Pulse transit time measured from the ECG:
an unreliable marker of beat-to-beat blood pressure

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Payne, R. A., C. N. Symeonides, D. J. Webb, and S. R. J. Maxwell. Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure. J Appl Physiol 100: 136–141, 2006. First published September 1, 2005; doi:10.1152/japplphysiol.00657.2005.—The arterial pulse-wave transit time can be measured between the ECG R-wave and the finger pulse (rPTT), and has been shown previously to have a linear correlation with blood pressure (BP). We hypothesized that the relationship between rPTT, pre-ejection period (PEP; the R-wave/mechanical cardiac delay), and BP would vary with different vasoactive drugs. Twelve healthy men (mean age 22 yr) were studied. Beat-to-beat measurements were made of rPTT (using ECG and photoplethysmograph finger probe), intra-arterial radial pressure, PEP (using cardiac bioimpedance), and transit time minus PEP (pPTT). Four drugs (glyceryl trinitrate, angiotensin II, norepinephrine, salbutamol) were administered intravenously over 15 min, with stepped dosage increase every 5 min and a 25-min saline washout between agents. All subjects in all conditions had a negative linear correlation (R² = 0.39) between rPTT and systolic BP (SBP), generally constant between different drugs, apart from four subjects who had a positive rPTT/SBP correlation with salbutamol. The 95% limits of agreement between measured and rPTT-predicted SBP were ±17.0 mmHg. Beat-to-beat variability of rPTT showed better coherence with SBP variability than it did with heart rate variability (P < 0.001). PEP accounted for a substantial and variable proportion of rPTT (12–35%). Diastolic (DBP) and mean arterial BP (MAP) correlated poorly with rPTT (R² = 0.02 and 0.08, respectively) but better with pPTT (rPTT corrected for PEP, R² = 0.41 and 0.45, respectively). The 95% limits of agreement between measured and pPTT-predicted DBP were ±17.3 mmHg. In conclusion, the negative correlation between rPTT and SBP is generally constant, even with marked hemodynamic perturbations. However, the relationship is not reliable enough for rPTT to be used as a surrogate marker of SBP, although it may be useful in assessing BP variability. DBP and MAP cannot be predicted from rPTT without correction for PEP. The significant contribution of PEP to rPTT means that rPTT should not be used as a marker of purely vascular function.

pre-ejection period; pulse-wave transit time

MONITORING OF BLOOD PRESSURE (BP) in a clinical or research setting is often performed using techniques that evolved in the 19th century (31). However, traditional sphygmomanometry is unable to monitor the short-term dynamic variability that occurs with BP, and the invasive nature of arterial cannulation limits its use to critically ill patients. A noninvasive beat-to-beat measurement of BP would be extremely valuable. A number of approaches have been developed, including most notably finger blood-volume clamping (28) and arterial tonometry (29). Although some studies have suggested that there is reasonable accuracy with these systems (32, 40), the technology itself is generally expensive, cumbersome, and prone to movement artifact.

An alternative technique involves measuring the transit time of the pulse pressure wave through the arterial tree. Measurement of pulse transit time involves detecting the pulse arrival at two separate arterial sites. This can be achieved easily distally using infrared photoplethysmography, and differential pulse transit time measured between finger and toe, as detected by photoplethysmography, has indeed been shown to satisfactorily reflect changes in pulse-wave velocity measured by Doppler ultrasound (23). The ECG R-wave is often used as a proximal timing point because it is simple to detect and tolerant of motion artifact. However, importantly, there is a considerable delay between the onset of electrical cardiac activity and the start of mechanical ventricular ejection (22). This delay is comprised of both the electromechanical delay and the period of isovolumic contraction, and is referred to as the pre-ejection period (PEP).

It has been suggested that, because a near-linear correlation exists between transit time measured from the R-wave (rPTT) and BP, rPTT might be used as a surrogate marker of pressure (9). The use of rPTT in this way was originally described in the 1950s (34), and considerable research was subsequently performed on its application in the study of cardiovascular feedback, mainly in the field of psychophysiology (9, 19, 33, 37). There have been several studies that revisited the technique in recent years, probably due to the increasing ease with which signal analysis can be carried out using modern technology (1, 7, 14, 26). However, little work has been published on the effects of vasoactive drugs on this measurement in humans. In particular, studies have not been carried out quantifying PEP or comparing rPTT with invasive BP measurement.

This study used various vasoactive drugs to produce differing cardiac and vascular responses. The rationale was to compare changes in transit time measurements with the clinical “gold standard” for BP measurement over a wide BP range and under different conditions of vascular tone and cardiac contractility. We hypothesized that the relationship between intra-arterial BP and rPTT would vary following the administration of different vasoactive drugs due to differing effects on the vascular and cardiac components of rPTT.

METHODS

Studies were carried out in healthy men, aged 18–25 yr, with no history of cardiovascular disease and taking no regular medications. Informed consent was obtained from all participants. The protocol
was approved by the local research ethics committee and conformed to the requirements of the Declaration of Helsinki.

Studies were performed in a quiet, temperature-controlled (22 ± 2°C) environment after at least 1 h of acclimatization. Subjects were allowed a light breakfast not less than 4 h before attending and were requested to refrain from alcohol, caffeine, nicotine, or medications for the preceding 24 h. Studies were conducted with the subject lying supine. Continuous beat-to-beat measurements of BP, transit time, and PEP were made throughout the entire study protocol.

All drugs were administered via a 20-gauge intravenous cannula sited in the antecubital fossa of the dominant arm. The infusion rate was kept constant at 1 ml/min. After an initial 20-min 0.9% saline run-in period, four drugs were given, each for 15 min, with the dose increased every 5 min. A 25-min washout period followed each drug. Drugs given were glyceryl trinitrate (0.1, 1, 4 μg·kg⁻¹·min⁻¹), angiotensin II (2, 6, 12 ng·kg⁻¹·min⁻¹), norepinephrine (20, 60, 120 ng·kg⁻¹·min⁻¹), and salbutamol (albuterol, 0.4, 1.2, 2.4 μg·kg⁻¹·min⁻¹). Drug order was not randomized. Salbutamol was given last due to its relatively long half-life. Dose ranges and washout periods were based on previous studies and selected for their anticipated effects on BP and heart rate (HR) (10, 12, 15, 30, 38, 39). Glyceryl trinitrate was selected for anticipated decreases in BP (12, 15). Norepinephrine and angiotensin II increase mean arterial pressure (MAP) to a similar degree, but the former also increases peripheral resistance.

Subjects were all healthy, nonsmoking men, age 22 ± 1.7 yr, who took regular noncompetitive exercise. Average height and weight were 178 ± 6 cm and 75 ± 4.8 kg, respectively. Resting oscillometric brachial BP was 126/75 ± 10.8/7.7 mmHg, and 12-lead ECGs were normal in all subjects. Total and high-density lipoprotein cholesterol were 158 ± 23 and 55 ± 13 mg/dl, respectively, with normal serum biochemistry and blood count. Maximal change from baseline in hemodynamic parameters are given in Table 1, with dose response plotted in Fig. 1. Glyceryl trinitrate caused an increase in rPTT, pPTT, and HR, and decreases in SBP, DBP, and MAP. Angiotensin II and norepinephrine caused increases in SBP, DBP, and MAP, and decreases in rPTT and pPTT. SBP and pulse pressure increases tended to be greater with norepinephrine than angiotensin II, but this difference did not achieve statistical significance (P = 0.11). PEP and HR responses were variable between subjects, but overall both decreased with norepinephrine and did not change with angiotensin II. Despite the similar change in BP, decreases in PEP and rPTT were significantly greater with norepinephrine than with angiotensin II (P = 0.005 and P = 0.002, respectively). Salbutamol reduced DBP, MAP, rPTT, and PEP and increased HR and pPTT. The SBP response was varied and, overall, did not significantly change; eight subjects had a significant increase in SBP, whereas four had a clear decrease. Baseline values of SBP, DBP, MAP, and HR were not constant between drug phases (P < 0.05 by ANOVA), due in particular to increases in all four parameters before salbutamol administration. This was mirrored by decreases in rPTT, pPTT, and PEP. The relationship between PTT and BP in a typical subject is shown in Fig. 2.

rPTT had an inverse linear correlation with SBP (combined average across all subjects and drugs R² = 0.39). There was no significant difference in correlation coefficient (P = 0.88) or slope (P = 0.69) between different drugs by repeated-measures ANOVA. rPTT was significantly (P < 0.01) better correlated with SBP than it was with either DBP (R² = 0.02) or MAP (R² = 0.08). Furthermore, rPTT showed significant differences in correlation with DBP (P < 0.001) and MAP (P < 0.001) between different drugs. pPTT was more strongly correlated (P < 0.001) with DBP (R² = 0.41) and MAP (R² = 0.45) than it was with SBP (R² = 0.33). The correlation between pPTT and DBP was unaffected by different drugs (P = 0.11). The same was true for pPTT and MAP (P = 0.39). However, the pPTT-SBP correlation was different between drugs (P < 0.01).

The value of rPTT and pPTT as predictors of SBP and DBP, respectively, was assessed based on the assumption that it would be possible to obtain an ideal calibration slope for each
individual equating to the average linear regression slope for all drugs. The 95% limits of agreement for predicted vs. actual BP were ±17.0 mmHg (SBP/rPTT) and ±17.3 mmHg (DBP/PTT). Percentage-predicted values falling within 5, 10, and 15 mmHg of actual value [based on British Hypertension Society system for assessing BP measurement accuracy (25)] were 44, 66, and 73%, respectively, for SBP, and 42, 64, and 72%, respectively, for DBP.

Average power spectra over all drugs are shown in Fig. 3. An example of the similarity in SBP and rPTT variability is given in Fig. 4. Mean coherence between SBP and rPTT variability was significantly (P < 0.001) greater at both lower and higher frequencies (0.58 ± 0.37 and 0.70 ± 0.33, respectively) than coherence of HR and rPTT variability (0.46 ± 0.41 and 0.52 ± 0.38, respectively). There was no significant difference in coherence between HR and either rPTT or SBP for lower (P = 0.33) or higher (P = 0.16) frequencies. Coherence was not significantly affected by drug type or dosage (P = 0.96) and is shown in Fig. 4.

DISCUSSION

The association between pulse transit time and BP was studied extensively in the field of psychophysiology (9, 11, 19, 33, 37) in the 1970s and 1980s, and more recently by Ochiai et al. (26) and Chen et al. (7). rPTT has also been used to predict BP in a clinical setting (14). The present study is the first to examine simultaneously the effects of vasoactive drugs on rPTT, PEP, and invasively measured BP in humans.

The expected hemodynamic changes occurred with all four drugs, although the SBP response to salbutamol was mixed. rPTT had a negative correlation with SBP, which was relatively unaffected by different drugs in the population as a whole. rPTT also appeared to be useful as a marker of SBP variability. However, DBP and MAP were weakly correlated with rPTT, although more strongly related to pPTT.

SBP is dependent on both vascular function and ventricular contraction, and so it is perhaps unsurprising that rPTT, a composite measure of both vascular and cardiac activity, is correlated with SBP. However, although in the study population as a whole the correlation between rPTT and SBP appeared relatively unaffected by drugs, this finding must be treated with caution. There were slight differences in the rPTT response between norepinephrine and angiotensin II, despite similar BP profiles. Furthermore, it should be noted that four subjects in this study had positive correlations between rPTT and SBP during the administration of salbutamol. This drug has positive inotropic and chronotropic β2-adrenergic effects, as well as causing peripheral arterial relaxation. Although a fall in PEP is associated with an increase in cardiac inotropy, this does not necessarily relate to an increase in SBP, as any potential pressure rise

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Table 1. Maximal change from baseline for different agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>rPTT (ms)</th>
<th>PEP (ms)</th>
<th>pPTT (ms)</th>
<th>Heart Rate, beats/min</th>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>MAP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTN</td>
<td>260 (17)</td>
<td>95 (15)</td>
<td>164 (12)</td>
<td>63 (7)</td>
<td>134 (12)</td>
<td>66 (5)</td>
<td>85 (6)</td>
</tr>
<tr>
<td>Maximum</td>
<td>276 (18)</td>
<td>92 (16)</td>
<td>184 (26)</td>
<td>77 (9)</td>
<td>122 (10)</td>
<td>61 (6)</td>
<td>77 (6)</td>
</tr>
<tr>
<td>Change</td>
<td>15.3 (11.4)</td>
<td>-3.5 (10.6)</td>
<td>20.6 (16.0)</td>
<td>14.3 (5.2)</td>
<td>-12.6 (8.1)</td>
<td>-4.5 (5.0)</td>
<td>-7.8 (4.9)</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>266 (19)</td>
<td>100 (15)</td>
<td>166 (23)</td>
<td>62 (8)</td>
<td>139 (13)</td>
<td>67 (6)</td>
<td>84 (6)</td>
</tr>
<tr>
<td>Baseline</td>
<td>257 (23)</td>
<td>105 (19)</td>
<td>150 (21)</td>
<td>60 (10)</td>
<td>156 (13)</td>
<td>82 (7)</td>
<td>102 (8)</td>
</tr>
<tr>
<td>Maximum</td>
<td>-9.2 (8.1)</td>
<td>5.9 (11.5)</td>
<td>-15.2 (7.0)</td>
<td>-2.6 (8.4)</td>
<td>17.5 (8.3)</td>
<td>15.0 (4.4)</td>
<td>18.1 (5.4)</td>
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<tr>
<td>Change</td>
<td>-22.4 (10.5)</td>
<td>-7.6 (10.1)</td>
<td>-14.4 (7.6)</td>
<td>-4.0 (6.4)</td>
<td>22.9 (14.5)</td>
<td>12.3 (5.5)</td>
<td>17.4 (8.3)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>261 (15)</td>
<td>95 (19)</td>
<td>165 (18)</td>
<td>61 (8)</td>
<td>141 (10)</td>
<td>68 (6)</td>
<td>86 (7)</td>
</tr>
<tr>
<td>Baseline</td>
<td>238 (18)</td>
<td>87 (19)</td>
<td>151 (20)</td>
<td>57 (8)</td>
<td>164 (13)</td>
<td>81 (8)</td>
<td>104 (10)</td>
</tr>
<tr>
<td>Maximum</td>
<td>-22.4 (10.5)</td>
<td>-7.6 (10.1)</td>
<td>-14.4 (7.6)</td>
<td>-4.0 (6.4)</td>
<td>22.9 (14.5)</td>
<td>12.3 (5.5)</td>
<td>17.4 (8.3)</td>
</tr>
<tr>
<td>Change</td>
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<td>29.9 (14.2)</td>
<td>59.1 (7.6)</td>
<td>2.5 (19.0)</td>
<td>-31.7 (4.3)</td>
<td>-23.3 (6.0)</td>
</tr>
</tbody>
</table>

Values are means (SD) for all subjects. GTN, glyceryl trinitrate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; rPTT, pulse transit time measured between the ECG R-wave and the finger pulse; pPTT, pulse transit time minus preejection period (PEP). *P < 0.01; †P < 0.05.

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Fig. 1. Mean dose response graphs for blood pressure (BP; thick line), heart rate (HR; broken line), and pulse transit time (PTT) and preejection period (PEP) (thin lines). Data were averaged over 60-s intervals for clarity. See individual labels for separate BP and time components. SBP, systolic BP; DBP, diastolic BP; MBP, mean BP; rPTT, PTT measured between the ECG R-wave and the finger pulse; pPTT, PTT minus PEP; bpm, beats/min.
may be offset by decreases in pressure augmentation by reflected waves or changes in aortic stiffness (24). It would therefore appear inappropriate to use rPTT as a predictor of SBP in all persons, particularly for assessing changes due to vasoactive drugs. Moreover, even using an idealized calibration slope, the limits of agreement between predicted and actual BP were wide, although similar inaccuracies have been described previously between sphygmomanometric and direct arterial pressure measurements (2, 36).

These data also show that PEP accounts for a substantial and variable proportion of rPTT, ranging from ~12 to 35%. A number of relatively recent studies have employed rPTT as a marker of vascular function (3, 4), but this study demonstrates that the use of rPTT purely for the assessment of arterial stiffness is inappropriate and should be avoided, as PEP cannot be assumed to remain constant. Other devices, such as the Colin VP-1000 (Colin), have eliminated PEP by utilizing the phonocardiogram to time cardiac ejection. The phonocardiogram is regarded by many as the ideal way of determining systolic time intervals. The principal disadvantage, however, compared with bioimpedance, is that it requires accurate identification of two timing points rather than simply one: first, the end of cardiac ejection (the second heart sound); second, the left ventricular ejection period (measured by identifying the dicrotic notch using a proximal arterial pulse wave).

rPTT may nonetheless offer a potentially valuable means of detecting beat-to-beat changes in SBP. Indeed, with regular

Fig. 2. Linear regression analysis of PTT and BP relationship in typical subject with glyceryl trinitrate (GTN; ◆), angiotensin II (☉), norepinephrine (△), and salbutamol (□). Figure shows relationship between rPTT (left) and pPTT (right) with systolic (top), mean (middle), and diastolic (bottom) BP.
recalibration to standard oscillometric BP as suggested by Chen et al. (7), rPTT offers the opportunity to assess BP variability and detect sudden or transient hemodynamic changes. BP and HR variability are considered to offer important insights into vasomotor activity, have been associated with clinical outcomes, including cardiovascular death, and may be used in assessment of autonomic neuropathy (27). Sympathetic modulation of BP alters the HR through the actions of the sinoaortic baroreflex; coherence between these two measures therefore reflects baroreflex activity (20). rPTT shows beat-to-beat variability closer to that of SBP than HR and, therefore, may have a role in the assessment of vasomotor control and BP variability.

pPTT, but not rPTT, was strongly inversely correlated with DBP and MAP. Furthermore, the correlation was inconsistent between pPTT and SBP. These findings are both consistent with the fact that arterial stiffness, and therefore vascular pulse transit time (i.e., pPTT), is dependent on MAP rather than SBP. In many circumstances, SBP and DBP/MAP are positively associated with each other. This has led others to inappropriately use rPTT to predict both these variables (6, 14), with DBP calculated following adjustment for HR. However, the divergent SBP and DBP/MAP responses to salbutamol in eight subjects in this study have not been reported in previous published work in this field, and the present data suggest that rPTT cannot be used to predict DBP or MAP without a knowledge of PEP, regardless of the HR response.

This study has a few limitations. Baseline values of BP were not constant before each drug, tending to rise steadily over the course of the study, particularly after norepinephrine. Due to the short half-life of both pressor agents in particular, it seems unlikely that the rise in BP is entirely accounted for by direct drug effects. Randomizing drug order was not carried out because the much longer half-life of salbutamol necessitated its administration last and it was not justifiable to carry out the separate elements of the study on different days, because this would have required repeated arterial cannulation. The washout periods were also kept relatively short to minimize the duration of cannulation.

Despite these points, the aim of the different drugs was to achieve a wide range of BP under varying conditions of vascular tone, and this was still achieved even if the hemodynamic effects of one drug had not completely resolved before the administration of the next. The use of fluid-filled manometer tubing introduces a degree of inaccuracy between pressure at the catheter tip and that at the more proximal transducer. However, this discrepancy was constant between subjects, and fluid-filled manometer tubes are nonetheless regarded as the gold standard in clinical practice. HR is a potential confounding factor (21) in the assessment of vascular stiffness and BP, although debate continues over whether reported increases in pulse-wave velocity with HR are genuine (13). Importantly, however, the large change in HR seen with salbutamol does not affect the interpretation of DBP being more important than SBP as a determinant of pPTT, because a high HR would, if anything, increase arterial stiffness and thus reduce vascular transit time.

In conclusion, this study demonstrates that rPTT has a negative correlation with SBP, which although relatively unaffected by vasoactive drugs in some persons is not reliable enough to enable rPTT to be a surrogate marker of SBP. Furthermore, the significant contribution of PEP to rPTT means that use of the latter parameter as a marker of purely vascular function should be avoided. However, rPTT may have a role in the assessment of BP variability and rapid pressure change. The association of pPTT with DBP/MAP means that use of rPTT as a predictor of diastolic or mean pressure is inadvisable.

GRANTS

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REFERENCES