Reply: Letter to Editor

Non-invasive assessment of carotid arterial wave speed and distensibility

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To the Editor: We would like to thank Maynard et al. for their interest in our work and raising important questions with a Letter to Editor. We are also please to reply as follows.

Comparisons

First of all, we are not aware of any studies that directly measured local wave speed (c) in similar exercise conditions to those performed in our study. This indeed limits the ability to compare our results with those found previously by other investigators. Specifically, the literature offered by Mynard et al., may not enable a fair scientific comparison, for several reasons. At the level of timing, Mutter et al. (10) measured c post aerobic exercise, whilst in our work c was measured during heavy exercise. In fact, the trend of our results agree with that of (10) at > 5 minutes post-exercise with c returning to control values. Further, the works of both Rakobowchuk et al. (14) and Babcock et al. (1) report c values at rest before and after exercise but not during exercise; an important aim and novel contribution of our present work.

Several additional differences between our study and those of (14) and (1) relate to the cohorts involved and methodology used in determining c. Participants of our study (13) comprised of exclusively young male athletes, whereas, the cohorts participating in those two studies were recreational active in (14) and a mix that included both athletes and inactive in (1). In relation to determining c, the studies suggested in the Letter to Editor for comparisons used different fundamental assumptions that limit a direct comparison. Whilst the lnDU-loop method assumes unidirectional waves in the earliest period of systole, it is not subject to the calibration and methodological issues of applanation tonometry, which involves forcefully flattening an arterial segment by pushing against a bone. In the case of the carotid artery, this is particularly difficult during exercise. In addition, the potential variable force applied by the operator(s) presents a question on the reproducibility. Therefore, these user-dependent issues associated with applanation tonometry make it difficult to use the results in (1) as "the" carotid PWV reference value. One distinct advantage of the lnDU-loop method, however, is that it provides a means for determining c using measurements, which are direct and local to a specific arterial segment. It is worth noting that we have previously demonstrated the reproducibility of the lnDU-loop method (12) and the results agree with those in (13). At 40 % of maximum workload c values of the current study is 9.5 m/s closely agreed with 9.7 m/s during exercise in (12).

Furthermore, classical work by Bramwell and Hill (5), Histand and Anliker (7) have established that c is a function of pressure in several arteries of various mammals, and of flow velocity in (7). Table III – Fig. 9 in (5) shows an increase of 50% in pressure leads to 100% increase in c. Similar patterns could be seen in Fig. 5 in (7). In our work (13) systolic pressure increased by 45%, carotid flow by 50%, ΔU by 93%, heart rate by 200%, and cardiac output by 270%, all at 70% workrate intensity compared to at rest condition. These hemodynamic changes resulted in an increase in ΔD by 58% and the carotid wall during exercise at that level must have experienced a significant increase in both wall stress and Young's modules. Therefore, 136% increase in c under such hemodynamic conditions is not very surprising.

lnDU-loop: Theoretical considerations

Secondly, the notion of the lnDU-loop method (6) is prone to increasing 'true' c in the carotid artery may not be supported theoretically. According to (6) c can be calculated as

$$\boldsymbol{c = \frac{1}{2}\frac{dU_{\pm}}{dlnD_{\pm}}} \qquad \textbf{(1)}$$

A reflected wave in the carotid artery that is compression in nature (BCW) as generally accepted would decrease the term dU in equation (1), leading to a decrease of c. We acknowledge that a backward decompression wave (BDW) arriving in early systole would increase dU leading to a possible increase in c, however, we are not aware of any published work to suggest the existence of BDC in the carotid artery in early systole.

Further, the same notion is not supported by the literature and it is in a diametrically opposite position with findings of Segers et al., who reported a decrease in c when using the lnDU-loop method, also at the carotid artery (15). Furthermore, this notion is not supported experimentally as we validated the method in vitro (9) and reported the possibility of decreasing 'true' wave speed, inline with the theoretical expectations, in the presence of a large positive wave reflection; such as those resulting when the measurement and positive reflection sites are in close proximity (3).

Furthermore, we believe that using c determined by the lnDU-loop method with the Bramwell-Hill (BH) equation to derive pulse pressure may not be theoretically permitted. This is because such approach will violate the constituents involved in deriving equation (1). The lnDU-loop equation for determining c deals with differential quantities, which are the microscopic elemental changes of flow velocity and diameter, respectively, dU and dD, and their inter-changeability with macroscopic changes of pressure and area (ΔP and ΔA) such as those used in the BH equation (2) has to be exercised with caution as it will likely lead to errors.

$$\boldsymbol{c = \frac{1}{\sqrt{\rho \frac{1}{A} \frac{\Delta A}{\Delta P}}}} \qquad \textbf{(2)}$$

For equation (1) to be valid in determining c, waves must be unidirectional, hence the choice of using the microscopic parameters in early systole, when it maybe reasonable to assume only forward waves exist. However, with a mix of forward and backward waves in mid-to-late systole, the equation loses its validity to determine c. It follows; using c determined with the lnDU-loop in equation (2) for the purpose of establishing pulse pressure ΔP, as proposed by Maynard et al., must be related to the diameter changes corresponding (and restricted) to the duration of the initial linear portion of the loop. Otherwise, it renders the calculations outside the validity domain of equation (1), leading to errors as evidenced by the unrealistic ΔP of 500 mmHg calculated during exercise in the Letter to Editor at hand.

If c is determined using equation (1) and is used with the BH equation, it is possible to calculate the change in pressure (ΔP^*) that is related to the initial linear portion of the lnDU-loop by rearranging the BH equation terms

$$\boldsymbol{\Delta P^* = 2\rho c^2 \, \Delta D^* / D_i} \qquad \textbf{(3)}$$

where ΔD^* and D_i are the macroscopic change in diameter corresponding to initial linear portion of the lnDU-loop and the initial diameter, respectively. Using this approach gives average values across our cohort of $\Delta P^* = 18 \pm 6$ mmHg at rest and 92 ± 65 mmHg at 70% Wmax, which are vastly different from those obtained using ΔP and ΔD over the whole cardiac cycle being 78 ± 31 mmHg at rest and 545 ± 366 mmHg at 70% W_{max}. The latter values are close to those calculated by Maynard et al., from our average values in (13).

<u>Velocity profile</u>

We agree with Maynard et al. that mean velocity is difficult to measure using Doppler ultrasound. However, the authors appear to have assumed incorrectly that we use maximum velocity in the calculations of c. We have used mean velocity in this and in our earlier work (2). Even if the ultrasound scanner being used for data acquisition does not provide mean velocity, we determine it by tracing the outer, inner envelopes of the ultrasound, and use the mean waveform as shown **Fig 1** of (4). It is worth noting that both the maximum and mean velocity waveforms are usually parallel; thus provide the same slope of the initial linear part of the lnDU-loop. We have also compared the results of using mean vs. maximum velocity waveforms in determining c using the lnDU-loop method and found no difference (unpublished data). This observation is in line with the theoretical understanding of a blunt flow profile in large arteries; i.e negligible difference between mean and maximum velocity. Whilst we acknowledge that for a parabolic profile of fully developed Poisuelle flow, the maximum is approximately double mean velocity, a conservative entrance length (L) to reach fully developed flow, L= 0.05ReD; where Re is carotid Reynold's number = 500 and D is an average carotid diameter = 0.008m. Consequently, L will need to be 20 cm, which is longer than most human common carotid arteries.

We also agree with Maynard et al. that the method proposed by Kowalski et al. (8) maybe practical, but in our opinion robustness remains to be widely demonstrated. This is because the pressure is measured non-invasively with considerable variation between devices (11), and linearity assumptions are made in the calibration involving two different vessels of different locations, dimensions and wall mechanical properties.

In conclusion, in the absence of direct comparable measurements of wave speed in the carotid artery during exercise, and the lack of evidence of backward decompression wave existing in early systole, the lnDU-loop technique should not be claimed to increase wave speed. Such claims are not supported theoretically or experimentally. Also, mixing the microscopic and macroscopic terms of the lnDU-loop and Bramwell and Hill techniques may not be allowed for the purpose of calculating pulse pressure, as this is likely to introduce substantial errors.

References

1. **Babcock MC**, **Lefferts WK**, **Hughes WE**, **Fitzgerald KL**, **Leyer BK**, **Redmond JG**, **Heffernan KS**. Acute effect of high-intensity cycling exercise on carotid artery hemodynamic pulsatility. *Eur J Appl Physiol* 115: 1037–1045, 2015.
2. **Borlotti A**, **Khir AW**, **Rietzschel ER**, **De Buyzere ML**, **Vermeersch S**, **Segers P**. Noninvasive determination of local pulse wave velocity and wave intensity: changes with age and gender in the carotid and femoral arteries of healthy human. *J Appl Physiol* 113: 727–35, 2012.
3. **Borlotti A**, **Li Y**, **Parker KH**, **Khir AW**. Experimental evaluation of local wave speed in the presence of reflected waves. *J Biomech* 47: 87–95, 2014.
4. **Borlotti A**, **Vermeersch S**, **Rietzschel E**, **Segers P**, **Khir AW**. A comparison between local wave speed in the carotid and femoral arteries in healthy humans: application of a new method. *Conf Proc IEEE Eng Med Biol Soc* 2010: 2857–60, 2010.
5. **Bramwell JC**, **Hill A V.** The Velocity of the Pulse Wave in Man. *Proc R Soc B Biol Sci* 93: 298–306, 1922.
6. **Feng J**, **Khir AW**. Determination of wave speed and wave separation in the arteries using diameter and velocity. *J Biomech* 43: 455–462, 2010.
7. **Histand MB**, **Anliker M**. Influence of flow and pressure on wave propagation in the canine aorta [Online]. *Circ Res* 32: 524–529, 1973. http://www.ncbi.nlm.nih.gov/pubmed/4702044.
8. **Kowalski R**, **Beare R**, **Willemet M**, **Alastruey J**, **Smolich JJ**, **Cheung MMH**, **Mynard JP**. Robust and practical non-invasive estimation of local arterial wave speed and mean blood velocity waveforms. *Physiol Meas* 38: 2081–2099, 2017.
9. **Li Y**, **Khir AW**. Experimental validation of non-invasive and fluid density independent methods for the determination of local wave speed and arrival time of reflected wave. *J Biomech* 44: 1393–9, 2011.
10. **Mutter AF**, **Cooke AB**, **Saleh O**, **Gomez Y-H**, **Daskalopoulou SS**. A systematic review on the effect of acute aerobic exercise on arterial stiffness reveals a differential response in the upper and lower arterial segments [Online]. *Hypertens Res* 40: 146, 2016. http://dx.doi.org/10.1038/hr.2016.111.

11. **Papaioannou TG**, **Karageorgopoulou TD**, **Sergentanis TN**, **Protogerou AD**, **Psaltopoulou T**, **Sharman JE**, **Weber T**, **Blacher J**, **Daskalopoulou SS**, **Wassertheurer S**, **Khir AW**, **Vlachopoulos C**, **Stergiopulos N**, **Stefanadis C**, **Nichols WW**, **Tousoulis D**. Accuracy of commercial devices and methods for noninvasive estimation of aortic systolic blood pressure a systematic review and meta-analysis of invasive validation studies. *J Hypertens* 34: 1237–1248, 2016.
12. **Pomella N**, **Wilhelm EN**, **Kolyva C**, **González-Alonso J**, **Rakobowchuk M**, **Khir AW**. Common Carotid Artery Diameter, Blood Flow Velocity and Wave Intensity Responses at Rest and during Exercise in Young Healthy Humans: A Reproducibility Study. *Ultrasound Med Biol* 43: 943–957, 2017.
13. **Pomella N**, **Wilhelm EN**, **Kolyva C**, **González-Alonso J**, **Rakobowchuk M**, **Khir AW**. Non-invasive Assessment of the Common Carotid Artery Hemodynamics with Increasing Exercise Workrate Using Wave Intensity Analysis. *Am J Physiol Circ Physiol* (2018). doi: 10.1152/ajpheart.00667.2017.
14. **Rakobowchuk M**, **Stuckey MI**, **Millar PJ**, **Gurr L**, **Macdonald MJ**. Effect of acute sprint interval exercise on central and peripheral artery distensibility in young healthy males. *Eur J Appl Physiol* 105: 787–795, 2009.
15. **Segers P**, **Swillens A**, **Taelman L**, **Vierendeels J**. Wave reflection leads to over- and underestimation of local wave speed by the PU- and QA-loop methods: Theoretical basis and solution to the problem. *Physiol Meas* 35: 847–861, 2014.