Similarity between the suprasystolic wideband external pulse wave and the first derivative of the intra-arterial pulse wave

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Background. Wideband external pulse (WEP) monitoring, using a broad bandwidth piezoelectric sensor located over the brachial artery under the distal edge of a sphygmanometer cuff, can be used for evaluating the contour of the arterial pressure pulse wave. The pulse contour contains valuable information relating to cardiovascular function which may be of clinical use in addition to blood pressure measurements. The aim of this study was to compare the shape of the WEP signal during inflation of the cuff to suprasystolic pressure, with intra-arterial pressure waves, after the administration of vasoactive drugs.

Methods. Radial intra-arterial and suprasystolic WEP waveforms were recorded in 11 healthy men (mean 23 yr) before and at the end of infusion of glyceryl trinitrate, angiotensin II, norepinephrine, and salbutamol. Waveform similarity was assessed by comparing the timing and pressure of incident and reflected waves and by root mean square error (RMSE).

Results. The WEP signal was found to closely resemble the first derivative of intra-arterial pressure. The WEP signal could be used to derive an arterial pressure wave with minimal bias in the timing of incident [−8 (18) ms, mean (SD)] and reflected [−1 (24) ms] waves. Augmentation index was underestimated by WEP [−7 (18)%). WEP also provided a measure of compliance which correlated with pulse wave velocity (r = −0.44). RMSE values after the administration of each of the four drugs mentioned earlier were 12.4 (3.8), 17.7 (5.0), 22.1 (11.7), and 28.9 (22.4) mm Hg, respectively. Changes in derived WEP signals were similar to those measured by arterial line with all drugs.

Conclusions. The suprasystolic WEP signals can be used to derive arterial pressure waves which, although not identical, track changes in the intra-arterial pulse wave induced by vasoactive drugs.

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smooth muscle activity, endothelial function, and mean distending arterial pressure. Increased arterial stiffness is a major contributing factor to elevated systolic and pulse pressures and has been shown to be associated with target organ damage and with increased mortality independent of blood pressure. Furthermore, increased pressure augmentation, as a consequence of increased arterial stiffness, has been shown to be an important determinant of cardiac work and myocardial perfusion and is associated with adverse cardiovascular outcome.

Analysis of the pulse shape can also be used for determining direct measurements or indirect estimates of cardiac function, such as left ventricular ejection time or cardiac output, respectively. At present, there is little evidence for an association between perioperative complications and admission blood pressures of <180/110 mm Hg. An alternative means of preoperative risk stratification, such as pulse contour analysis, may therefore be more useful than blood pressure measurement alone, but the technique ideally needs to be simple and practical.

In clinical practice, monitoring of the pressure wave using intra-arterial methods is widespread in the setting of acute illness and anaesthesia. However, the invasive nature of this technique makes it unsuitable for most research studies or for general clinical use. Non-invasive applanation tonometry has been successfully used in a clinical research setting for pulse wave analysis, but adequate practice and training are essential. Wideband external pulse (WEP) monitoring was first described in 1988 by Blank and colleagues as an alternative non-invasive technique for evaluating the arterial pressure pulse. Using a broad bandwidth (0.1–2000 Hz) piezoelectric sensor placed over the brachial artery under the distal edge of a sphygmomanometer cuff, they described changes in the externally recorded arterial waveform as a function of cuff pressure. They noted that, at suprasystolic cuff pressures, the resulting waveform, transmitted through soft tissues and cuff material rather than the vasculature, exhibited a typical shape consisting of three peaks and two troughs, although the nature of these contour features was not examined further. It is an attractive technique, as it uses potentially simple and cheap technology, can be performed quickly, and requires minimal operator training, in comparison with other non-invasive assessments of arterial function such as tonometry or vascular ultrasound.

This method has recently been incorporated into a commercial system (Pulsecor, Auckland, New Zealand) for the assessment of vascular function. We hypothesized that the features of the suprasystolic WEP signal would be closely related to the shape of the invasively measured arterial pressure pulse. We examined the relationship by recording both signals in healthy volunteers after the administration of vasoactive pharmacological agents to achieve large changes in the pressure contour through disturbance of blood pressure, the intrinsic properties of the arterial wall, and cardiac contractility.

Methods

Study population

The study was conducted at The University of Edinburgh’s Clinical Research Centre in accordance with the principles of the Declaration of Helsinki and was approved by the local research ethics committee. Written informed consent was obtained from each volunteer. Eleven healthy men, aged 20–25 yr (mean 23) were enrolled. Exclusion criteria included taking any regular medication, contraindication to arterial cannulation or any of the study drugs, and the presence of cardiovascular or other significant illness. Subjects were studied after 4 h of fasting and 24 h of abstinence from caffeine, alcohol, and nicotine.

Arterial pressure was measured invasively at the non-dominant radial artery. A 20G 80 mm catheter (BP7-95 440, Vygon, Ecouen, France) was inserted under local anaesthesia (lidocaine 1%) using the Seldinger technique and connected by semi-rigid fluid-filled tubing to a disposable pressure transducer (TruWave, Edwards LifeSciences, Saint-Prex, Switzerland) positioned level with the right atrium. Transducers were factory-calibrated and exceeded AAMI standards for performance interchangeability, with a sensitivity of 5 μV V−1 mm Hg−1 ±1% and a non-linearity of the greater of ±1.5% or ±1 mm Hg. The natural frequency of the system was 40 Hz. Waveforms were recorded at 200 Hz using a custom amplifier and analogue–digital converter interfaced to LabVIEW 6.1 data-logging software (National Instruments, Newbury, UK).

The WEP signal was recorded using two adjacent 1.5 cm diameter piezoelectric sensors (frequency range 0.1 to >1000 Hz) placed beneath the distal edge of a blood pressure cuff directly over the axis of the contralateral brachial artery (Pulsecor). The distal sensor was positioned 1 cm from the cuff edge. No differences were subsequently found between proximal and distal sensors, and data are therefore reported for the distal sensor only. Measurements were made with the cuff temporarily inflated to 30 mm Hg above systolic pressure. The waveform was recorded at 200 Hz, thus band-limiting the signal, using software developed by Ilixir Ltd (Auckland, New Zealand). Signal processing was performed using MATLAB (R12) (The MathWorks Inc., Natick, MA, USA) and LabVIEW software.

Pulse wave velocity (PWV) was calculated determining the transit time of the pulse between the proximal aorta and finger, as previously described. The proximal pulse wave was detected determining the B-point of the
transthoracic cardiac bioimpedance waveform recorded using an NCCOM3 Cardiodynamic Monitor (BoMed Medical Systems, Irvine, CA, USA). This point has been shown to correspond to the start of mechanical ventricular ejection. The distal pulse was recorded simultaneously at the fingertip using infrared photoplethysmography. The start of the finger pulse wave was determined using an intersecting tangent algorithm, as described by Chiu and colleagues. Photoplethysmography has been favourably compared with more established methods for the measurement of PWV. The straight-line distance between the sternal notch and fingertip was used as a surrogate for the true vascular path length.

Waveform feature analysis
Waveforms were recorded during ~30 s intervals at each time point. The 30 s signal was then ensemble-averaged to provide a single representative waveform for each individual subject at each individual time point. A preliminary visual inspection found the WEP signal to resemble the first derivative of arterial pressure, $dP/dt$. The original WEP waveform ($\text{WEPS}$) was therefore compared directly with the first derivative of the arterial pressure wave ($\text{ARTS}$) and was also integrated to provide an estimated pressure waveform ($\text{WEPA}$) for comparison with the original intra-arterial signal ($\text{ARTA}$). $\text{WEPS}$ and $\text{WEPA}$ were normalized to the same amplitude range as $\text{ARTS}$ and $\text{ARTA}$, respectively.

The $\text{WEPS}$ signal has been noted by others to have three principal waves ($S_1$, $S_2$, $S_3$). These were recognized using turning and inflection points identified from the zero crossing points of the first through to third derivatives of the signal in a similar manner to that previously described for arterial waveforms. The timing ($T$) and pressure ($P$) were noted at all three corresponding points, in addition to the trough between $S_1$ and $S_2$. The $\text{WEPA}$ and $\text{ARTA}$ signals were analysed by employing similar methods to identify the incident and first reflected waveforms ($A_1$, $A_2$) and using corresponding pressures to calculate $AIx$ from the equation $100\times(P_{A2}-\text{DBP})/(P_{A1}-\text{DBP})$. These parameters are shown in Figure 1. The Pulsecor system also estimates compliance (expressed in mm Hg ml$^{-1}$) from a first-order linear equation on the basis of a natural logarithm of the ratio of amplitudes of $P_{S1}$ and $P_{S2}$ on the $\text{WEPS}$ waveform, but does not use measures of flow or volume.

The overall difference between waveforms was calculated by taking the root mean square error (RMSE) of the

![Fig 1](image-url)
two signals, after synchronization using the offset between the peaks of the WEPs and ARTs waveforms.

**Experimental protocol**

All studies were conducted in a quiet, temperature-controlled environment [22 (°C), after 1 h acclimatization, with the subject in the supine position. After a saline 0.9% 20 min run-in period, four drugs were administered for 15 min, with the dose increased every 5 min. Drugs and doses were glyceryl trinitrate (GTN; 0.1, 1, 4 μg kg⁻¹ min⁻¹; Clinalfa, Läufelfingen, Switzerland), norepinephrine (20, 60, 120 μg kg⁻¹ min⁻¹; Levoephed, Abbott, Maidenhead, UK), and salbutamol (albuterol; 0.4, 1.2, 2.4 μg kg⁻¹ min⁻¹, Ventolin, Allen and Hanburys, Uxbridge, UK). All were administered i.v. at a constant rate of 1 ml min⁻¹; Nitrocine, Schwarz, Chesham, UK), angiotensin II (2, 6, 12 ng kg⁻¹ min⁻¹; Clinalfa, Läufelfingen, Switzerland), norepinephrine (20, 60, 120 ng kg⁻¹ min⁻¹; Levoephed, Abbott, Maidenhead, UK), and salbutamol (albuterol; 0.4, 1.2, 2.4 μg kg⁻¹ min⁻¹, Ventolin, Allen and Hanburys, Uxbridge, UK). All were administered i.v. at a constant rate of 1 ml min⁻¹ through a 20G cannula sited in the antecubital fossa of the right arm. A 25 min washout period was allowed after each drug, with salbutamol given last because of its longer half-life. The order was not randomized, and doses and washout periods were based on published literature to produce consistent and predictable changes in arterial pressure and arterial tone: a decrease in arterial pressure because of positive chronotropic and inotropic lation, and a marked tachycardia and increase in systolic pressure; 27 both norepinephrine and angiotensin II were expected to increase mean pressure, and arterial tone: a decrease in arterial pressure and arterial tone; a decrease in arterial pressure because of peripheral vasodilatation, and a marked tachycardia and increase in systolic pressure because of positive chronotropic and inotropic effects. 30 Pulse transit time and arterial pressure data at each time point have been published elsewhere. 21 WEP and intra-arterial recordings were made immediately before each drug and at the end of the highest dose.

**Statistical analysis**

Data are presented as mean (SD). Changes in physiological parameters with each drug, relative to the respective baseline, were evaluated by paired t-tests. Changes in baseline between drugs were assessed by repeated measures analysis of variance (rmANOVA). The nature of the correlation between equivalent parameters obtained from WEP and intra-arterial signals was evaluated by linear regression analysis. Comparison of the different methodologies was expressed in terms of mean bias and limits of agreement, as recommended by Bland and Altman. 31 Linear regression correlation coefficients between the difference and mean of both measures were computed to evaluate any tendency for bias to increase or decrease over the measurement range. PWV is inversely proportional to compliance and the nature of this correlation may vary between individuals; an average correlation coefficient was therefore computed for all individuals. Statistical analysis was performed using SPSS 12.0 (SPSS Inc., USA). P-values <0.05 were considered statistically significant.

**Results**

Changes in haemodynamic values are given in Table 1. Mean arterial pressure (MAP) and diastolic blood pressure (DBP) decreased with GTN and salbutamol, and increased with norepinephrine and angiotensin II. Systolic blood pressure; 28 29 salbutamol was predicted to cause a increase in pressure and arterial tone: a decrease in arterial pressure and arterial tone; a decrease in arterial pressure because of peripheral vasodilatation, and a marked tachycardia and increase in systolic pressure because of positive chronotropic and inotropic effects. 30 Pulse transit time and arterial pressure data at each time point have been published elsewhere. 21 WEP and intra-arterial recordings were made immediately before each drug and at the end of the highest dose.

### Table 1 Changes in haemodynamics with individual drugs. Values are mean (so). * indicates significant (P<0.05) change. Abbreviations are as per text

<table>
<thead>
<tr>
<th>Haemodynamic parameter</th>
<th>GTN</th>
<th>Angiotensin II</th>
<th>Norepinephrine</th>
<th>Salbutamol</th>
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<td>SBP (mm Hg)</td>
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<td>DPB (mm Hg)</td>
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<td>Intra-arterial waveform</td>
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| WEPₓ and ARTₓ (mm Hg)  |     | Before        | End            | Before     | End        | Before     | End        |
| WEPₛ and ARTₛ (mm Hg s⁻¹) |     | Before        | End            | Before     | End        | Before     | End        | Before     | End        |
pressure (SBP) increased with norepinephrine and angiotensin II, and decreased significantly with GTN only. Baseline values of SBP, DBP, and MAP varied between drugs (P<0.05 by rmANOVA), with an increase in all values exclusively before salbutamol. Heart rate at baseline did not vary between drugs (P=0.33).

PWV, ARTA, Aix, and WEPS \( P_{S1}/P_{S2} \) ratio decreased with GTN and salbutamol, and increased with norepinephrine and angiotensin II. Compliance measured by GTN and salbutamol, and increased with norepinephrine administration. Regression analysis confirmed a strong positive correlation between the two methods with respect to those obtained directly from the arterial signal, and similar changes occur with both techniques during the administration of pharmacological agents. Although it is important to note that the RMSE was substantial with all drugs (4–5 mm Hg is the limit of accuracy of devices for recording arterial pressure), and that this may therefore limit the role of suprasystolic WEPS analysis as an accurate alternative to direct intra-arterial pressure recording or applanation tonometry, the WEP responses nonetheless tracked those of the arterial line and can thus still be considered a potentially useful means of evaluating cardiovascular function. Furthermore, in addition to the obvious benefits of being non-invasive, the WEP system has the advantage that it has potentially far less operator dependency than tonometry and could be incorporated relatively easily into standard oscillometric sphygmomanometer devices and utilized in pre-admission screening or during preoperative management.

The WEP signal was integrated (WEP\(_A\)) to assess how accurately the arterial pressure wave contour could be estimated. Similarities in wave shape are shown in Figure 1b. RMSE values were large (Table 1) and statistically greater with salbutamol only (P<0.05). The WEP\(_A\) signal appeared slightly damped relative to ART\(_A\), although the timings of reflected waves were similar. Regression analysis (Table 2) confirmed that \( T_{A1} \) and \( T_{A2} \) occurred at similar times, although the bias of the \( T_{A2}−T_{A1} \) time delay became more positive with increasing values (Fig. 3). Aix showed a consistent bias of \(-7 (18\%)\) across the measurement range relative to intra-arterial measurements (Fig. 3).

### Discussion

This study is the first to describe the relationship between the contours of the suprasystolic WEP signal and the intra-arterial pressure wave, and the effect of vasoactive drugs on the former. We have shown that the suprasystolic WEP signal resembles the first derivative of intra-arterial pressure and can therefore be used to estimate the arterial pressure wave. Time delays and measurements of reflected wave amplitude measured by WEP analysis correlate with those obtained directly from the arterial signal, and similar changes occur with both techniques during the administration of pharmacological agents. Although it is important to note that the RMSE was substantial with all drugs (4–5 mm Hg is the limit of accuracy of devices for recording arterial pressure), and that this may therefore limit the role of suprasystolic WEP analysis as an accurate alternative to direct intra-arterial pressure recording or applanation tonometry, the WEP responses nonetheless tracked those of the arterial line and can thus still be considered a potentially useful means of evaluating cardiovascular function. Furthermore, in addition to the obvious benefits of being non-invasive, the WEP system has the advantage that it has potentially far less operator dependency than tonometry and could be incorporated relatively easily into standard oscillometric sphygmomanometer devices and utilized in pre-admission screening or during preoperative management.

It has been suggested by the manufacturers of Pulsecor that the \( S2−S1 \) delay is inversely related to PWV;\(^{26}\) a similar relationship with PWV has been proposed for the time delay between systolic and diastolic peaks on the finger photoplethysmograph waveform.\(^{33}\) The current study found that the \( T_{S2}−T_{S1} \) delay, measured by both WEPs and the first derivative of the arterial pressure pulse, decreased with all drugs, except GTN, which caused a small non-significant increase. The \( T_{A2}−T_{A1} \) delay, measured from the arterial pressure pulse, also decreased with both pressor agents and salbutamol, although the latter not significantly. The \( T_{S2}−T_{S1} \) and \( T_{A2}−T_{A1} \) time delay findings were similar to each other, but not in line with either expected or measured PWV.
responses. Changes in the magnitude of reflected waves, because of changes in peripheral impedance mismatch, may affect the timing of wave peaks and thus alter the apparent velocity of reflections. It can also be difficult to identify S2 in circumstances of marked vasodilatation and increased heart rate. These factors may in part explain the time delay findings described. GTN given in similar doses to those used in the present study has been shown to have only small effects on the finger pulse systolic–diastolic time delay, despite large changes in the relative amplitude.

Fig 2  Bland–Altman plots of WEP measures (difference and mean of actual WEP value and that derived from first derivative of arterial pressure). Dashed lines represent mean bias and 95% limits of agreement (±1.96σ).
of these wave components, and thus inaccuracy in identifying S2 or A2 may have been particularly important with this drug. The decrease in PWV with salbutamol in this study is because of peripheral vasodilatation and a decrease in MAP, offsetting any potential increase as a result of tachycardia. The corresponding decrease in $T_{S2} - T_{S1}$ (and to a lesser extent, $T_{A2} - T_{A1}$) is not consistent with this PWV change and may also be explained by the factors described earlier. These findings were identified with both WEP and arterial line and consistent in all subjects, suggesting this is a genuine phenomenon. Regardless of the precise cause of these findings, it would therefore appear unwise to use these time delays as a surrogate marker of PWV.

The ratio of amplitudes of the original WEP$_S$ signal showed changes similar to AIx and PWV. However, as pointed out by Millasseau and colleagues, it is difficult to relate directly values obtained from the derivative of the pulse waveform to the biomechanical properties of the cardiovascular system. The ratio of amplitudes is also used by Pulsecor to obtain a measure of vascular compliance, and the values obtained in the current study correlate with measured PWV. It is important to note, however, that the currently unpublished mathematical function used to derive compliance is not validated and is based on small subject numbers. Furthermore, the compliance value is an estimate only, as neither volume nor flow is known. The current study was not designed to validate the accuracy of the compliance values, and a measure of vascular function obtained directly from the waveform was thus considered more relevant. In this respect, AIx is an established and useful marker of vascular function, although not a direct measure of arterial compliance. WEP-derived arterial pressure waves showed changes in AIx similar to those directly measured using the arterial line. As the correlation may have been inflated by pooling data across interventions known to alter AIx, baseline data were examined alone. This analysis revealed that the positive correlation persisted ($r=0.42, P<0.01$) with a similar degree of bias $[-7.7 \pm 12.7\%]$. The bias between the two methods probably reflects the damping of the WEP$_A$ waveform, with a relatively smaller $P_{A2}$ amplitude. It remains
uncertain whether WEP signals can be used to evaluate central haemodynamics, although this would appear possible, given that radial AIx correlates closely with derived aortic AIx.\textsuperscript{36}

Blank and colleagues\textsuperscript{19} described a similar appearance of the suprasystolic WEP pulse contour to that observed in the present study. Below systolic pressure, the suprasystolic signal became obscured, with the waveform taking on the intra-arterial pressure pulse contour as cuff pressure approached diastolic pressure. Below diastolic pressure, the signal diminished in size, as it requires adequate coupling between the sensor surface and the skin. Although they did not compare the suprasystolic shape directly with intra-arterial pressure, they acknowledged that this waveform was probably still intrinsically related to the arterial pressure pulse and may therefore contain clinically important information. This is supported by the current study. In addition, Blank found that the suprasystolic signals had less high frequency energy than diastolic WEP signals, the latter correlating directly with intra-arterial pressure. This may explain the apparent damping of the arterial pressure signals derived from the suprasystolic WEP traces in the current study and is presumably related to the effects of pulse transmission through the upper limb tissues and inflated cuff. The principal advantage of using the suprasystolic WEP waveform, as opposed to the sub-systolic or diastolic signals, is that adequate coupling of the sensor to the skin is always present, and that a signal comprised of any diastolic component is avoided.

It is still not clear why the WEP signal resembles the derivative of the intra-arterial pressure wave. Occlusion of the brachial artery does not prevent the distal propagation of vibrations resembling the original pulse waveform through the air-filled cuff and non-vascular tissues. If the air-filled cuff is considered a low-impedance continuation of the artery, then a reflection would be expected to occur at the interface, which would be subject to a 90° phase shift, effectively inverting it.\textsuperscript{3} Assuming these two signals (normal and inverted) are of similar magnitude and slightly offset in time from one another, then the sum of the two amplitudes will be a function of the pressure gradient and thus resemble the first derivative. Alternatively, the signal may represent the effects of obstructed flow, generating waves similar to the flow wave which is closely related to the pressure gradient in peripheral vessels. However, these suggestions are purely speculative, and additional studies are required to understand the mechanics underlying generation of the suprasystolic WEP signal and whether the signal is affected by non-vascular parameters, such as cuff material or size.

The use of fluid-filled manometer tubing for the measurement of intra-arterial pressure is a weakness of this study. Invasive monitoring was selected in preference to tonometry, as there is no operator dependency. Measurement error because of sub-optimal damping was minimized during the study by using a short tube length.

The increased fundamental frequency of heart rate during the administration of salbutamol might account for the greater RMSE observed between WEP and intra-arterial signals with this drug. Cannulation of the radial artery is safer than that of the brachial artery, and different arms were used for measurements owing to the loss of the ipsilateral radial pulse signal upon brachial cuff inflation. The resulting comparison of different anatomical sites may therefore partially account for the differences seen between actual and WEP-derived pressure signals but is unlikely to influence the conclusions reached. A further limitation of the study is the failure of haemodynamic responses to return to baseline after the administration of norepinephrine. The physiological changes were probably not directly because of the drug, as its half-life is very short, but rather due to a natural stress response to the prolonged study. Indeed there was a trend for arterial pressure to increase throughout the experiment. However, the failure of the response to return to baseline after norepinephrine did not prevent the study achieving the aim of comparing waveforms under widely varying pharmacologically induced haemodynamic circumstances.

In conclusion, the supra-systolic WEP signal appears to correlate strongly with the first derivative of the intra-arterial pressure wave and is able to detect changes in the pulse waveform induced by vasoactive drugs similar to those measured by invasive monitoring. The arterial pulse contour recorded using alternative methodologies has already been shown to be clinically relevant. Further work is therefore merited to investigate the true nature of the supra-systolic WEP signal, whether it can be used in the study of cardiovascular physiology in disease states, and to evaluate reproducibility in a larger population.

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