muscle contraction following sequential infusions of saline (control) and lidocaine (1, 2 and 5 μg/100mL)

Discussion

- There is a possibility that vasodilation occurs via the myogenic response of vascular smooth muscle or within the perivascular nerve plexus, but results do not lead to a definitive conclusion.
- Lidocaine as a pharmacological tool could potentially play a role in exploring skeletal muscle blood flow in response to exercise, but the mechanisms for this are poorly understood[5].
- Exercise hyperemia in conjunction with the drug lidocaine may not be the answer in order to see the effects of vasodilation in human subjects.
- The vasodilator responses to exercise during lidocaine and saline infusion were not similar to the animal model findings and should be investigated further to make any conclusions[4].

Conclusions

- Rapid dilation is not blocked or attenuated by lidocaine in humans and further studies are needed to understand regulation of skeletal muscle blood flow.

Acknowledgements

Special thanks to: our study volunteers, the Integrative Human Physiology Lab, and the staff of the Clinical Research and Translational Unit at St. Mary's Campus, Mayo Clinic.
Funding Information: National Institutes of Health Research Grants HL-119337

MAYO CLINIC

Title Safe Area: Title text should appear within this area

Author/Affiliation Area: Authors, affiliations and subbrand names should snap to the top of this area and flow downward.

Brand Safe Area: '
safe area for the log
patterns, high-contra
ng
gh

e
fi
g
is

er provides a brand
os, illustrations,
within this area.
iation may be

Methods

- Healthy human participants between the ages of 18-40 years old who fasted for 4 hours prior to the study were instrumented with a 3-lead ECG to measure heart rate. A brachial artery catheter was placed under aseptic conditions for beat-by-beat blood arterial monitoring and drug infusions.
- A Doppler ultrasound image was taken of the brachial artery in the subjects' arms. Forearm volume was also measured via volume displacement and a maximum voluntary contraction was performed using a handgrip dynamometer.
- Forearm blood flow (FBF) was determined by measurements of brachial artery mean blood velocity (MBV) and vessel diameter. The echo-Doppler, a hand-held 10.5 MHz linear probe operating in B-mode, was positioned over the brachial artery and blood flow was calculated as FBF = MBV x r^2, where r is the vessel radius. Forearm vascular conductance (FVC) was then calculated as FVC = FBF/MAP x 100, expressed in mL/min/100mmHg.
- Forearm tissue volume (FAV) was used to determine the rate for drug infusion for saline and lidocaine. Subjects performed a single 1 second contraction at 40% of MVC three times over the study period with 5 minutes of rest between the respective lidocaine infusions of 1, 2, and 5 μg/100mL (Figure 3).

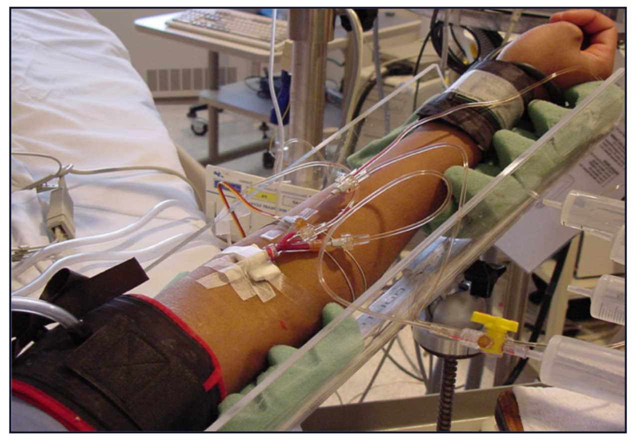


Figure 1. Standard instrumentation setup for brachial arterial catheter placement in a human subject. A strain gauge was placed around the forearm for measurement of volume changes following saline (baseline) and lidocaine infusion.

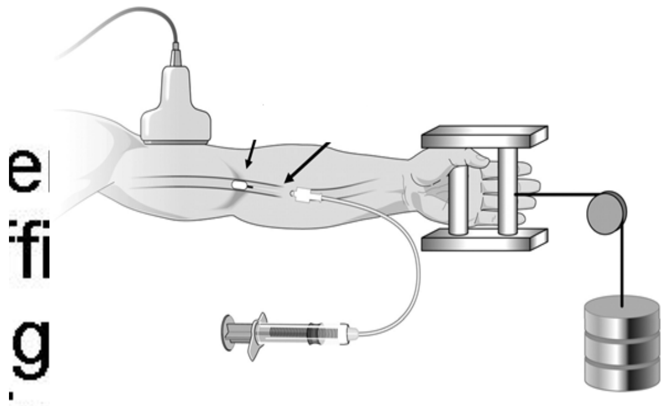
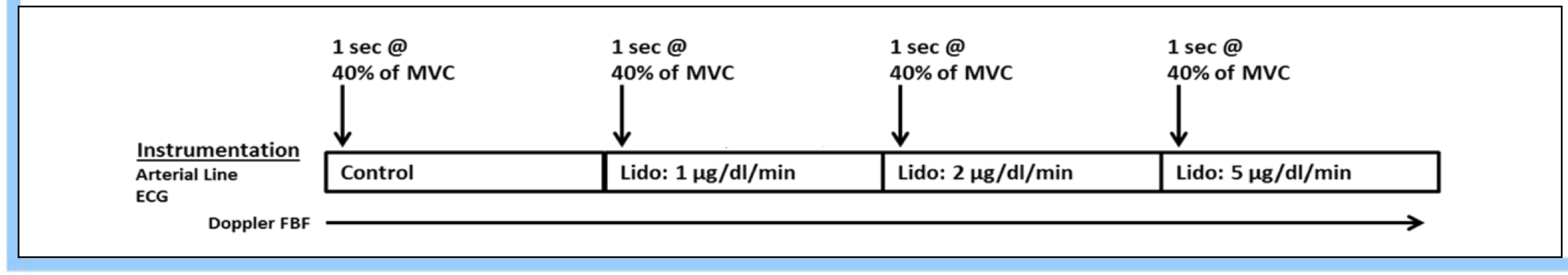


Figure 2. Flow-mediated dilation technique using Doppler ultrasound and a handgrip device set to 40% of MVC. The participant was infused with saline and the respective dose of lidocaine with ultrasound guidance to view brachial artery responses.

a: Research text, figures, tables and graphs should appear
lo photos, illustrations, patterns, high-contrast backgrounds,
lowed in the margins.

s in the template when possible.

Figure 1. Timeline for sequence of events for each subject. The participant was instructed to perform a 1s contraction at 40% max, followed by 5 minutes of recovery. Doses are increased after each 5 minute session and repeat the MVC.



Copyright Line: Copyright graphic should appear at bottom right under last text/figure box. Recommend graphic be placed no more than 1.5" from bottom of poster.