Reply: Letter to Editor

Non-invasive assessment of carotid arterial wave speed and distensibility

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50	**To the Editor:** We would like to thank Maynard et al. for their interest in our work and raising
51	important questions with a Letter to Editor. We are also please to reply as follows.
52	
53	**Comparisons**
54	First of all, we are not aware of any studies that directly measured local wave speed (c) in
55	similar exercise conditions to those performed in our study. This indeed limits the ability to
56	compare our results with those found previously by other investigators. Specifically, the literature
57	offered by Mynard et al., may not enable a fair scientific comparison, for several reasons. At the
58	level of timing, Mutter et al. (10) measured c post aerobic exercise, whilst in our work c was
59	measured <u>during</u> heavy exercise. In fact, the trend of our results agree with that of (10) at > 5
60	minutes post-exercise with c returning to control values. Further, the works of both Rakobowchuk
61	et al. (14) and Babcock et al. (1) report c values at rest before and after exercise but not <u>during</u>
62	exercise; an important aim and novel contribution of our present work.
63	Several additional differences between our study and those of (14) and (1) relate to the
64	cohorts involved and methodology used in determining c. Participants of our study (13) comprised
65	of exclusively young male athletes, whereas, the cohorts participating in those two studies were
66	recreational active in (14) and a mix that included both athletes and inactive in (1). In relation to
67	determining c, the studies suggested in the Letter to Editor for comparisons used different
68	fundamental assumptions that limit a direct comparison. Whilst the lnDU-loop method assumes
69	unidirectional waves in the earliest period of systole, it is not subject to the calibration and
70	methodological issues of applanation tonometry, which involves forcefully flattening an arterial
71	segment by pushing against a bone. In the case of the carotid artery, this is particularly difficult
72	during exercise. In addition, the potential variable force applied by the operator(s) presents a
73	question on the reproducibility. Therefore, these user-dependent issues associated with
74	applanation tonometry make it difficult to use the results in (1) as "the" carotid PWV reference
75	value. One distinct advantage of the lnDU-loop method, however, is that it provides a means for
76	determining c using measurements, which are direct and local to a specific arterial segment. It is
77	worth noting that we have previously demonstrated the reproducibility of the lnDU-loop method
78	(12) and the results agree with those in (13). At 40 % of maximum workload c values of the current
79	study is 9.5 m/s closely agreed with 9.7 m/s during exercise in (12).
80	Furthermore, classical work by Bramwell and Hill (5), Histand and Anliker (7) have
81	established that c is a function of pressure in several arteries of various mammals, and of flow
82	velocity in (7). Table III – Fig. 9 in (5) shows an increase of 50% in pressure leads to 100% increase
83	in c. Similar patterns could be seen in Fig. 5 in (7). In our work (13) systolic pressure increased by
84	45%, carotid flow by 50%, ΔU by 93%, heart rate by 200%, and cardiac output by 270%, all at 70%
85	workrate intensity compared to at rest condition. These hemodynamic changes resulted in an
86	increase in ΔD by 58% and the carotid wall during exercise at that level must have experienced a
87	significant increase in both wall stress and Young's modules. Therefore, 136% increase in c under
88	such hemodynamic conditions is not very surprising.
89	
90	**lnDU-loop: Theoretical considerations**
91	Secondly, the notion of the lnDU-loop method (6) is prone to increasing 'true' c in the
92	carotid artery may not be supported theoretically. According to (6) c can be calculated as

93
$$c = \frac{1}{2}\frac{dU_{\pm}}{dlnD_{\pm}} \tag{1}$$

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

99   Further, the same notion is not supported by the literature and it is in a diametrically
100   opposite position with findings of Segers et al., who reported a decrease in c when using the lnDU-
101   loop method, also at the carotid artery (15). Furthermore, this notion is not supported
102   experimentally as we validated the method in vitro (9) and reported the possibility of decreasing
103   'true' wave speed, inline with the theoretical expectations, in the presence of a large positive
104   wave reflection; such as those resulting when the measurement and positive reflection sites are in
105   close proximity (3).
106   Furthermore, we believe that using c determined by the lnDU-loop method with the
107   Bramwell-Hill (BH) equation to derive pulse pressure may not be theoretically permitted. This is
108   because such approach will violate the constituents involved in deriving equation (1). The lnDU-
109   loop equation for determining c deals with differential quantities, which are the microscopic
110   elemental changes of flow velocity and diameter, respectively, dU and dD, and their inter-
111   changeability with macroscopic changes of pressure and area (ΔP and ΔA) such as those used in
112   the BH equation (2) has to be exercised with caution as it will likely lead to errors.

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

114   For equation (1) to be valid in determining c, waves must be unidirectional, hence the
115   choice of using the microscopic parameters in early systole, when it maybe reasonable to assume
116   only forward waves exist. However, with a mix of forward and backward waves in mid-to-late
117   systole, the equation loses its validity to determine c. It follows; using c determined with the lnDU-
118   loop in equation (2) for the purpose of establishing pulse pressure ΔP, as proposed by Maynard et
119   al., must be related to the diameter changes corresponding (and restricted) to the duration of the
120   initial linear portion of the loop. Otherwise, it renders the calculations outside the validity domain
121   of equation (1), leading to errors as evidenced by the unrealistic ΔP of 500 mmHg calculated
122   during exercise in the Letter to Editor at hand.
123   If c is determined using equation (1) and is used with the BH equation, it is possible to
124   calculate the change in pressure (ΔP^*) that is related to the initial linear portion of the lnDU-loop
125   by rearranging the BH equation terms

126    $$\Delta P^* = 2\rho c^2 \, \Delta D^*/D_i \qquad\qquad (3)$$

127   where ΔD^* and D_i are the macroscopic change in diameter corresponding to initial linear portion
128   of the lnDU-loop and the initial diameter, respectively. Using this approach gives average values
129   across our cohort of $\Delta P^* = 18 \pm 6$ mmHg at rest and 92 ± 65 mmHg at 70% Wmax, which are
130   vastly different from those obtained using ΔP and ΔD over the whole cardiac cycle being 78 ± 31
131   mmHg at rest and 545 ± 366 mmHg at 70% W_{max}. The latter values are close to those calculated
132   by Maynard et al., from our average values in (13).
133
134   **Velocity profile**
135   We agree with Maynard et al. that mean velocity is difficult to measure using Doppler
136   ultrasound. However, the authors appear to have assumed incorrectly that we use maximum
137   velocity in the calculations of c. We have used mean velocity in this and in our earlier work (2).
138   Even if the ultrasound scanner being used for data acquisition does not provide mean velocity, we
139   determine it by tracing the outer, inner envelopes of the ultrasound, and use the mean waveform
140   as shown **Fig 1** of (4). It is worth noting that both the maximum and mean velocity waveforms are
141   usually parallel; thus provide the same slope of the initial linear part of the lnDU-loop. We have
142   also compared the results of using mean vs. maximum velocity waveforms in determining c using
143   the lnDU-loop method and found no difference (unpublished data). This observation is in line with
144   the theoretical understanding of a blunt flow profile in large arteries; i.e negligible difference
145   between mean and maximum velocity. Whilst we acknowledge that for a parabolic profile of fully
146   developed Poisuelle flow, the maximum is approximately double mean velocity, a conservative

147 entrance length (L) to reach fully developed flow, L= 0.05ReD; where Re is carotid Reynold's
148 number = 500 and D is an average carotid diameter = 0.008m. Consequently, L will need to be 20
149 cm, which is longer than most human common carotid arteries.
150   We also agree with Maynard et al. that the method proposed by Kowalski et al. (8) maybe
151 practical, but in our opinion robustness remains to be widely demonstrated. This is because the
152 pressure is measured non-invasively with considerable variation between devices (11), and
153 linearity assumptions are made in the calibration involving two different vessels of different
154 locations, dimensions and wall mechanical properties.
155
156   **In conclusion**, in the absence of direct comparable measurements of wave speed in the
157 carotid artery during exercise, and the lack of evidence of backward decompression wave existing
158 in early systole, the lnDU-loop technique should not be claimed to increase wave speed. Such
159 claims are not supported theoretically or experimentally. Also, mixing the microscopic and
160 macroscopic terms of the lnDU-loop and Bramwell and Hill techniques may not be allowed for the
161 purpose of calculating pulse pressure, as this is likely to introduce substantial errors.
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167   **References**
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