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Research Paper

Adrenergic and myogenic regulation of viscoelasticity in the vascular bed of the human forearm

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This study tested the hypothesis that the compliance (C) and viscoelasticity (K) of the forearm vascular bed are controlled by myogenic and/or α-adrenergic receptor (αAR) activation. Heart rate (HR) and waveforms of brachial artery blood pressure (Finometer) and forearm blood flow (Doppler ultrasound) were measured in baseline conditions and during infusion of noradrenaline (NA; αAR agonist), with and without phentolamine (αAR antagonist; $n = 10$; 6 men and 4 women). These baseline and αAR-agonist-based measures were repeated when the arm was positioned above or below the heart to modify the myogenic stimulus. A lumped Windkessel model was used to quantify the values of forearm C and K in each set of conditions. Baseline forearm C was inversely, and K directly, related to the myogenic load ($P < 0.001$). Compared with saline infusion, C was increased, but K was unaffected, with phentolanine, but only in the 'above' position. Compliance was reduced ($P < 0.001$) and K increased ($P = 0.06$) with NA infusion (main effects of NA) across arm positions; phentolamine minimized these NA-induced changes in C and K for both arm positions. Examination of conditions with and without NA infusion at similar forearm intravascular pressures indicated that the NA-induced changes in C and K were due largely to the concurrent changes in blood pressure. Therefore, within the range of arm positions used, it was concluded that vascular stiffness and vessel wall viscoelastic properties are acutely affected by myogenic stimuli. Additionally, forearm vascular compliance is sensitive to baseline levels of αAR activation when transmural pressure is low.

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Blood flow in the intact cardiovascular system is oscillatory owing to the pulsatile nature of pressure generated by the heart and the viscoelastic properties of the arterial walls. Vascular viscoelasticity (K) is a combination of pure elasticity, and viscous resistance to stretch (Westerhof & Noordergraaf, 1970; Gow, 1980; Armentano *et al.* 1995*b*; Zamir, 2005; Westerhof *et al.* 2009) which enables the vascular wall to accommodate large volumes of blood during systole. In a viscoelastic vessel, there is added resistance to the rate at which volume is changing, which has a damping effect on the swings in pressure and volume within the cardiac cycle.

The integration of compliance (C) and K into the mechanics of pulsatile flow has been, to a large extent, confined to a theoretical or mathematical understanding of these effects (Milnor, 1989; Nichols & O'Rourke, 1990; Zamir, 2000). The application of the Windkessel modelling approach by Otto Frank (for review see Westerhof *et al.* 2009) initiated this mathematical approach with emphasis on the interaction of blood pressure and vascular properties that affect cardiac afterload. However, these pressure variations in the large central arteries are affected only partially by peripheral vasomotor properties. A study of the mechanical properties of the peripheral vascular bed, which contribute to organ blood flow distally, is required in order to fully understand normal and abnormal vascular control.

Different approaches have been developed to study peripheral vascular oscillatory properties. One approach emphasizes the study of large artery 'distensibility' using

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non-invasive measures of relative diameter changes in large arteries for a given pulsatile pressure. These studies indicate that the compliance of large conduit vessels displays sensitivity to intravascular pressure (Bank *et al.* 1995; Zheng & Murray, 2009) and reflexive sympathetic activation (Boutouyrie *et al.* 1994; Salzer *et al.* 2008). Armanteno and colleagues (Armentano *et al.* 1995*a*,*b*; Gamero *et al.* 2000) have advanced methods to infer viscoelastic properties of conduit vessels mathematically, based on pressure–volume relationships.

Secondly, experimental studies of vessel wall viscoelastic properties at the microcirculatory level have been done using *in vitro* examinations. These studies indicate that viscoelastic properties are expressed in microvessels through mechanism(s) that reflect the extracellular matrix, but also through properties inherent to the smooth muscle cells (Gore & Bohlen, 1975; Siegman *et al.* 1976*a*,*b*); that is, the contractile element contributes to the viscoelasticity of a vascular wall. If viscoelasticity incorporates a complex integration of wall matrix and vascular smooth muscle, then this property should be modifiable by mechanisms that change smooth muscle excitation. Such factors include the myogenic or pressure-dependent and the neurogenic or α-adrenergic receptor (αAR)-based mechanisms. Studies using *in vitro* conditions indicate that the myogenic response can be modulated by sympathetic neurotransmitters such as noradrenaline, raising the possibility of synergistic control of the vasculature between myogenic and neurogenic stimuli (Schubert & Mulvany, 1999). Whether such *in vitro* studies translate into features of control over pulsatile flow in the intact vascular bed remains to be established.

While providing information regarding the behaviour of single vessels from discrete locations along the vascular tree, the above approaches cannot provide information on the intact oscillatory behaviour of a peripheral vascular bed in physiological conditions. Thus, recent adaptations of the lumped Windkessel approach, combined with methods to obtain concurrent waveforms of blood flow and pressure in the intact vascular bed, have introduced a methodological opportunity to quantify and study the relationship between vascular mechanics and pulsatile flow of a lumped peripheral vascular bed in humans (Zamir *et al.* 2007, 2009). This approach enables assessment of the *in vivo* levels of the compliance and viscoelasticity in varying conditions and was applied in the present study to examine the impact of myogenic and αAR-based control over the vascular bed of the human forearm.

Our working hypothesis is that compliance and/or viscoelasticity are controlled properties of the vessel wall and of an intact peripheral vascular bed. The purpose of this study was to test the specific hypothesis that the compliance and viscoelasticity of the human forearm vascular bed are controlled by myogenic and/or αAR stimuli. These control features were studied during manipulations of αAR activation with phentolamine (PH) and/or noradrenaline (NA) that were superimposed upon a varied myogenic background achieved by varying arm positions relative to the heart.

Table 1. Participant characteristics ($n = 10$)

	Mean	±SD
Age (years)	27	3
Height (cm)	172	7
Weight (kg)	70	13
HR (beats min^{-1})	56	8
MAP (mmHg)	85	6
SBP (mmHg)	117	7
DBP (mmHg)	68	6
$\dot{Q}$ (l min^{-1})	4.36	1.00

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; $\dot{Q}$, cardiac output; and SBP, systolic blood pressure. Blood pressure measures were obtained by manual sphygmomanometry with the arm at heart level.

Methods

Subjects

Ten healthy, normotensive participants (6 men and 4 women; age range 23–31 years; Table 1) volunteered for the study. The participants were asked to abstain from alcohol, nicotine and caffeine as well as physical activity for 24 h prior to testing. Based on responses to a health questionnaire, all participants were free from cardiovascular or neurological disease, allergies and medications contraindicative to participation. For the female participants, there was no standardization for the timing of the measurements relative to the menstrual cycle or the use of oral contraceptives. All participants provided informed written consent. The protocol was approved by The University of Western Ontario Ethics Committee for Research on Human Subjects and conformed with the provisions of the latest revision of the Declaration of Helsinki.

Data acquisition

While supine, a venous catheter was inserted into an antecubital vein of the left arm for delivery of pharmacological agents. Heart rate was determined from the electrocardiogram. Continuous blood pressure measures were obtained from the middle finger of the right hand using photoplethysmographic methods (Finometer^{TM}; Finapres Medical Systems BV, Amsterdam, The Netherlands). From these Finometer measures, continuous brachial artery blood pressure waveforms and cardiac output ($\dot{Q}$) were obtained via recalculation

from directly recorded finger pressure values of the right arm (Schutte *et al.* 2003; Bogert *et al.* 2004; Bogert & Van Lieshout, 2005). We have shown previously that the calculated brachial artery waveform accurately represents the true waveform as assessed by applanation tonometry (Zamir *et al.* 2007). In addition, manual measures of systemic blood pressure were obtained from the left arm at heart level during the steady-state periods of the study segments that are defined below.

The diameter as well as blood flow waveforms of the right brachial artery were assessed using ultrasound imaging (B-mode, 7.5 MHz, GE System Five) and Doppler ultrasound (4.7 MHz, GE System Five), respectively. Brachial artery diameters were measured at end diastole. The location at which the ultrasound-based measures were taken was marked prior to commencement of testing to ensure consistency across the protocol trials.

All analog data were sampled at 1000 Hz and collected online using the PowerLab data acquisition system (PowerLab; ADInstruments, Castle Hill, NSW, Australia). Data collection began after at least 30 min of supine posture. Between trials, blood flow variables stabilized in each arm position before data collection resumed for the subsequent trial.

Protocol design

The myogenic stimulus was modified by altering the position of the right arm relative to the heart (Netea *et al.* 1998), producing a hydrostatically mediated change in vascular pressure of about 20 mmHg. Across participants, the arm was raised to a position of 18 ± 3 cm above the heart (Above condition), reducing vascular pressure by ∼13 mmHg (relative to the heart), and lowered to 10 ± 2 cm below heart level (Below condition), increasing vascular pressure by ∼7 mmHg. The relatively smaller deflection of arm position in the Below position prevented potential shoulder discomfort over the duration of the study. Within each arm position, the αAR activation levels were varied by infusing NA against a background of saline (Control) or PH in two separate trials. The Control trial consisted of a continuous saline infusion for 26 min ($1\ \mathrm{ml\ min^{-1}}$) whereby, in each of the two arm positions, a baseline data collection period of 5 min was followed by NA infusion for 5 min ($100\ \mathrm{ng\ kg^{-1}\ min^{-1}}$; Harvard infusion pump model no. PHD 22/2000) and then by 8 min of recovery to allow haemodynamic variables to return to baseline levels. The PH trial followed the same protocol as the Control trial, with PH infused continuously (PH; $200\ \mu\mathrm{g\ min^{-1}}$) over the 26 min period. The NA was co-infused with PH using a second manifold port of the stopcock. With the PH trial, it was possible to block baseline αAR activation and to confirm the αAR impact of the NA infusion. The order of arm position was randomized for each of the Control and PH trials; however, the saline infusion trial was conducted first in all participants owing to the lengthy (∼20 min) half-life of PH. The height sensor for the Finometer was active during the protocol so that rapid changes in systemic blood pressure could be monitored during drug infusions. The forearm intravascular pressure was calculated from the mean Finometer-based blood pressures using the hydrostatic equivalent of blood pressure in each arm position (Netea *et al.* 1998).

Data analysis

Between 30 and 60 s of representative data were obtained from the fourth minute of the Baseline and NA infusion periods. These data were used to calculate an average for all haemodynamic variables in each set of conditions. Total peripheral resistance (TPR) was calculated as mean arterial pressure (MAP) divided by flow rate ($\dot{Q}$). Systemic vascular conductance (SVC) was calculated as $\dot{Q}$/MAP. Forearm blood flow (FBF) was calculated as the cross-sectional area of the brachial artery during diastole × FBV.

Forearm vascular properties were assessed using a modified four-element lumped Windkessel model, namely resistance (R), compliance (C), viscoelasticity (K) and inertance (L; Zamir *et al.* 2007). The model requires pressure and flow waveforms measured simultaneously from the brachial artery. The pressure waveform is used to derive a calculated blood flow waveform, based on values of C, K and L that are adjusted in an iterative manner to achieve agreement between the calculated and the measured flow waveforms. At least two different selections of 10 consecutive cardiac cycle waves were used for each set of conditions.

Statistical analysis

The effects of NA and arm position on baseline variables were assessed with repeated-measures two-way ANOVA (Statistical Analysis System version 9.1, SAS Inc., Cary, NC, USA). The effects of NA infusion and arm position on the change from baseline in vasomotor responses to NA infusion (i.e. ΔC) were then assessed using repeated-measures two-way ANOVA. Significant main effects and interactions were assessed further using Tukey's *post hoc* analysis. Directional hypotheses were proposed in this study because it was suspected that if myogenic and/or αAR mechanisms affect vascular bed compliance or viscoelasticity, they would do so in a particular manner. For example, on the basis that vascular stretch (myogenic input) and αAR activation produces vasoconstriction, it would be expected that increases in these stimuli would decrease vascular compliance and increase viscoelasticity. Probability levels were accepted as statistically significant if $P < 0.05$. Data are expressed as means ± SD.

Table 2. Effect of arm position and noradrenaline (NA) infusion, with and without phentolamine (PH) infusion, on systemic haemodynamics during baseline conditions and during the fourth minute of NA infusion

	Control trial				Phentolamine trial			
	Above		Below		Above		Below	
Arm position	Baseline	NA	Baseline	NA	Baseline	NA	Baseline	NA
HR (beats min^{-1})	55 ± 8	48 ± 7*	55 ± 8	48 ± 8*	59 ± 8	59 ± 8	62 ± 9†	61 ± 9
MAP[a] (mmHg)	101 ± 6	120 ± 5*	102 ± 6	117 ± 9*	99 ± 8	106 ± 11‡	101 ± 5	106 ± 8‡
SBP[a] (mmHg)	114 ± 7	139 ± 7*	116 ± 8	135 ± 12*	114 ± 9	123 ± 13‡	114 ± 7	123 ± 10‡
DBP[a] (mmHg)	76 ± 5	83 ± 5*	74 ± 7	80 ± 6*	71 ± 8	74 ± 7‡	75 ± 9	75 ± 6‡
PP[a] (mmHg)	38 ± 6	55 ± 8*	41 ± 7	55 ± 11	43 ± 5	49 ± 11‡	40 ± 6	48 ± 8‡
$\dot{Q}$[b] (l min^{-1})	4.40 ± 0.91	4.10 ± 0.95	5.22 ± 0.95	4.77 ± 1.34	4.82 ± 1.38	5.36 ± 1.63	5.87 ± 1.50	6.21 ± 1.7
TPR[b] (mmHg l^{-1} min^{-1})	20 ± 5	25 ± 6*	19 ± 5	27 ± 7*	19 ± 5	19 ± 5‡	18 ± 6	19 ± 5‡
SVC[b] (l min^{-1} mmHg^{-1})	0.05 ± 0.01	0.04 ± 0.01*	0.06 ± 0.01	0.05 ± 0.01*	0.06 ± 0.01	0.06 ± 0.02‡	0.06 ± 0.02	0.06 ± 0.02‡
Dia (cm)	3.73 ± 0.07	3.66 ± 0.08	3.63 ± 0.07	3.49 ± 0.08	3.62 ± 0.08	3.59 ± 0.07	3.59 ± 0.08	3.51 ± 0.08
FBF (ml min^{-1})	20 ± 9	17 ± 7	20 ± 8	16 ± 6	22 ± 13	23 ± 13	27 ± 16	23 ± 14
FVR (mmHg ml^{-1} min^{-1})	4.8 ± 2.4	5.6 ± 2.4*	4.5 ± 2.1	6.7 ± 3.1*	4.2 ± 2.4	4.7 ± 2.4	5.1 ± 3.0	5.3 ± 2.5

Values are means ± SD. Abbreviations: Dia, brachial artery diameter; DBP, diastolic blood pressure; FBF, forearm blood flow; FVR, forearm vascular resistance; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; $\dot{Q}$, cardiac output; SBP, systolic blood pressure; SVC, systemic vascular conductance; and TPR, total peripheral resistance. [a] Blood pressures represent brachial artery values after a calculated removal of the Finometer's height correction (note that mean systemic pressures with NA infusion and arm position are shown in Fig. 1). [b] Values of $\dot{Q}$ were obtained from the Modelflow calculation performed by the Finometer with height correction applied; therefore, $\dot{Q}$, TPR and SVC values reflect the impact of NA infusion during a particular arm position but cannot be used to infer the impact of arm position on $\dot{Q}$. *Significantly different from baseline ($P < 0.05$) within each arm position; † significantly different from Control Baseline ($P < 0.05$); ‡ significantly different from Control NA ($P < 0.05$).

Results

Systemic haemodynamics

Effect of arm position. During both Control and PH trials, moving the arm from Below to Above (or vice versa) had no effect on any central haemodynamic variable (Table 2).

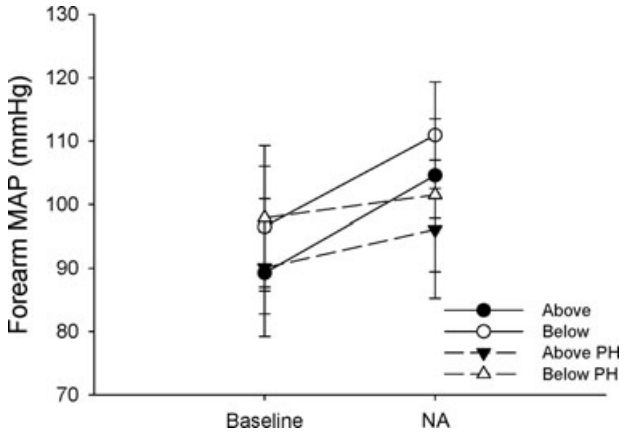

Figure 1. Mean arterial pressure (MAP) in the forearm during baseline conditions (with saline infusion) and during the fourth minute of noradrenaline infusion (NA; 100 ng kg^{-1} min^{-1}) with arm positioned above and below heart level.
The NA was infused with and without phentolamine (PH). The tests were repeated with the arm positioned above (Above) and below heart level (Below). Values represent Finometer-based determinations of brachial artery pressure without height correction applied. Arm position effect, $P < 0.01$; NA effect, $P < 0.01$; and arm position × NA effect, $P < 0.01$.

Effect of noradrenaline infusion and phentolamine blockade. In the Control trial, NA infusion increased systemic MAP compared with the baseline period for both the Above (∼19 mmHg) and the Below (∼15 mmHg) arm positions (main effect of NA, $P < 0.05$; Table 2). This pressor response was prevented with phentolamine. The same pattern of changes were observed for both systolic and diastolic blood pressures, with pressor responses observed during NA infusion but not when infused with phentolamine (Table 2). In the Control trial, heart rate (HR) decreased with NA infusion compared with baseline in both arm positions ($P < 0.05$; Table 2). This effect on HR was prevented with concurrent infusion of phentolamine. The rise in MAP with NA infusion occurred concurrently with a reduction in systemic vascular conductance ($P < 0.05$), an effect that was reversed by pretreatment with phentolamine (Table 2).

Forearm vascular properties

Effect of arm position and noradrenaline on forearm vascular pressure. Compared with Below, the calculated distending pressure in the brachial artery was reduced by positioning the arm above the heart (Fig. 1; $P < 0.05$); however, this change in position did not result in changes in brachial artery diameter or total blood flow (Table 2). Forearm MAP increased to a similar extent with NA infusion in both the Above (from 89 ± 6 to

105 ± 5 mmHg) and Below positions (from 97 ± 10 to 111 ± 8 mmHg), comparing Baseline and NA infusion, respectively ($P < 0.01$). This response was prevented by phentolamine.

Forearm vascular compliance. Graphs showing individual variations and group means in C and K following NA and NA + PH infusions are provided in Fig. 2 for both arm positions.

During the Control trial, forearm C was greater in the Above (0.0065 ± 0.0031 ml mmHg^{-1}) compared with the Below position (0.0044 ± 0.0015 ml mmHg^{-1}; main effect of arm position, $P < 0.05$; Fig. 2). Likewise, during the phentolamine trial, C was 0.0079 ± 0.0033 ml mmHg^{-1} in Above and 0.0045 ± 0.0023 ml mmHg^{-1} in Below (Fig. 2).

Forearm C was reduced with NA infusion ($P < 0.001$) during each arm position in the Control trial, and this effect was minimized by PH (Fig. 2); however, the absolute decrease in C (ΔC) with NA infusion was -0.0025 ± 0.002 ml mmHg^{-1} in Above and -0.0014 ± 0.001 ml mmHg^{-1} in Below (n.s.). Likewise, the relative changes (%Δ) in C measured during NA infusion were -33 ± 21 and -32 ± 16% for the Above and Below conditions, respectively (n.s.).

Forearm vascular viscoelasticity. Compared with Above baseline, the mean forearm K was greater in the Below arm position (Fig. 2; main effect, $P < 0.001$). Compared with baseline, K increased modestly with NA infusion (Fig. 2; main effect of NA, $P = 0.06$; achieved $\beta = 0.11$ in Above and $\beta = 0.34$ in Below); however, the increase in K (ΔK) with NA infusion was 0.015 ± 0.05 mmHg ml^{-1} min^{-1} in Above and 0.061 ± 0.06 mmHg ml^{-1} min^{-1} in Below ($P = 0.14$). Likewsie, the relative increase (%Δ) in K with NA was variable across participants and similar in both the Below (45 ± 50%) and Above positions (29 ± 48%; n.s.). The interaction terms between arm position and NA infusion for both ΔK and %ΔK were not significant.

It is possible that the changes in C or K with NA infusion were related to the systemic changes in blood pressure rather than a direct αAR effect. Thus, the contributions of αAR activation to C and K in conditions of similar mean intravascular pressure were explored. Figure 3 demonstrates the effect of removing baseline αAR activation without change in forearm intravascular pressure. In this case, PH infusion caused an increase in C in the Above position only, relative to baseline ($P < 0.05$); however, PH alone did not affect values of K in either arm position. In addition, the impact of elevating αAR activation above baseline levels at similar

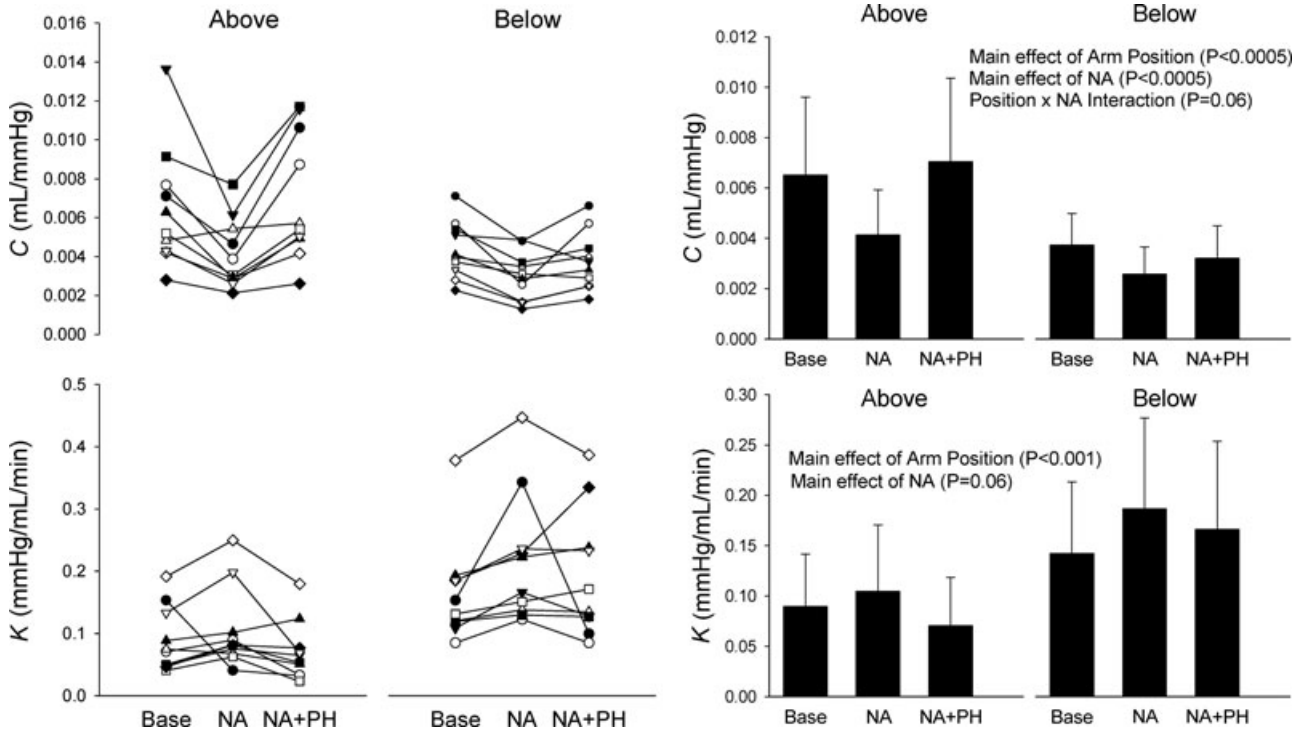

Figure 2. Individualized (Left) and grouped (Right) changes in compliance (*C*) and viscoelasticity (*K*) to noradrenaline (NA) infusion during different arm positions.
Left panel shows the impact of 100 ng kg^{-1} min^{-1} noradrenaline (NA) infusion or NA + phentolamine (NA + PH) on forearm vascular bed compliance (*C*; top panel) and viscoelasticity (*K*; bottom panel) with arm held above (Above) and below heart level (Below). Noradrenaline was delivered during a control period of saline infusion or phentolamine (PH). Main effects are noted. Mean values are provided in the right panel.

forearm vascular pressures was examined by contrasting the Above + NA *versus* Below control conditions. Values of C in Above + NA (0.004 ± 0.002 ml mmHg^{-1}) were the same as Below baseline (0.004 ± 0.001 ml mmHg^{-1}; n.s.). Values of K were 0.105 ± 0.07 mmHg ml^{-1} min^{-1} in Above + NA and 0.166 ± 0.08 mmHg ml^{-1} min^{-1} in Below baseline ($P = 0.09$; achieved $\beta = 0.62$).

Discussion

This study examined the impact of myogenic and αAR stimuli on the compliance and viscoelasticity of the forearm vascular bed. The results provided evidence that both forearm vascular C and K are affected acutely by arm position and, by inference, myogenic stimuli. Only C was affected by baseline levels of αAR activation, and this response was apparent only at low transmural pressures (arm Above). A role of αAR activation in the control of K was not supported, because the relationship between K and αAR stimulation was accounted for by concurrent changes in intravascular pressure. Thus, it was concluded that both C and K exhibit sensitivity towards myogenic stimuli, that baseline levels of αAR activation reduce C during conditions of lower transmural pressures and that there is no compelling evidence for an independent effect of αAR activation on the viscoelasticity of the forearm vascular bed.

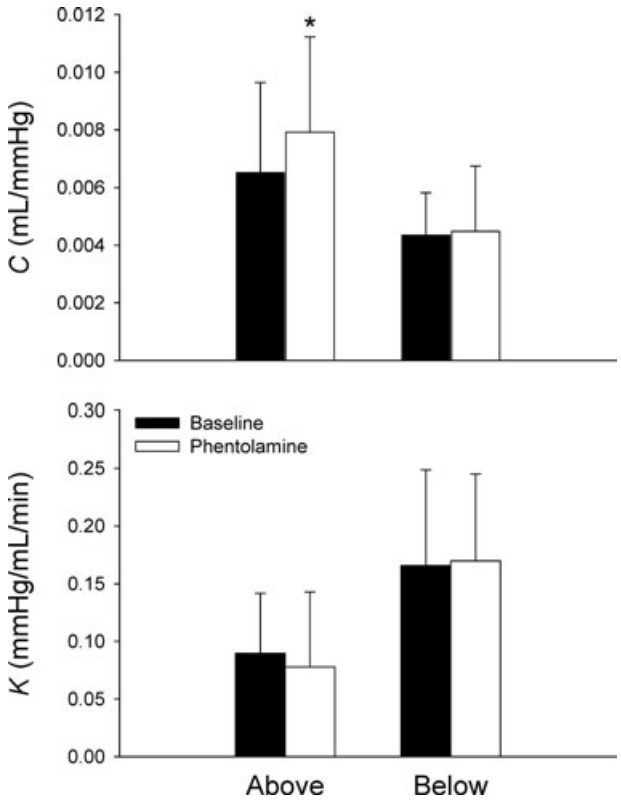

Figure 3. Effect of phentolamine on the lumped values of forearm compliance (*C*) and viscoelasticity (*K*) with the arm positioned above (Above) or below heart level (Below)
*Significantly different from saline or baseline conditions ($P < 0.05$).

Myogenic response

The first major observation of the present study was that forearm vascular bed compliance was increased, and viscoelasticity reduced, when the arm was positioned Above *versus* Below the heart. These results replicate our previous observations of the impact of arm position on forearm vascular bed compliance (Zamir *et al.* 2007) and introduce the study of viscoelastic properties as well. While only two positions were used in the present study, they do support recent observations of a non-linear inverse relationship between intravascular pressure and vascular elasticity in the human forearm (Zheng & Murray, 2009). The increase in C with arm elevation is also consistent with observed increases in the systolic component of the forearm blood flow waveform without changes in total forearm blood flow or brachial diameter (Tschakovsky *et al.* 1996; Shoemaker *et al.* 1996, 1998; Zamir *et al.* 2007).

Changing arm positions relative to the heart induces a change in intravascular pressure that is proportionate to the hydrostatic gradient (Netea *et al.* 1998). Therefore, it is expected that concurrent changes in both C and K were induced by a pressure-induced myogenic response. It is not known how quickly these adaptations to hydrostatic pressure occur. In the present study, the arm was maintained in a given position for several minutes before measures were made. It is expected that the viscous properties of the vessel wall would produce some stretch-relaxation in such a model, as is reported in *in vitro* models (Siegman *et al.* 1976*a*,*b*). Thus, any acute pressure-induced change in K might be underestimated if some stretch-relaxation occurred. The extent to which a stretch-relaxation effect changes the resistance to pulsatile stretch is not addressed in the present study. Nonetheless, the expression of viscoelastic properties during prolonged stretch-relaxation phenomena is likely to differ from that expressed during pulsatile stretch that occurs within the time frame of the cardiac cycle. Also, in the framework that K actively limits the elasticity of a vascular segment, it would follow that the contractile state of vascular smooth muscle should influence K and this would then influence C.

This conclusion that C and K are acutely affected by a pressure-dependent mechanism must be considered within the context of possible changes in αAR activation that occur with changes in arm position. The issue of αAR control and whether it differs between arm positions is discussed below; however, it is noteworthy to indicate here that the present study offers two observations that discount the potential role of αAR activation in the

pressure-dependent changes in C and K. The first is that a change in arm position had no effect on systemic haemodynamic variables; there were no apparent reflexive stimuli to elicit or represent a change in autonomic nervous system activity. Second, the decrease in C and increase in K with NA infusion were accounted for by the concurrent change in blood pressure, regardless of whether the data were reported in absolute or relative terms (this issue is expanded upon below). Therefore, existing data with NA infusion suggest that any impact of systemic changes in sympathetic activation with arm position would be minimal.

Adrenergic response

Noradrenaline infusion consistently resulted in increased MAP, FVR and TPR and decreased SVC in a phentolamine-sensitive manner, indicating that these changes were induced by αAR activation. Consistent with previous work, infusion of phentolamine did not affect baseline MAP in supine subjects (Sander *et al.* 1999; Tulppo *et al.* 2005). Importantly, PH alone did not impact the effect of arm position on C or K.

In the present study, NA infusion increased FVR, representing its effect on the overall steady-state calibre of the forearm vascular bed downstream from the brachial artery measurement site. However, NA infusion in the left arm did not affect the diameter of the brachial artery in the right arm where our measures were made. These results are consistent with previous work by Salzer *et al.* (2008) and Dyson *et al.* (2006), who observed unchanged diastolic brachial diameter measures during sympathoexcitatory sessions of lower body negative pressure and cold pressor tests. Although an earlier study reported brachial artery constriction when NA was infused (Bank *et al.* 1995), it is noted that, in this earlier study, the constriction was observed at the site of infusion (arterial infusions), whereas, in the present study, diameter measures were taken from the contralateral arm during venous infusions.

A second major question addressed in the present study was whether or not αAR exerted a direct effect on either C or K of the forearm vascular bed. Evidence from isolated vessels suggests that viscoelastic properties of a moderately sized arteriole depend upon tissue bath calcium but not on a change in membrane potential or intracellular sources of calcium, as would be elicited by agonist-based stimuli (Siegman *et al.* 1976*a*; Bevan, 1985; Schubert *et al.* 2008). This does not exclude a potential role of adrenergic control of viscoelastic properties, because αAR subtypes enhance calcium influx through voltage-dependent and voltage-independent calcium channels (Graham *et al.* 1996; Piascik & Perez, 2001). These *in vitro* data cannot predict whether αAR activation can affect on C or K in the intact system. At first glance, the present changes in absolute values of C and K with NA infusion indicate that adrenergic activation can affect vascular compliance and viscoelastic behaviour and that this effect is similar across a range of physiological hydrostatic pressures in the human forearm. Nonetheless, NA infusion increased mean arterial pressure in both arm positions, raising concern regarding interpretation of the change in C and K with αAR stimulation. In this scenario, it is difficult to separate the direct effects of NA on vascular oscillatory properties from the effects due to changes in pressure that could move the vascular bed along its lumped volume–pressure curve. Two subanalyses were performed to test this possibility. First, the values of C and K were compared between baseline conditions and following Phentolamine infusion. Mean arterial pressure was the same in each set of conditions, providing an opportunity to examine the influence of αAR at the same distending pressure, at least in baseline conditions. Based on this analysis, it appears that there is a small impact of chronic, or baseline, αAR activation on forearm vascular bed C but not K, at least when transmural pressure is relatively low. Second, comparing conditions of similar forearm intravascular pressure but different levels of αAR activation produced values of K that weighed in favour of sensitivity to pressure and not NA. Therefore, there was minimal direct effect of increased adrenergic receptor activation on forearm C or K that was not accounted for by concurrent changes in blood pressure.

Overall, the only evidence in the present study that αAR activation affected vascular bed mechanics was the increase in C following αAR blockade in the Above position. These observations indicate that baseline levels of αAR exert some influence on forearm vascular bed compliance in a manner that appears to be inversely related to transmural pressure. This observation is consistent with results from Bank *et al.* (1995), who used intravascular ultrasound in the human brachial artery and observed that NA infusion produced greater absolute changes in brachial artery compliance under lower transmural pressures.

The inability to expose a sympathetic effect on vasomotor stiffness in the Below position might be explained by the additive neural influence of the venoarteriolar reflex (Henriksen *et al.* 1983) in the dependent limb. In this scenario, a given dose of αAR blockade may not produce the same effect as it might when local or systemic sympathetic outflow is lower. Yet, phentolamine did block the effect of NA infusion on forearm vascular resistance in both the Above and Below conditions and would, therefore, be expected to block smaller levels of activation. Also, Ping & Johnson (1992) reported that lidocaine did not alter the vasoconstrictor response to increased vascular pressure when sympathetic activation was increased. These observations discount a role of venoarteriolar reflex-mediated increases in vascular bed C or K.

The differences in ability to detect neurogenic impact on *C* between arm positions raise the question of whether there is a threshold between the two positions at which baseline αAR effects on vascular elastic behaviour can be detected. Such a threshold may be the hydrostatic indifference point. This speculation is based on our earlier observations that reflexive increases in sympathetic outflow, induced by a moderate level of orthostatic stress through lower body suction, did reduce forearm vascular bed *C* (Zamir *et al.* 2007). In that study, lower body suction did not change mean arterial pressure, and the arm was positioned at heart level. Such details regarding myogenic–neurogenic interactions in vascular bed mechanics will require additional research.

Methodological considerations and study limitations

The vascular wall contains collagen, smooth muscle cells and elastic fibres as the primary load-bearing components. It is these factors that determine the compliance of a vascular wall (*C*) and the inherent resistance of that vascular wall to distension (*K*) with each cardiac cycle. The extent to which each of collagen or elastin contributes to *C* or *K* cannot be determined from the present study.

This study focused on α-adrenergic control of oscillatory vascular parameters. Other sympathetic cotransmitters, such as ATP (Burnstock, 1995) and neuropeptide Y (Zukowska-Grojec & Vaz, 1988; Jackson *et al.* 2004), may also play a role in this vascular regulatory process but in a manner that is not known.

We have relied on the Finometer for brachial artery blood pressure waveforms. Earlier, we verified that the Finometer waveforms are predicted accurately (Zamir *et al.* 2007). Also, in the review stage of this study, we determined that the height sensor has no direct impact on the blood pressure waveform (unpublished observations; Frances *et al.* 2011). However, the impact of the height sensor correction on waveform timing and model outcomes will require additional investigation.

The value of the modelling approach used to obtain information about the oscillatory vasomotor control in the forearm is that it can estimate functional characteristics of the intact vascular bed and it is self-validating, based on the use of measured pressure and flow waveforms. While useful in testing hypotheses in the intact vascular bed, we acknowledge that vascular responses to pressure loads are emphasized in moderately sized arterioles (Meininger *et al.* 1987) and are likely to be affected by regional differences in αAR concentration (Faber, 1988; Ohyanagi *et al.* 1991) or after receptor contractile coupling (Minneman, 1988). As a result, the difference in control of vascular *C* and *K* over the different levels of the arterial tree cannot be determined.

Conclusions

The present findings demonstrated that, within the range of arm positions used, the compliance and viscoelastic properties of the forearm vascular bed are sensitive to acute changes in myogenic stimuli. Additionally, forearm vascular compliance is sensitive to baseline levels of αAR activation when transmural pressure is low. We did not observe convincing evidence that myogenic and αAR mechanisms interact to affect forearm vascular *C* or *K* or that *K* was independently controlled by αAR activation at baseline or following NA infusion. The results provide compelling evidence that the compliance of a vascular bed is a controlled contributor to oscillatory blood flow and that *K* and *C* together appear to incorporate the contractile element of the vascular wall into a dynamic system that can defend the responsiveness of the system to changes in pressure or flow (Zamir *et al.* 2009).

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