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

Running Title: Central hemodynamic estimation

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ABSTRACT

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

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

49 arterial wave reflection

INTRODUCTION

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

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

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

METHODS

This study is reported in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[10]

PARTICIPANTS

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

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

EXPERIMENTAL DESIGN

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

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

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

PULSE WAVE ANALYSIS: EXPERIMENTAL ARM

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

The PPamp is the ratio of peripheral pulse pressure to cPP multiplied by 100. The cAIx is defined as the cAP expressed as a percentage of cPP, where cAP is defined as the maximum cSBP minus the pressure at the inflection point. The Pf and Pb wave pressures were determined by assuming a triangular flow wave.[13] This method creates a triangular-shaped flow wave by matching the start, peak, and end of the flow wave to the timings of the foot, inflection point, and incisura of the aortic pressure wave. The RM was calculated as Pb/Pf.

PULSE WAVE ANALYSIS: CONTROL ARM

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

DUPLEX DOPPLER ULTRASOUND: EXPERIMENTAL ARM

A 11-2 mHz linear array probe (LOGIQ P6, GE Healthcare, Wauwatosa, USA) was used to record brachial artery brightness-mode images and pulsed doppler waveforms.[16,17] The 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 (Dd),
165 systolic (Ds), mean diameters (D_{mean}), and distention (Dist.).[18,19] 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 (ΔBF), shear rate,
169 oscillatory index (OI), conductance, and local arterial stiffness (beta-stiffness index [β]).
170 Shear rate (s^{-1}) was calculated as 4*mean velocity/diameter, blood flow as mean vessel
171 area*mean blood velocity*60, conductance (ml·min·mmHg) as mean blood flow/MAP,
172 and OI as retrograde shear rate / (antegrade shear rate + retrograde shear)*100.[20] The
173 values for OI range from 0 to 50, where zero is strictly antegrade shear and 50 is purely
174 oscillatory. The β was calculated as ln(SBP/DBP)/[(Ds-Dd)/Dd].
175

CONTINUOUS-WAVE ULTRASOUND: TRANS-AORTIC

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

SAMPLE SIZE

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

STATISTICS

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

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

RESULTS

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

EXPERIMENTAL ARM MEASUREMENTS

Pulse Wave Analysis

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

Ultrasound

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

239 V_{sys}, V_{neg}, ΔBF 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 *β*, Dist, V_{sys}, and ΔBF. Conversely, positioning the arm 30° below heart level led to
242 significantly increased *β,* significantly decreased V_{sys} and ΔBF, 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

ASSOCIATIONS BETWEEN CENTRAL AND LOCAL HEMODYNAMIC MEASURES

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

DISCUSSION

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

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

STRENGTHS AND LIMITATIONS

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

brachial artery, and SphygmoCor originally developed a proprietary transfer function for use with radial artery tonometry. However, a proprietary transfer function has been developed specifically for the XCEL,[12] and central hemodynamic outcomes derived from the XCEL have been validated using both radial artery tonometry[12,30,31] and high-fidelity invasive catheterization.[24,25]

CENTRAL SYSTOLIC BLOOD PRESSURE

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

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.[19,32] The
328 decreased downstream resistance may have directly influenced cSBP; however, decreased
329 peripheral resistance would be expected to decrease cSBP.[33] Alternatively, the altered
330 systolic blood velocity may indicate mismatched pulsatile-pressure-flow relations.[33,34] In
331 turn, mean diameter is an indicator of the tone of the vessel, and a major determinant of
332 local BP.[33] 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*.[3] 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*,[3] we found that

cAIx significantly decreased (-4.7%) in the contralateral arm, predominantly when the experimental arm was raised. We further extend the findings of Pucci *et al* [3] by reporting that (i) change in experimental arm cAIx was found to be associated with change in brachial artery retrograde blood velocity and brachial arterial stiffness, and (ii) Pb did not significantly change with arm tilting.

Antegrade blood velocity was particularly susceptible to the arm being raised, whereas brachial arterial stiffness was specifically susceptible to the arm being lowered. Antegrade blood velocity may have directly influenced the shape of the local pressure waveform, or may have simply been the consequence of increased downstream vascular resistance.[32] Considering the changes in antegrade blood velocity were small, the later explanation is more likely. Interestingly, brachial arterial stiffness increased with arm lowering while the cAIx decreased, which is opposite to what was expected. As such, perhaps it is not surprising that while both antegrade blood velocity and brachial arterial stiffness did decrease the hierarchical linear modelling estimate for change in cAIx with arm tilting, the standard error for the estimate did not decrease and nor did the residual (within-subject) variance. This indicates that while antegrade blood velocity and brachial arterial stiffness are associated with cAIx, other factors do contribute to a change in cAIx. One explanation is that at least part of the cAIx change is not artificial, and that arm tilting does have a small systemic effect. Indeed, contrary to Pucci *et al*,[3] we observed changes to cAIx in the contralateral arm, and these changes are supported by small but robust changes in

systemic vascular resistance. Pucci *et al*[3] may not have observed changes to cAIx in the contralateral arm as a result of the wide age range of study subjects.

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

IMPLICATIONS

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

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.[38] Findings from the current study, along with previous work from our group and
388 others, [3,6–9] 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[39,40] 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,[39] the other that reflection magnitude (Pb/Pf) better
399 predicts cardiovascular events than cAIx.[40] 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

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

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

REFERENCES

1 Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T *et al.* Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007; **50**: 197–203.

2 McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Hear J* 2014; **35**: 1719–1725.

3 Pucci G, Battista F, Anastasio F, Sanesi L, Gavish B, Butlin M *et al.* Effects of gravity-induced upper-limb blood pressure changes on wave transmission and arterial radial waveform. *J Hypertens* 2016; **34**: 1091–1098.

4 Stoner L, Faulkner J, Lowe A, D ML, J MY, Love R *et al.* Should the augmentation index be normalized to heart rate? *J Atheroscler Thromb* 2014; **21**: 11–16.

5 Westerhof BE, Guelen I, Westerhof N, Karemaker JM, Avolio A. Quantification of wave reflection in the human aorta from pressure alone: a proof of principle. *Hypertension* 2006; **48**: 595–601.

6 Young Y, Abdolhosseini P, Brown F, Faulkner J, Lambrick D, Williams MA *et al.* Reliability of oscillometric central blood pressure and wave reflection readings: Effects of posture and fasting. *J Hypertens* 2015; **33**: 1588–1593.

7 Stoner L, Credeur D, Fryer S, Faulkner J, Lambrick D, Gibbs BB. Reliability of pulse waveform separation analysis: Effects of posture and fasting. *J Hypertens* 2017; **35**: 501–505.

8 Stoner L, Stone K, Hanson ED, Faulkner J, Fryer S, Credeur D. Reliability of pulse waveform separation analysis responses to an orthostatic challenge. *Hypertens Res* 2018; **41**: 176–182.

9 Mitchelmore A, Stoner L, Lambrick D, Sykes L, Eglinton C, Jobson S *et al.* Oscillometric central blood pressure and central systolic loading in stroke patients: Short-term reproducibility and effects of posture and fasting state. *PLoS One* 2018; **13**: e0206329.

10 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–1457.

11 Stoner L, Lambrick DM, Faulkner J, Young J. Guidelines for the Use of Pulse Wave Analysis in Adults and. *J Atheroscler Thromb* 2012; **5**: 1–3.

12 Butlin M, Qasem A, Avolio AP. Estimation of central aortic pressure waveform features derived from the brachial cuff volume displacement waveform. *Conf Proc IEEE Eng Med Biol Soc* 2012; **2012**: 2591–2594.

13 Qasem A, Avolio A. Determination of aortic pulse wave velocity from waveform decomposition of the central aortic pressure pulse. *Hypertension* 2008; **51**: 188–195.

14 Jones SC, Bilous M, Winship S, Finn P, Goodwin J. Validation of the OSCAR 2 oscillometric 24-hour ambulatory blood pressure monitor according to the International Protocol for the validation of blood pressure measuring devices. *Blood Press Monit* 2004; **9**: 219–223.

15 Goodwin J, Bilous M, Winship S, Finn P, Jones SC. Validation of the Oscar 2 oscillometric 24-h ambulatory blood pressure monitor according to the British Hypertension Society protocol. *Blood Press Monit* 2007; **12**: 113–117.

16 Stoner L, Sabatier MJ. Use of ultrasound for non-invasive assessment of flow-mediated dilation. *J Atheroscler Thromb* 2012; **19**: 407–421.

17 Stoner L, Sabatier M. Assessments of endothelial function using ultrasound. *Applied aspects of ultrasonography in humans,* 2012.http://cdn.intechopen.com/pdfs/35863/InTech-Assessment_of_endothelial_function_using_ultrasound.pdf.

18 Stoner L, McCully KK. Peak and time-integrated shear rates independently predict flow-mediated dilation. *J Clin Ultrasound* 2012; **40**: 341–351.

19 Stoner L, McCully KK. Velocity Acceleration as a Determinant of Flow-Mediated Dilation. *Ultrasound Med Biol* 2012; **38**: 580–592.

20 Credeur DP, Vana LM, Kelley ET, Stoner L, Dolbow DR. Effects of Intermittent Pneumatic Compression on Leg Vascular Function in People with Spinal Cord Injury: A Pilot Study. *J Spinal Cord Med* 2017; **0**: 1–9.

21 Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sport Exerc* 2009; **41**: 3–13.

22 Cohen J. *Statistical power analysis for the behavioral sciences*. Academic Press: New York ; London, 1969.

23 Raudenbush SW, Bryk AS. *Hierarchical linear models: Applications and data analysis methods*. Sage, 2002.

24 Shoji T, Nakagomi A, Okada S, Ohno Y, Kobayashi Y. Invasive validation of a novel brachial cuff-based oscillometric device (Sphygmo Cor XCEL) for measuring central blood pressure. *J Hypertens* 2017; **35**: 69–75.

25 Nakagomi A, Shoji T, Okada S, Ohno Y, Kobayashi Y. Validity of the augmentation index and pulse pressure amplification as determined by the SphygmoCor XCEL device: a comparison with invasive measurements. *Hypertens Res* 2018; **41**: 27–32.

26 Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD *et al.* Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertens (Dallas, Tex 1979)* 2009; **54**: 375–83.

27 Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H *et al.* Central blood pressure measurements and antihypertensive therapy: a consensus document. *Hypertension* 2007; **50**: 154–160.

28 Gaddum NR, Keehn L, Guilcher A, Gomez A, Brett S, Beerbaum P *et al.* Altered dependence of aortic pulse wave velocity on transmural pressure in hypertension revealing structural change in the aortic wall. *Hypertension* 2015; **65**: 362–369.

29 Tschakovsky ME, Hughson RL. Venous emptying mediates a transient vasodilation in the human forearm. *Am J Physiol Hear Circ Physiol* 2000; **279**: H1007-14.

30 Peng X, Schultz MG, Abhayaratna WP, Stowasser M, Sharman JE. Comparison of Central Blood Pressure Estimated by a Cuff-Based Device With Radial Tonometry. *Am J Hypertens* 2016; **29**: 1173–1178.

31 Hwang MH, Yoo JK, Kim HK, Hwang CL, Mackay K, Hemstreet O *et al.* Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. *J Hum Hypertens* 2014; **28**: 475–481.

32 Stoner L, Young JM, Fryer S, Sabatier MJ. The importance of velocity acceleration to flow-mediated dilation. *Int J Vasc Med* 2012; **2012**: 589213.

33 Caro CG, Pedley TJ, Schroter RC, Seed WA. The systemic arteries. In: *The mechanics of the circulation*. Cambridge University Press: Cambridge, UK, 2012, pp 239–242.

34 Adamson SL, Whiteley KJ, Langille BL. Pulsatile pressure-flow relations and pulse-wave propagation in the umbilical circulation of fetal sheep. *Circ Res* 1992; **70**: 761–772.

35 Segers P, Carlier S, Pasquet A, Rabben SI, Hellevik LR, Remme E *et al.* Individualizing the aorto-radial pressure transfer function: feasibility of a model-based approach. *Am J Physiol Hear Circ Physiol* 2000; **279**: H542-9.

36 Cheng HM, Chuang SY, Sung SH, Yu WC, Pearson A, Lakatta EG *et al.* Derivation and validation of diagnostic thresholds for central blood pressure measurements based on long-term cardiovascular risks. *J Am Coll Cardiol* 2013; **62**: 1780–1787.

37 Sharman JE, Marwick TH, Gilroy D, Otahal P, Abhayaratna WP, Stowasser M *et al.* Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. *Hypertension* 2013; **62**: 1138–1145.

38 Jaccoud L, Rotaru C, Heim A, Liaudet L, Waeber B, Hohlfeld P *et al.* Major impact of body position on arterial stiffness indices derived from radial applanation tonometry in pregnant and nonpregnant women. *J Hypertens* 2012; **30**: 1161–1168.

39 Wang KL, Cheng HM, Sung SH, Chuang SY, Li CH, Spurgeon HA *et al.* Wave reflection and arterial stiffness in the prediction of 15-year all-cause and cardiovascular mortalities: a community-based study. *Hypertension* 2010; **55**: 799–805.

40 Chirinos JA, Kips JG, Jacobs Jr. DR, Brumback L, Duprez DA, Kronmal R *et al.* Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2012; **60**: 2170–2177.

FIGURES

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

TABLES

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

Abbreviations: ES, effect size (partial eta squared), where 0.01, 0.06, and 0.14 represent a small, medium, and large effect, respectively; Cont., contrast; LCI, lower confidence interval (95%); UCI, upper confidence interval (95%);

ΔBF, change in blood flow (systole – diastole); cAIx, central augmentation index; cAIx75, cAIx normalize to a heart rate of 75 bpm; cAP, central augmentation pressure; β, beta index stiffness; BF_{mean}, mean blood flow; Cond., conductance; cSBP, central systolic blood pressure; DBP, diastolic blood pressure; Dist, distention (brachial diameter change); D_{mean}, mean arterial (brachial) diameter; MAP, mean arterial blood pressure; Pf, aortic forward pressure wave; Pb, aortic backward pressure wave; PP_{amp}, pulse pressure amplitude; OI, oscillatory index; RM, reflection magnitude; SBP, systolic blood pressure; shear, shear rate; V_{dia}, diastolic

545 blood velocity; V_{mean}, mean blood velocity; V_{neg}, negative (retrograde) blood velocity; V_{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_{mean}, mean arterial (brachial) diameter; HR, heart rate; PP_{amp}, pulse pressure amplitude;
554 MAP, mean arterial blood pressure; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular
555 resistance

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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°, rather than 1° or 30° change to aid interpretation. Measurements we
560 only conducted at -30°, 0° and 30°.

561 Abbreviations: D_{mean}, brachial artery mean diameter; V_{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°, rather than 1° or 30° change to aid interpretation. Measurements we
566 only conducted at -30°, 0° and 30°.

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

568

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_{amp} (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_{mean} (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
β	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_{dia} (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_{sys} (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_{mean} (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_{neg} (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_{mean} (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
ΔBF (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^{-1})	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_{amp} (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_{Osccar} (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_{USCOM} (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 ($d{\cdot}sec{\cdot}cm^{-5}$)	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	*P*	Est.	SE	*P*	Est.	SE	*P*
Fixed Effects									

Intercept (-30°)	β_{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°)	β_{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_{sys}	β_{20}				-0.02	0.1	0.008	-0.13	0.1	0.026	cSBP change per 1 unit V_{sys}
D_{mean}								8.1	4.1	0.012	cSBP change per 1 unit D_{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

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	*P*	Est.	SE	*P*	Est.	SE	*P*	
Fixed Effects											
Intercept (-30°)	β_{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°)	β_{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_{neg}					-1.66	0.70	0.029	-1.69	0.08	0.020	cAIx change per 1 unit V_{neg}
β								-0.19	0.66	0.038	cAIx change per 1 unit β
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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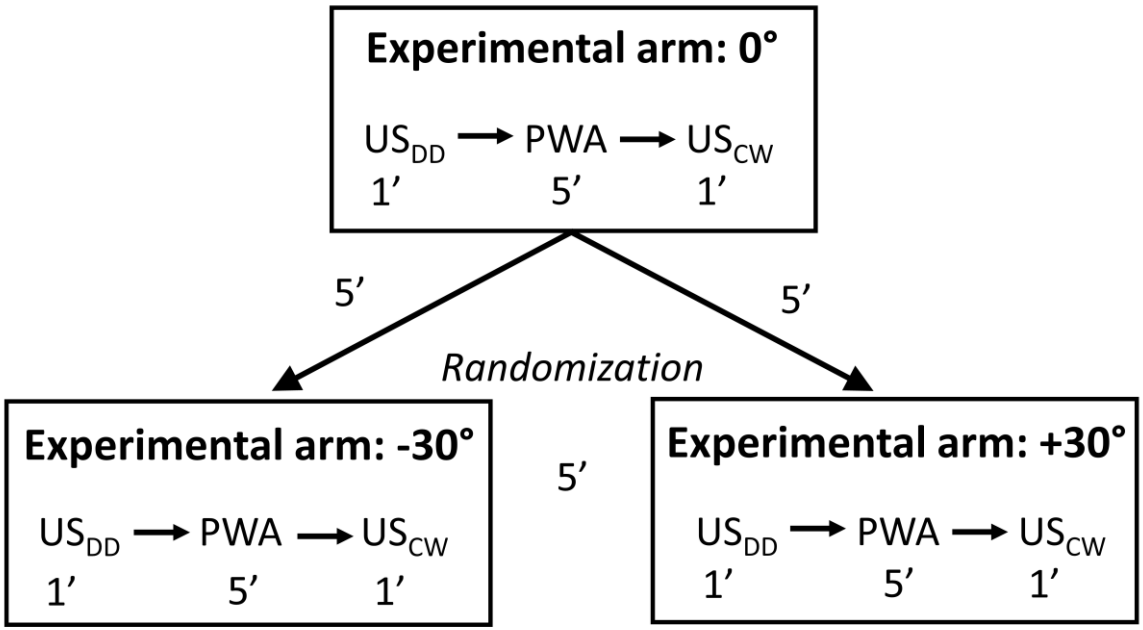

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