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8 **The impact of upper-limb position on estimated central blood pressure waveforms**

9

10 **Running Title:** Central hemodynamic estimation

11

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27 **ABSTRACT**

28 Pulse wave analysis (PWA) utilizes arm blood pressure (BP) waveforms to estimate aortic  
29 waveforms. The accuracy of central BP waveform estimation may be influenced by  
30 assessment site local hemodynamics. This study investigated whether local hemodynamic  
31 changes, induced via arm tilting +/-30° relative to heart level, affect estimated central  
32 systolic BP (cSBP) and arterial wave reflection (central augmentation index, cAIx; aortic  
33 backward pressure wave, Pb). In 20 healthy adults (26.7 y [SD 5.2], 10 F) brachial BP  
34 waveforms were simultaneously recorded on experimental and control arms. The  
35 experimental arm was randomly repositioned three times (heart level, -30° heart level,  
36 +30° heart level), while the control arm remained fixed at heart level. For the  
37 experimental arm, arm repositioning resulted in a large (partial eta-squared >0.14) effect  
38 size (ES) change in SBP (ES=0.75,  $P<0.001$ ), cSBP (ES =0.81,  $P<0.001$ ), and cAIx (ES =0.75,  
39  $P=0.002$ ), but not Pb (ES =0.06,  $P=0.38$ ). In the control arm, cAIx (ES =0.22,  $P=0.013$ ) but  
40 not SBP or cSBP significantly changed. Change in experimental arm cSBP was partially  
41 explained by brachial systolic blood velocity ( $P=0.026$ ) and mean diameter ( $P=0.012$ ),  
42 while change in cAIx was associated with brachial retrograde blood velocity ( $P=0.020$ ) and  
43 beta stiffness ( $P=0.038$ ). In conclusion, manipulation of assessment site local  
44 hemodynamics, including the blood velocity profile and local arterial stiffness, had a large  
45 effect on estimated cSBP and cAIx, but not Pb. These findings do not invalidate PWA  
46 devices but do suggest that the accuracy of the estimated aortic pressure waveform is  
47 dependent on stable peripheral hemodynamics.

- 48 **KEY WORDS:** posture; arterial stiffness; pulse wave analysis; central blood pressure;  
49 arterial wave reflection

**50 INTRODUCTION**

51 Pulse wave analysis (PWA) devices permit the estimation of central hemodynamic  
52 properties, including arterial wave reflection (central augmentation index [cAIx], aortic  
53 backward pressure wave [Pb]), and central systolic blood pressure (cSBP). Considering that  
54 cSBP more closely reflects left ventricular and cerebrovascular load than brachial  
55 pressure,<sup>1,2</sup> and is a more accurate marker of cardiovascular risk,<sup>2</sup> PWA is increasingly  
56 attractive to epidemiologists and clinicians. However, the accuracy of central  
57 hemodynamic estimates may be influenced by local hemodynamic changes.

58

59 Local pressure hemodynamics are influenced by gravitational changes, including small  
60 variation in the assessment site level relative to the heart. Such variation may occur with  
61 incorrect positioning of the arm, change in posture, or while using ambulatory devices.  
62 Pucci *et al.*<sup>3</sup> examined the importance of gravitational changes by tilting the upper-limb  
63 30° above and 30° below heart level during supine PWA assessments. This experimental  
64 model is simple yet effective in that local hemodynamics are likely to be manipulated in  
65 the absence of central hemodynamic changes. Pucci *et al.*<sup>3</sup> observed that peripherally  
66 derived indexes of cSBP and cAIx appeared ‘older’ when the upper arm was raised and  
67 ‘younger’ when the upper arm was lowered. These changes occurred in the experimental  
68 arm despite no observable change in the fixed position (heart level) control arm,  
69 suggesting that ‘changes’ to the estimated central waveform were likely an artifact of local  
70 hemodynamic manipulation.

71

72 Unfortunately, Pucci *et al.*<sup>3</sup> did not measure important local hemodynamic properties,  
73 such as blood flow and local arterial stiffness. Further, cAlx but not Pb was measured. cAlx  
74 is known to be affected by the reflected wave transit time,<sup>4</sup> whereas Pb is thought to be  
75 independent of the transit time<sup>5</sup> and has been demonstrated to be more resistant to  
76 changes in posture.<sup>6-9</sup> Therefore, the primary objective of this study was to investigate the  
77 effects of local hemodynamic manipulation, induced by tilting the arm +/-30 degrees  
78 relative to heart level, on PWA estimated cSBP, cAlx and Pb. The secondary objective was  
79 to determine the association between change in estimated cSBP, cAlx and Pb and change  
80 in local hemodynamic properties (arterial stiffness, blood velocity/flow).

81

## 82 **METHODS**

83 This study is reported in accordance with STROBE (Strengthening the Reporting of  
84 Observational Studies in Epidemiology) guidelines.<sup>10</sup>

85

## 86 PARTICIPANTS

87 Twenty young (18 – 40 y), healthy women (n=10) and men were recruited from a large  
88 state university. A healthy population sample was recruited to mitigate the risk of age- or  
89 disease-related influences on BP. Participants were excluded if they reported any known  
90 cardio-metabolic disorders, were taking medications known to affect cardiovascular  
91 function, or reported cigarette smoking. Ethical approval was obtained from the University

92 of North Carolina at Chapel Hill institutional review board, and all participants provided  
93 written informed consent prior to participating in the study.

94

#### 95 EXPERIMENTAL DESIGN

96 Participants were familiarized with all experimental procedures. Subsequently, all  
97 measures were collected on a single occasion in a quiet, dimly lit and environmentally  
98 controlled room between 7am and 10am. Participants fasted for 12h, consuming only  
99 water, and refraining from supplement intake that morning. Participants also avoided  
100 strenuous physical activity and alcohol for 24 h prior to experimentation. Prior to  
101 measurement commencement, participants rested quietly in the supine position for 20-  
102 min, with both arms at heart level and stretched at a right angle.<sup>11</sup> The experimental arm  
103 was supported on a table with an adjustable height and tilting surface, and the control  
104 arm was fixed at heart level.

105

106 The experimental timeline is depicted in **Figure 1**. For each participant, measurements  
107 were made with the experimental arm in three positions: heart level (0°), -30° heart level,  
108 and +30° heart level, separated by 5 min rest prior to measurements. Re-positioning to +/-  
109 30° heart level was randomized, using two sets of 10 unique numbers generated from a  
110 number range of 1-20 ([www.randomizer.org](http://www.randomizer.org)). At each experimental arm position PWA  
111 assessments were simultaneously made on both arms. A control arm was used to  
112 determine whether any changes in the estimated central BP waveform were real or an

113 artifact of local hemodynamic manipulation. Experimental arm local hemodynamic  
114 changes were measured using Duplex Doppler ultrasound. Lastly, to confirm central  
115 hemodynamic stability, continuous wave ultrasound was used to obtain trans-aortic  
116 Doppler flow profiles. All measurements were made in triplicate, with one min rest  
117 between readings, and the closest two recordings were averaged.

118

### 119 PULSE WAVE ANALYSIS: EXPERIMENTAL ARM

120 Oscillometric pressure waveforms were recorded by a single operator using a SphygmoCor  
121 XCEL device (AtCor Medical, Sydney, Australia). An appropriately sized cuff was selected  
122 according to manufacturer guidelines (small adult 17–25 cm, adult 23–33 cm, large adult  
123 31–40 cm) and placed around the left upper arm. Each measurement cycle lasted ~60 s.  
124 The upper arm cuff was initially inflated to measure brachial systolic (SBP) and diastolic  
125 (DBP) blood pressure, and then reinflated 5 s later to 10 mmHg below DBP to acquire a  
126 volumetric displacement signal for 10 s.<sup>12</sup> The brachial waveforms were calibrated using  
127 the cuff-measured SBP and DBP, and mean arterial pressure (MAP) was derived by  
128 integrating the area under the curve. A corresponding aortic pressure waveform was  
129 generated using a validated proprietary transfer function and calibrated using DBP and  
130 MAP.<sup>12</sup> The aortic waveform was used to derive central: cSBP, diastolic BP (cDBP), pulse  
131 pressure (cPP), pulse pressure amplitude (PPamp), augmentation pressure (cAP), cAIx,  
132 cAIx normalized to a heart rate of 75 bpm (cAIx@75), aortic backward pressure wave (P<sub>b</sub>),  
133 aortic forward pressure wave (P<sub>f</sub>), and reflection magnitude (RM).

134

135 The PPamp is the ratio of peripheral pulse pressure to cPP multiplied by 100. The cAlx is  
136 defined as the cAP expressed as a percentage of cPP, where cAP is defined as the  
137 maximum cSBP minus the pressure at the inflection point. The Pf and Pb wave pressures  
138 were determined by assuming a triangular flow wave.<sup>13</sup> This method creates a triangular-  
139 shaped flow wave by matching the start, peak, and end of the flow wave to the timings of  
140 the foot, inflection point, and incisura of the aortic pressure wave. The RM was calculated  
141 as  $P_b/P_f$ .

142

#### 143 PULSE WAVE ANALYSIS: CONTROL ARM

144 Oscillometric pressure waveforms were recorded on the upper arm using an Oscar 2  
145 (SunTech Medical, Morrisville, USA) and a cuff identical in size to the one used for the  
146 XCEL device. The Oscar 2 incorporates the same patented BP model as the XCEL, and has  
147 been validated according to the British Hypertension Society and the European Society of  
148 Hypertension International Protocol.<sup>14,15</sup> Measurements included cSBP, cDBP, cPP, PPamp,  
149 cAP, cAlx, and cAlx@75. The Oscar 2 does not currently measure Pb, Pf or RM.

150

#### 151 DUPLEX DOPPLER ULTRASOUND: EXPERIMENTAL ARM

152 A 11-2 mHz linear array probe (LOGIQ P6, GE Healthcare, Wauwatosa, USA) was used to  
153 record brachial artery brightness-mode images and pulsed doppler waveforms.<sup>16,17</sup> The  
154 ultrasound probe was placed on the brachial artery, 5-10 cm proximal to the antecubital

155 fossa. The isonation angle was kept constant between 45° and 60° and the sample volume  
156 included most of the vessel. Three 10 s video recordings were taken at 30 Hz using an  
157 external video capture system (AV.io HD Frame Grabber, Epiphan Video, CA), during which  
158 the participant was asked to hold their breath without prior inhalation.

159

160 The captured videos were analysed offline using specialized image analysis software (FMD  
161 Studio®, QUIPU, Italy), which outsourced (30 Hz) brachial artery diameters as well as  
162 antegrade and retrograde blood velocities. Blood velocities were analysed by tracing the  
163 peak envelope of the spectral waveform. Subsequently, custom-written Visual Basic code  
164 was used to fit peaks and troughs to the diameter waveforms to calculate diastolic ( $D_d$ ),  
165 systolic ( $D_s$ ), mean diameters ( $D_{mean}$ ), and distention (Dist.).<sup>18,19</sup> The Visual Basic software  
166 also automated the calculation of study outcomes: mean blood velocity ( $V_{mean}$ ), diastolic  
167 blood velocity ( $V_{dia}$ ), systolic blood velocity ( $V_{sys}$ ), retrograde blood velocity ( $V_{neg}$ ), mean  
168 blood flow ( $BF_{mean}$ ), change in blood flow over the cardiac cycle ( $\Delta BF$ ), shear rate,  
169 oscillatory index (OI), conductance, and local arterial stiffness (beta-stiffness index [ $\beta$ ]).  
170 Shear rate ( $s^{-1}$ ) was calculated as  $4 \cdot \text{mean velocity} / \text{diameter}$ , blood flow as  $\text{mean vessel}$   
171  $\text{area} \cdot \text{mean blood velocity} \cdot 60$ , conductance ( $\text{ml} \cdot \text{min} \cdot \text{mmHg}$ ) as  $\text{mean blood flow} / \text{MAP}$ ,  
172 and OI as  $\text{retrograde shear rate} / (\text{antegrade shear rate} + \text{retrograde shear}) \cdot 100$ .<sup>20</sup> The  
173 values for OI range from 0 to 50, where zero is strictly antegrade shear and 50 is purely  
174 oscillatory. The  $\beta$  was calculated as  $\ln(\text{SBP}/\text{DBP}) / [(D_s - D_d) / D_d]$ .

175

176 CONTINUOUS-WAVE ULTRASOUND: TRANS-AORTIC

177 Stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR) were  
178 measured at each arm position using continuous-wave Doppler ultrasound (USCOM 1A,  
179 Uscom, Sydney, Australia). A single operator placed a 3.3MHz continuous-wave probe  
180 over the acoustic window at the level of the sternal notch to obtain trans-aortic Doppler  
181 flow profiles. Three 12 s recordings were taken for each arm position and the closest two  
182 were averaged. The BPs from the control arm were used to calculate SVR.

183

184 SAMPLE SIZE

185 Sample size calculations were based on cAlx, which has lower between-day reliability than  
186 the primary outcome, cSBP,<sup>6</sup> and is similarly reliable to Pb.<sup>7</sup> The mean change in derived  
187 cAlx reported following upper-limb tilt (+30<sup>0</sup> or -30<sup>0</sup>) from heart level is approximately  
188 10% (data estimated from pooled data), but the smallest change reported is  
189 approximately 5%.<sup>3</sup> The typical error of cAlx measurement using the SpygmoCor XCEL is  
190 5.2% for uncontrolled conditions.<sup>6</sup> Using a conservative typical change during arm tilt of  
191 5% and a conservative typical error of 5.2%, with the maximum chances of a Type I error  
192 set at 5%, and a Type II error of 20%, we estimated the approximate number of  
193 participants required at 19.<sup>21</sup> To permit even distribution by sex, the sample size was  
194 inflated to 20.

195

196 STATISTICS

197 Statistical analyses were performed using Statistical Package for Social Sciences version 25  
198 (SPSS, Inc., Chicago, Illinois) and Hierarchical Linear Modelling-6 (Scientific Software  
199 International, Inc., Lincolnwood, Illinois). Statistical significance was defined as  $p < 0.05$   
200 (two tailed). To test for the main effect of arm position on each outcome analysis of  
201 variance (ANOVA) for repeated measurement was used, after verification of the normality  
202 of distributions. Homogeneity of variance was evaluated using Mauchly's test of sphericity  
203 and, when violated, the Greenhouse-Geisser adjustment was used. In the event of a  
204 significant main effect, pairwise comparisons against heart level measurements were  
205 conducted. Effect sizes (ES) are reported using partial eta-squared ( $\eta^2_p$ ), where 0.01, 0.06,  
206 and 0.14 represent a small, medium, and large effect, respectively.<sup>22</sup>

207

208 Hierarchical Linear Modelling (HLM) was used to address the final objective, i.e.,  
209 associations between change in estimated cSBP and arterial wave reflection and change in  
210 local artery hemodynamics. Three models were run for each analysis. Model 1 specified  
211 arm tilting (arm position relative to heart level), and was used to estimate measurement  
212 reliability.<sup>23</sup> Model 2 specified the predictor which most strongly associated with outcome,  
213 as a group-centered to determine whether change in this variable helps to explain within-  
214 subject variation for change in the outcome. Model 3 specified the next strongest  
215 predictor variable as a group-centered covariate.

216

## 217 **RESULTS**

218 Local and central hemodynamic data for the experimental arm were successfully collected  
219 from all 20 participants (26.7 y [SD 5.2], 50% women, BMI 24.0 kg/m<sup>2</sup> [SD 2.8]). For the  
220 control arm, PWA measurements were unsuccessful for one participant for an unknown  
221 reason. Additionally, ultrasound measures were unsuccessful on one participant due to  
222 poor video quality. These two participants were similar to the remainder of the population  
223 in terms of demographics and baseline hemodynamic measures.

224

## 225 EXPERIMENTAL ARM MEASUREMENTS

### 226 Pulse Wave Analysis

227 All measurements are reported in **Table 1**. We observed no significant main effects of arm  
228 tilting on HR, PPamp, Pb, Pf or RM. However, there were large (ES=0.27-0.82), significant  
229 main effects of arm tilting on MAP, DBP, SBP, cSBP, cAP, cAIx, and cAIx75. Pairwise  
230 contrasts indicate that maneuvering the arm 30° above heart level resulted in significantly  
231 decreased MAP, DBP, SBP, cSBP, but non-significant changes in cAP, cAIx, and cAIx75.  
232 Conversely, positioning the arm 30° below heart level led to significantly increased MAP,  
233 DBP, SBP, cSBP, significantly decreased cAP and cAIx, and resulted in a non-significant  
234 decrease in cAIx75.

235

### 236 Ultrasound

237 We observed non-significant main effects for  $V_{\text{mean}}$ ,  $BF_{\text{mean}}$ , conductance, and shear rate.  
238 However, there were large (ES=0.20-0.60), significant main effects for distension,  $\beta$ ,  $V_{\text{dia}}$ ,

239  $V_{sys}$ ,  $V_{neg}$ ,  $\Delta BF$  and  $OI$ . Pairwise contrasts indicate that maneuvering the arm 30° above  
240 heart level resulted in significantly increased  $V_{dia}$ ,  $OI$  and  $V_{neg}$ , and a non-significant change  
241 in  $\beta$ ,  $Dist$ ,  $V_{sys}$ , and  $\Delta BF$ . Conversely, positioning the arm 30° below heart level led to  
242 significantly increased  $\beta$ , significantly decreased  $V_{sys}$  and  $\Delta BF$ , and had a non-significant  
243 effect on distention,  $V_{mean}$ , and  $V_{neg}$ .

244

#### 245 CONTROL MEASUREMENTS: CONTROL ARM AND TRANS-AORTIC

246 All measurements are reported in **Table 2**. When the experimental arm was repositioned,  
247 we observed no significant main effects for HR, SBP, cSBP,  $PP_{amp}$ , or cAP. However, there  
248 were large ( $ES=0.19-0.32$ ) and significant main effects for MAP, DBP, cAIx and cAIx75.  
249 Pairwise contrasts indicate that maneuvering the experimental arm 30° above heart level  
250 resulted in significantly increased MAP and DBP and significantly decreased cAIx and  
251 cAIx75 in the control arm. Positioning the experimental arm 30° below heart level also led  
252 to significantly increased MAP and DBP in the control arm but had a non-significant effect  
253 on cAIx and cAIx75.

254

255 We observed no significant main effects for CO, SV or HR. However, there was a large  
256 ( $ES=0.25$ ) and significant main effect for SVR. Pairwise contrasts indicate that maneuvering  
257 arm 30° above heart level significantly increased SVR, whereas positioning the arm 30°  
258 below heart level had a non-significant effect on SVR.

259

260 ASSOCIATIONS BETWEEN CENTRAL AND LOCAL HEMODYNAMIC261 MEASURES

262 Data from 19 participant, for a total of 57 data points were available for the HLM models.  
263 Only cSBP and cAlx were modelled as these outcomes were influenced by arm tilting,  
264 whereas Pb was not. The ultrasound-derived local hemodynamic measures, which  
265 significantly changed in response to arm tilting, were considered for HLM analysis. Initially,  
266 each local hemodynamic variable was independently associated with cSBP and cAlx, using  
267 HLM. The variables which were significantly associated with cSBP or cAlx were specified as  
268 subject-centered in order of strength of association.  $V_{\text{sys}}$  and  $D_{\text{mean}}$ , and  $V_{\text{neg}}$  and  $\beta$  were  
269 found to be significant independent predictors of cSBP and cAlx, respectively. The HLM  
270 models for cSBP are reported in **Table 3**. Model 3 shows that, after controlling for  $V_{\text{sys}}$  and  
271  $V_{\text{mean}}$ , each 10° elevation in arm position, beginning at -30°, resulted in a 2.05 mmHg  
272 decrease in cSBP. The HLM models for cAlx are reported in **Table 4**. After controlling for  
273  $V_{\text{neg}}$  and  $\beta$ , each 10° elevation in arm position, beginning at -30°, resulted in a 0.16%  
274 increase in cAlx.

275

276 **DISCUSSION**

277 Non-invasive PWA devices have been demonstrated to provide reliable<sup>6-8</sup> and valid<sup>24,25</sup>  
278 estimates of central hemodynamic properties, and the prognostic value of cSBP has been  
279 recognized by expert consensus.<sup>2,26,27</sup> The current findings do not invalidate PWA devices  
280 but do suggest that the accuracy of the estimated aortic pressure waveform is dependent

281 on stable local hemodynamics at the assessment site. Local hemodynamic manipulation,  
282 induced through arm tilting, had a large effect on estimated cSBP and cAIx, but not Pb. We  
283 further add to the extant literature by observing a direct association of cSBP and cAIx with  
284 local hemodynamic factors. These findings provide mechanistic insight into the factors  
285 influencing the accuracy of PWA.

286

### 287 STRENGTHS AND LIMITATIONS

288 The strengths and limitations of this study need to be addressed to best contextualize the  
289 findings. A major strength is the simultaneous measurement of peripheral and central  
290 hemodynamic variables. Additionally, the homogenous group of young, healthy  
291 participant permitted measurement of sensitive changes in hemodynamic variables  
292 without the confounding influence of age or disease-status. However, there were some  
293 limitations. While our sample population did permit optimal signal to noise, further study  
294 with older and clinical populations is required to better generalize the findings. For  
295 example, in older participant sarterial wave reflection has been demonstrated to be less  
296 sensitive to change with arm tilting,<sup>3</sup> in hypertensive participants the relationship  
297 between BP and arterial stiffness may be different,<sup>28</sup> and the effects of sex are unknown.  
298 Additionally, we did not control for vasomotor changes resulting from arm movement.<sup>29</sup>  
299 However, the arm was moved slowly and was fully supported at all times, we did allow a  
300 5-min rest interval, and measurements were taken in triplicate. Lastly, the current study  
301 utilized an oscillometric device (XCEL) to estimate the aortic pressure waveform from the

302 brachial artery, and SphygmoCor originally developed a proprietary transfer function for  
303 use with radial artery tonometry. However, a proprietary transfer function has been  
304 developed specifically for the XCEL,<sup>12</sup> and central hemodynamic outcomes derived from  
305 the XCEL have been validated using both radial artery tonometry<sup>12,30,31</sup> and high-fidelity  
306 invasive catheterization.<sup>24,25</sup>

307

### 308 CENTRAL SYSTOLIC BLOOD PRESSURE

309 The overall displacement in peripheral SBP in the experimental arm was 15 mmHg, which  
310 is comparable to the 20 mmHg displacement reported by Pucci *et al.*<sup>3</sup> Of particular  
311 interest, the PP amplification (ratio of central to peripheral PP) did not change with arm  
312 tilting for either study, suggesting that local pressure wave transmission directly  
313 influences the estimated central waveform. The estimated central waveform was similarly  
314 affected in both studies despite Pucci *et al.*<sup>3</sup> recording the peripheral waveform at the  
315 radial artery with tonometry, and the current study estimating the peripheral waveform at  
316 the brachial artery with oscillometry. Further, the changes to local and estimated cSBP  
317 occurred despite no changes to SBP or cSBP estimated from the control arm. Herein, we  
318 extend the findings of Pucci *et al.*<sup>3</sup> by reporting that change in cSBP was found to be  
319 associated with local hemodynamic changes, including brachial artery systolic blood  
320 velocity and mean diameter.

321

322 Brachial artery systolic blood velocity was particularly susceptible to the arm being  
323 lowered, whereas brachial artery mean diameter was most susceptible to raising the arm.  
324 When lowering the arm, systolic blood velocity decreased despite no change in mean  
325 velocity, indicating that the shape of the velocity profile was altered rather than the  
326 overall volume of blood velocity. The change in systolic blood velocity shape may have  
327 been indicative of decreased downstream resistance as a result of blood pooling.<sup>19,32</sup> The  
328 decreased downstream resistance may have directly influenced cSBP; however, decreased  
329 peripheral resistance would be expected to decrease cSBP.<sup>33</sup> Alternatively, the altered  
330 systolic blood velocity may indicate mismatched pulsatile-pressure-flow relations.<sup>33,34</sup> In  
331 turn, mean diameter is an indicator of the tone of the vessel, and a major determinant of  
332 local BP.<sup>33</sup> However, mean diameter also plays an important general role in the local  
333 hemodynamic environment, including arterial stiffness and the blood velocity profile, and  
334 change in this variable may be indicative of more general change to the local  
335 environment. This may explain why, despite being associated with change in cSBP,  
336 specifying mean diameter in the hierarchical linear model did not reduce the change in  
337 cSBP with arm tilting.

338

### 339 ARTERIAL WAVE REFLECTION

340 In line with our BP findings, cAIx in the experimental arm changed similarly to that of Pucci  
341 *et al.*<sup>3</sup> cAIx increased when the arm was raised (albeit not significantly in the current  
342 study), and decreased when the arm was lowered. Contrary to Pucci *et al.*,<sup>3</sup> we found that

343 cAlx significantly decreased (-4.7%) in the contralateral arm, predominantly when the  
344 experimental arm was raised. We further extend the findings of Pucci *et al*<sup>3</sup> by reporting  
345 that (i) change in experimental arm cAlx was found to be associated with change in  
346 brachial artery retrograde blood velocity and brachial arterial stiffness, and (ii) Pb did not  
347 significantly change with arm tilting.

348

349 Antegrade blood velocity was particularly susceptible to the arm being raised, whereas  
350 brachial arterial stiffness was specifically susceptible to the arm being lowered. Antegrade  
351 blood velocity may have directly influenced the shape of the local pressure waveform, or  
352 may have simply been the consequence of increased downstream vascular resistance.<sup>32</sup>

353 Considering the changes in antegrade blood velocity were small, the later explanation is  
354 more likely. Interestingly, brachial arterial stiffness increased with arm lowering while the  
355 cAlx decreased, which is opposite to what was expected. As such, perhaps it is not  
356 surprising that while both antegrade blood velocity and brachial arterial stiffness did  
357 decrease the hierarchical linear modelling estimate for change in cAlx with arm tilting, the  
358 standard error for the estimate did not decrease and nor did the residual (within-subject)  
359 variance. This indicates that while antegrade blood velocity and brachial arterial stiffness  
360 are associated with cAlx, other factors do contribute to a change in cAlx. One explanation  
361 is that at least part of the cAlx change is not artificial, and that arm tilting does have a  
362 small systemic effect. Indeed, contrary to Pucci *et al*,<sup>3</sup> we observed changes to cAlx in the  
363 contralateral arm, and these changes are supported by small but robust changes in

364 systemic vascular resistance. Pucci *et al*<sup>3</sup> may not have observed changes to cAIx in the  
365 contralateral arm as a result of the wide age range of study subjects.

366

367 In contrast to cAIx, Pb did not significantly change in response to arm tilting. This finding  
368 supports previous work from our group indicating that, when compared to Pb, cAIx is  
369 more prone to error with change in body posture.<sup>6-8</sup> Two potential sources of error may  
370 have limited the estimation of arterial wave reflections using cAIx: (i) the reflected wave  
371 transit time, and (ii) the generalized transfer function used to generate the aortic pressure  
372 waveform. (i) The cAIx is affected by the reflected wave transit time, which is influenced  
373 by the reflected wave timing, amplitude, and ventricular function, and which are known to  
374 be influenced by a number of factors, including heart rate.<sup>4</sup> However, heart rate was not  
375 significantly affected by arm tilting. Alternatively, (ii) the generalized transfer function may  
376 less truly reproduce the high-frequency components required for cAIx computation than it  
377 does the low-frequency pressure harmonics required for Pb and Pf computation.<sup>35</sup>

378

### 379 IMPLICATIONS

380 Central BP measurement prognostic value has been recognized by expert consensus, and  
381 is gaining traction as a clinical outcome.<sup>2,26,27</sup> The traction is supported by the validation  
382 of diagnostic thresholds,<sup>36</sup> and evidence demonstrating that monitoring central BP, as  
383 opposed to conventional peripheral BP, aided in the management of hypertension,  
384 leading to decreased medication use without adverse effects on left ventricular mass.<sup>37</sup>

385 However, as with peripheral BP measures, central BP and arterial wave reflection are  
386 currently measured in both supine and seated positions, with the arm resting at various  
387 heights.<sup>38</sup> Findings from the current study, along with previous work from our group and  
388 others,<sup>3,6-9</sup> suggest that lack of procedural standardization may have meaningful  
389 implications for patient management.

390

391 Our findings may have particular relevance to 24-h ambulatory central BP devices, as  
392 changes in body posture and arm position may confound the accuracy of readings. As  
393 such, it is recommended that participants are instructed to remain supine during key  
394 measurement periods. Additionally, the current findings do indicate that Pb may be a  
395 more robust measure of arterial wave reflection than cAIx. Two large prospective  
396 studies<sup>39,40</sup> suggest that wave separation analysis may be superior to cAIx as a subclinical  
397 marker of cardiovascular disease – one reporting that Pb better predicts 15-year  
398 cardiovascular mortality than cAIx,<sup>39</sup> the other that reflection magnitude (Pb/Pf) better  
399 predicts cardiovascular events than cAIx.<sup>40</sup> Whether or not Pb is a superior ambulatory  
400 measure than cAIx warrants further attention.

401

## 402 **CONCLUSIONS**

403 This study investigated whether changes to the local hemodynamic environment, induced  
404 through arm tilting, affect estimated cSBP and indices of arterial wave reflection. Arm  
405 tilting had no effect on Pb. However, arm tilting did have a large effect on estimated cSBP

406 and cAIx in the experimental arm, but not in the control arm. The changes in cSBP and  
407 cAIx were partially explained by changes in local hemodynamic factors. These findings do  
408 not invalidate PWA devices but do suggest that the accuracy of the estimated aortic  
409 pressure waveform is dependent on stable peripheral hemodynamics at the measurement  
410 site.

411

412 **ACKNOWLEDGEMENTS**

413 None.

414 **CONFLICT OF INTEREST**

415 The authors declare that they have no conflict of interest

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523 **FIGURES**

524 **Figure 1.** Study design. The experimental arm was passively repositioned three times  
 525 (heart level [0°], below heart level [-30°], below heart level [+30°]), while the control arm  
 526 remained fixed at heart level. Following repositioning a 5 min rest preceded  
 527 measurements. Measurements on the experimental arm included pulse wave analysis  
 528 (PWA, XCEL) and duplex Doppler ultrasound (US<sub>DD</sub>). On the control arm PWA (Oscar 2)  
 529 measures were taken at the same time as experimental arm PWA measures. Lastly, for  
 530 each arm position a continuous wave ultrasound (US<sub>CW</sub>) probe was placed at the level of  
 531 the sternal notch to obtain trans-aortic Doppler flow profiles. All measurements were  
 532 made in triplicate.

533

534 **TABLES**

535 **Table 1.** Hemodynamic measures on the experimental arm (n=20)

536 Abbreviations: ES, effect size (partial eta squared), where 0.01, 0.06, and 0.14 represent a small, medium,  
 537 and large effect, respectively; Cont., contrast; LCI, lower confidence interval (95%); UCI, upper confidence  
 538 interval (95%);  
 539  $\Delta$ BF, change in blood flow (systole – diastole); cAIx, central augmentation index; cAIx75, cAIx normalize to a  
 540 heart rate of 75 bpm; cAP, central augmentation pressure;  $\beta$ , beta index stiffness; BF<sub>mean</sub>, mean blood flow;  
 541 Cond., conductance; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; Dist, distention  
 542 (brachial diameter change); D<sub>mean</sub>, mean arterial (brachial) diameter; MAP, mean arterial blood pressure; Pf,  
 543 aortic forward pressure wave; Pb, aortic backward pressure wave; PP<sub>amp</sub>, pulse pressure amplitude; OI,  
 544 oscillatory index; RM, reflection magnitude; SBP, systolic blood pressure; shear, shear rate; V<sub>dia</sub>, diastolic

545 blood velocity;  $V_{\text{mean}}$ , mean blood velocity;  $V_{\text{neg}}$ , negative (retrograde) blood velocity;  $V_{\text{sys}}$ , systolic blood  
 546 velocity

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549 **Table 2.** Control measurements: contralateral arm hemodynamic measures and central  
 550 output (n=19)

551 Abbreviations: cAIx, central augmentation index, AIx75, cAIx normalize to a heart rate of 75 bpm; cAP,  
 552 central augmentation pressure; CO, cardiac output; cSBP, central systolic blood pressure; DBP, diastolic  
 553 blood pressure;  $D_{\text{mean}}$ , mean arterial (brachial) diameter; HR, heart rate;  $PP_{\text{amp}}$ , pulse pressure amplitude;  
 554 MAP, mean arterial blood pressure; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular  
 555 resistance

556

557 **Table 3.** Hierarchical linear modeling estimates for change in central systolic blood  
 558 pressure (cSBP) with arm tilting (n=57 data points)

559 Note: the slopes are reported as a  $10^\circ$ , rather than  $1^\circ$  or  $30^\circ$  change to aid interpretation. Measurements we  
 560 only conducted at  $-30^\circ$ ,  $0^\circ$  and  $30^\circ$ .

561 Abbreviations:  $D_{\text{mean}}$ , brachial artery mean diameter;  $V_{\text{sys}}$ , systolic blood velocity;

562

563 **Table 4.** Hierarchical linear modeling estimates for change in central augmentation index  
 564 (cAIx) with arm tilting (n=20)

565 Note: the slopes are reported as a  $10^\circ$ , rather than  $1^\circ$  or  $30^\circ$  change to aid interpretation. Measurements we  
 566 only conducted at  $-30^\circ$ ,  $0^\circ$  and  $30^\circ$ .

567 Abbreviations:  $\beta$ , beta stiffness in the brachial artery;  $V_{\text{neg}}$ , negative (retrograde), blood velocity



569 **Table 1.** Hemodynamic measures on the experimental arm (n=57 data points)

	30° Above		Heart Level		30° Below		Significance		30° Above Heart				30° Below Heart			
	X	SD	X	SD	X	SD	P	ES	Cont.	LCI	UCI	P	Cont.	LCI	UCI	P
MAP (mmHg)	77.3	5.6	82.2	5.4	91.9	6.0	<0.001	0.82	-4.64	-7.6	-1.7	0.002	9.76	12	7.2	0.000
DBP (mmHg)	61.5	6.4	66.1	5.9	74.9	6.5	<0.001	0.80	-4.70	-7.5	-1.8	0.001	-13.3	-17	-9.9	0.000
SBP (mmHg)	110	5.3	114	6.3	125	7.7	<0.001	0.75	-4.38	-7.5	-1.3	0.005	10.4	14	6.5	0.000
cSBP (mmHg)	94.5	5.7	99.5	5.7	109	6.9	<0.001	0.81	-4.90	-7.8	-2.0	0.001	9.45	12	6.4	0.000
PP <sub>amp</sub> (ratio)	1.46	0.6	1.45	0.9	1.47	0.9	0.199	0.08	0.16	-0.1	0.4	0.430	0.27	-0.1	0.7	0.301
cAP (mmHg)	0.68	2.4	0.48	3.3	-1.55	4.2	0.002	0.29	0.20	-1.2	1.6	1.000	-2.15	-4.2	-0.2	0.033
cAix (%)	1.55	8.8	1.45	9.4	-4.63	12	0.002	0.27	0.10	-3.6	3.8	1.000	-6.20	-12	-0.7	0.023
cAix75 (%)	-8.05	10	-9.00	13	-15.1	15	0.005	0.27	0.56	-3.5	4.6	1.000	-6.22	-13	0.4	0.070
Pb (mmHg)	11.1	2.0	11.1	1.4	11.5	1.9	0.338	0.06	0.00	-0.8	0.8	1.000	0.45	-0.4	1.3	0.528
Pf (mmHg)	25.0	2.3	24.8	2.6	25.3	3.5	0.809	0.01	0.20	-1.5	1.9	1.000	0.50	-1.6	2.6	1.000
RM (%)	43.4	6.1	45.1	6.6	43.9	4.7	0.352	0.05	1.75	-5.9	2.4	0.840	-1.25	-4.6	2.1	1.000
HR (bpm)	52.2	8.5	52.5	9.3	51.6	7.9	0.651	0.02	0.30	-2.4	1.8	1.000	-0.88	-3.3	1.5	1.000
D <sub>mean</sub> (mm)	3.68	0.7	3.58	0.8	3.61	0.8	0.075	0.26	0.11	0.0	0.2	0.105	0.01	-0.1	0.1	1.000
Dist (mm)	0.08	0.0	0.07	0.0	0.05	0.0	0.002	0.29	0.01	0.0	0.0	0.537	-0.02	0.0	0.0	0.085
$\beta$	29.3	9.2	28.5	8.0	39.0	13	0.002	0.30	0.77	-6.0	7.5	1.000	10.5	3.3	18	0.004
V <sub>dia</sub> (cm/s)	1.21	1.4	0.00	0.0	0.00	0.0	<0.001	0.44	1.21	0.4	2.1	0.005	na			
V <sub>sys</sub> (cm/s)	84.8	15	81.7	16	62.9	14	<0.001	0.72	3.10	-2.9	9.1	0.564	-18.8	-26	-12	0.000
V <sub>mean</sub> (cm/s)	10.0	2.5	11.1	2.8	10.9	14	0.893	0.01	-1.08	-2.3	0.2	0.111	-0.16	-7.8	7.5	1.000
V <sub>neg</sub> (cm/s)	-3.41	2.6	-1.96	1.4	-1.80	1.4	0.000	0.36	-1.45	-2.6	-0.3	0.011	0.16	-0.5	0.8	1.000
BF <sub>mean</sub> (ml/min)	62.3	27	63.9	23	57.5	48	0.801	0.01	-1.55	-10	7.3	1.000	-6.33	-37	24	1.000
$\Delta$ BF (ml/min)	546	213	510	225	386	154	<0.001	0.60	-36.3	-19	92	0.300	-123	-187	-60.1	0.000
Cond. (ml/min/mmHg)	0.81	0	0.78	0.3	0.63	0.6	0.275	0.07	0.03	-0.1	0.1	1.000	-0.16	-0.5	0.2	0.837
Shear (s <sup>-1</sup> )	117	45	131	52	138	198	0.833	0.01	-20.2	-26	-1.7	0.022	6.42	-100	113	1.000
OI (ratio)	23.8	12	14.3	6.5	15.5	9.5	0.001	0.33	9.47	2.8	16	0.005	1.20	-3.8	6.2	1.000

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577 **Table 2.** Control measurements: contralateral arm hemodynamic measures and central output (n=19)

	30° Above		Heart Level		30° Below		Significance		30° Above Heart				30° Below Heart			
	X	SD	X	SD	X	SD	P	ES	Cont.	LCI	UCI	P	Cont.	LCI	UCI	P
MAP (mmHg)	82.1	6.8	79.9	5.8	81.9	6.3	0.002	0.32	2.26	0.6	3.9	0.006	1.9	0.5	3.4	0.007
DBP (mmHg)	64.6	5.6	62.2	5.9	64.7	6.2	0.002	0.30	2.30	0.8	3.9	0.003	2.5	0.4	4.6	0.020
SBP (mmHg)	117	9.7	115	8.6	117	8.6	0.166	0.10	1.50	-0.9	3.8	0.345	1.4	-0.3	3.2	0.139
cSBP (mmHg)	103	9.3	102	7.4	103	8.2	0.164	0.11	1.26	-1.0	3.6	0.493	-1.2	-0.7	3.0	0.360
PP <sub>amp</sub> (ratio)	1.39	0.8	1.37	0.7	1.38	0.8	0.270	0.07	0.19	-0.0	0.5	0.274	0.0	-0.1	-0.3	0.955
cAP (mmHg)	1.42	5.3	2.84	4.9	1.79	4.1	0.068	0.14	-1.37	-3.1	323	0.140	-1.1	-2.6	0.5	0.258
cAix (%)	2.53	15	7.21	12	3.26	11	0.013	0.22	-4.74	-9.3	-0.2	0.041	-3.9	-7.9	0.1	0.054
cAix75 (%)	-8.11	17	-3.00	15	-6.55	13	0.021	0.19	-5.21	-10.2	-0.2	0.039	-3.7	-8.5	1.2	0.181
HR <sub>oscar</sub> (bpm)	52.1	7.7	53.4	8.2	53.3	7.5	0.059	0.15	-1.47	-3.1	0.2	0.095	-0.2	-1.9	1.5	1.000
HR <sub>uscom</sub> (bpm)	51.8	9.3	52.3	10	52.1	8.3	0.906	0.01	-0.43	-2.5	1.7	1.000	-0.2	-3.2	2.8	1.000
CO (l/min)	4.30	1.3	4.46	1.3	4.41	0.9	0.344	0.06	-0.17	-0.4	0.0	0.044	-0.1	-0.4	0.3	1.000
SV (mL)	83.1	20	85.3	19	85.6	19	0.171	0.09	-2.25	-5.8	1.3	0.335	0.2	-3.5	3.9	1.000
SVR (d·sec·cm <sup>-5</sup> )	1653	425	1528	377	1569	331	0.004	0.25	125	47	202	0.001	41	-60	143	0.900

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590 **Table 3.** Hierarchical linear modeling estimates for change in central systolic blood pressure (cSBP) with arm tilting (n=20)

	Model 1			Model 2			Model 3		
	Est.	SE	<i>P</i>	Est.	SE	<i>P</i>	Est.	SE	<i>P</i>
Fixed Effects									

Intercept (-30°)	$\beta_{00}$	103	1.3	<0.001	103	1.3	<0.001	103	1.3	<0.001	Initial cSBP, arm at -30°
Arm Tilt (per 10°)	$\beta_{10}$	-2.39	0.2	<0.001	-1.82	0.3	<0.001	-2.05	0.3	<0.001	cSBP per 10° degree elevation
	$V_{\text{sys}}$	$\beta_{20}$			-0.02	0.1	0.008	-0.13	0.1	0.026	cSBP change per 1 unit $V_{\text{sys}}$
	$D_{\text{mean}}$							8.1	4.1	0.012	cSBP change per 1 unit $D_{\text{mean}}$
Random Variance											
Intercept	$U_{00}$	5.33		<0.001	5.38		<0.001	5.40		<0.001	Between-subject variance
Residual	$E$	3.26			2.99		3.23	2.85			Within-subject variance

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607 **Table 4.** Hierarchical linear modeling estimates for change in central augmentation index (AIx) with arm tilting (n=20)

		Model 1			Model 2			Model 3			
		Est.	SE	<i>P</i>	Est.	SE	<i>P</i>	Est.	SE	<i>P</i>	
Fixed Effects											
Intercept (-30°)	$\beta_{00}$	0.91	2.22	0.686	0.91	2.22	0.686	0.91	2.22	0.686	Initial cAIx, arm at -30°
Arm Tilt (per 10°)	$\beta_{10}$	0.92	0.34	0.015	0.48	0.39	0.240	0.16	0.39	0.692	cAIx per 10° degree elevation
	$V_{\text{neg}}$				-1.66	0.70	0.029	-1.69	0.08	0.020	cAIx change per 1 unit $V_{\text{neg}}$
	$\beta$							-0.19	0.66	0.038	cAIx change per 1 unit $\beta$
Random Variance											
Intercept	$U_{00}$	9.25		<0.001	9.22		<0.001	9.25		<0.001	Between-subject variance
Slope	$U_{10}$	0.97		0.030	0.93		0.059	0.74		0.298	Between-subject variance
Residual	$E$	4.87			5.04			4.93			Within-subject variance

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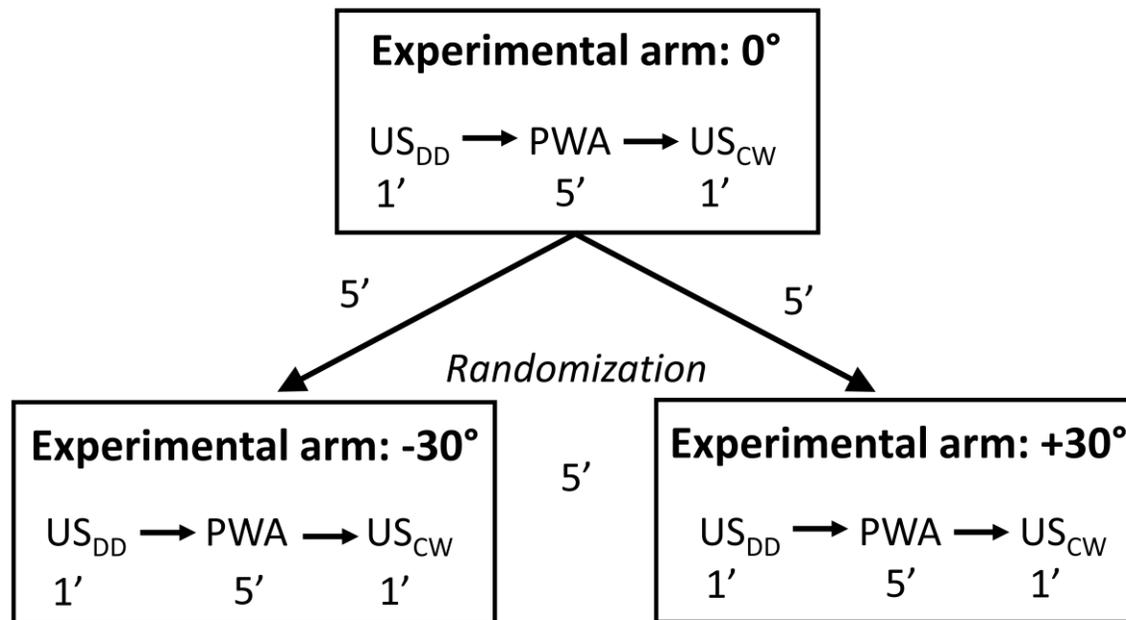
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