Hypertension Research (2017) 40, 811–818

www.nature.com/hr

ORIGINAL ARTICLE

Ejection time: influence of hemodynamics and site of measurement in the arterial tree

Yurie Obata[1,3], Maki Mizogami[2,3], Sarabdeep Singh[1], Daniel Nyhan[1], Dan E Berkowitz[1], Jochen Steppan[1] and Viachaslau Barodka[1]

The left ventricular ejection time is routinely measured from a peripheral arterial waveform. However, the arterial waveform undergoes constant transformation as the pulse wave propagates along the arterial tree. Our goal was to determine if the left ventricular ejection time measured peripherally in the arterial tree accurately reflected the ejection time measured through the aortic valve. Moreover, we examined/accessed the modulating influence of hemodynamics on ejection time measurements. Continuous wave Doppler waveform images through the aortic valve and the simultaneously obtained radial artery pressure waveforms were analyzed to determine central and peripheral ejection times, respectively. The peripheral ejection time was significantly longer than the simultaneously measured central ejection time (174.5 ± 25.2 ms *vs.* 120.7 ± 14.4 ms; $P<0.0001$; $17.4 \pm 8.7\%$ increase). Moreover, the ejection time prolongation was accentuated at lower blood pressures, lower heart rate and lower pulse wave velocity. The time difference between centrally and peripherally measured ejection times likely reflects intrinsic vascular characteristics. Moreover, given that the ejection time also depends on blood pressure, heart rate and pulse wave velocity, peripherally measured ejection times might need to be adjusted to account for changes in these variables.
Hypertension Research (2017) **40,** 811–818; doi:10.1038/hr.2017.43; published online 30 March 2017

Keywords: arterial blood pressure; ejection time; pulse wave velocity; transesophageal echocardiography.

INTRODUCTION

The arterial blood pressure (BP) waveform is transformed as it travels from the ascending aorta to the peripheral arteries.[1] In a healthy compliant vasculature systolic blood pressure (SBP) and pulse pressure (PP) increase, whereas diastolic blood pressure (DBP) decreases slightly from the central to the peripheral arterial tree. These changes are called BP amplifications.[2] The magnitude of these amplifications depends on intrinsic vascular properties such as the elastic modulus, arterial stiffness, pulse wave velocity (PWV), wave reflection sites and systemic vascular resistance.[3] Peripherally determined ejection time is measured from the foot of the peripheral arterial waveform (indicating the initiation of ejection) to the dicrotic notch (indicating aortic valve closure and end of ejection).[4] Since the arterial blood pressure waveform undergoes a transformation from the central to the peripheral vascular tree it is unknown whether the ejection time measured at the site of a peripheral artery accurately represents the ejection time at the level of the heart. This has important implications for clinical devices, which rely on a peripherally measured ejection time: for example, VaSera devices (Fukuda Denshi, Tokyo, Japan) rely on the duration from the end of ejection to the dicrotic notch on the peripheral pressure waveform (diastolic pulse transit time) to calculate the cardio-ankle vascular index (CAVI), which asseses vascular properties.[5] Other technologies that rely on peripherally measured ejection times are minimally and noninvasive cardiac output measuring devices, which use arterial pulse contour analysis such as the Vigileo-FloTrac system (Edwards Lifesciences, Irvine, CA, USA) and the LidCO rapid system (LidCO Ltd, Cambridge, UK). Unfortunately, they don't have great level of agreement with each other and the trending ability in critical care patients with abnormal peripheral vascular tone is limited.[6] It is possible that their bias and precision might be greatly improved if accurate ejection time would be taken into account.

To the best of our knowledge, the potential modulating influence of hemodynamics on central and peripheral ejection time measurements and any potential differences have not been previously studied. We hypothesize that peripheral ejection times overestimates central ejection times. Thus, the aims of the present study were: (1) to compare central ejection time derived from a continuous wave (CW) Doppler signal across the aortic valve to the simultaneously measured peripheral ejection time derived from an invasive arterial pressure waveform; and (2) determine the modulating

[1]Division of Cardiac Anesthesia, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, USA and [2]Department of Anesthesiology and Reanimatology, University of Fukui, Fukui, Japan
[3]These authors contributed equally to this work.
Correspondence: Dr V Barodka, Division of Cardiac Anesthesia, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, Zayed Tower 6208, 1800 Orleans Street, Baltimore, MD 21287, USA.
E-mail: vbarodk1@jhmi.edu
Received 22 December 2016; revised 24 February 2017; accepted 26 February 2017; published online 30 March 2017

influences of BP, heart rate (HR) and PWV on the relationship between these two ejection time measurements.

METHODS

Subjects

This retrospective observational study utilized the data from cardiac surgery patients who underwent surgery at The Johns Hopkins Hospital between October 2011 and September 2013 and our cardiac surgery intraoperative transesophageal echocardiography (TEE) database. The protocol was approved by the Johns Hopkins Medicine Institutional Review Boards (IRB00088711).

The inclusion criteria were as follows: patients 18 years of age or older undergoing any cardiothoracic surgery who had paired simultaneous images of radial arterial waveforms superimposed on the CW Doppler waveforms through the aortic valve. All images were obtained before the initiation of cardiopulmonary bypass (CPB) and with different values for BP. Exclusion criteria were arrhythmias and/or presence of an implanted cardiac pacemaker.

Measurements

Intraoperative care was similar in all patients, all of which received general anesthesia with a combination of midazolam (2–10 mg), fentanyl (750–2000 μg), vecuronium (10–20 mg) and isoflurane (0.5–1%). All patients had a 20 gauge radial arterial catheter for continuous BP measurements. A TEE probe was inserted after the induction of general anesthesia, and a comprehensive TEE examination performed by a cardiac anesthesiologist with advanced echocardiography certification using a Philips iE33 ultrasound machine (Philips Medical Systems, Amsterdam, the Netherlands). The arterial pressure and ECG waveforms were recorded and simultaneously projected onto the aortic valve CW Doppler waveforms by connecting the clinical monitor (GE Healthcare, Little Chalfont, UK) to the TEE machine at the identical speed of 75 mm s^{-1}. The CW Doppler images were obtained from either the deep trans-gastric or trans-gastric long axis views of the aortic valve. All images were stored on the clinical server and the offline measurements performed using the software 'Synapse Cardiovascular' (FUJIFILM, Tokyo, Japan). Only images obtained before initiation of cardiopulmonary bypass (CPB) were used for this analysis. We defined: t1 as the time interval from the start of ejection on the CW Doppler waveform to the initiation of the upstroke on the arterial waveform; t2 as the time interval from the end of the ejection on the CW Doppler waveform to the dicrotic notch on the arterial waveform; t3 as the duration of ejection on the CW Doppler waveform; and t4 as the duration of ejection measured from the initiation of the upstroke to the dicrotic notch on the arterial waveform. (Supplementary Figure 1) The time differences were calculated as $\Delta t1 = t2 - t1$ and $\Delta t2 = t4 - t3$. The normalized time differences were also calculated as $\Delta t1n\% = (t2 - t1)/t1 \cdot 100\%$ and $\Delta t2n\% = (t4 - t3)/t3 \cdot 100\%$. The systolic BP, diastolic BP and pulse pressure were measured from the simultaneously recorded arterial blood pressure waveform. The mean arterial pressure (MAP) was calculated according to the following formula: MAP = DBP+PP/3. HR was determined from the ECG signal, recorded on the same TEE image. PWV was obtained by dividing vascular path length (L) by t1. Vascular path length is the distance traveled by the pulse wave from the aortic valve to the site of the radial artery catheter. We estimated vascular path length using the formula L = (demi-span) − (hand length), where demi-span (distance from sternal notch to the tip of the fingers) and hand length were estimated from height, age and gender as described previously.[7,8]

Statistical analysis

We report continuous variables as mean ± s.d. or median (interquartile range: IQR), and categorical variables as proportions. Wilcoxon signed rank test was performed to compare t1, t2, t3 and t4. We used two methodologies to compare ejection time durations measured centrally and peripherally, $\Delta t1$ ($t2 - t1$) and $\Delta t2$ ($t4 - t3$). Their equivalence was assessed using a two one-sided 95% confidence interval approach. We defined the zone of indifference as 5% of average of $\Delta t2$, which is equivalent to ± 2.7 ms.[9,10] The relationship between two continuous variables was assessed using a simple linear regression analysis. To account for variability within a subject (or patient) an estimation of the effect of BP, HR and PWV on $\Delta t2$, a linear mixed model was created.[11] Due to high multicollinearity (Variance Inflation Factor: VIF > 10) among the BP variables (MAP, SBP, PP and DBP), we considered only MAP to study the association between $\Delta t2$ (outcome variable), and HR and MAP (predictor variables) after adjusting for age and the BMI of the patients.

The linear mixed model analysis was performed in R version 3.2.2 (R foundation for Statistical Computing, Vienna, Austria).[12] The rest of the analysis was performed with GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $P < 0.05$ and all tests were two sided.

Table 1 The demographic data and patient characteristics

Variable	*Data*
Number of patients	29
Age (years old)	
Median	67
IQR	60–71
Gender	
Female (%)	1 (3)
Male (%)	28 (97)
Height (cm)	
Median	175
IQR	168–178
BMI (kg m^{-2})	
Median	28
IQR	25–33
Operation	
Isolated CABG (%)	20 (69)
Valve (%)	3 (10)
CABG plus valve (%)	2 (7)
Others (%)	4 (14)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; IQR, interquartile range.

RESULTS

We identified 37 patients who had images of the radial arterial waveforms superimposed on the CW Doppler waveforms through the aortic valve. Eight patients who had only one image were excluded. None of the patients needed to be excluded for arrhythmias or an implanted cardiac pacemaker. A total of 495 data pairs (CW Doppler and peripheral blood pressure waveforms) from 29 patients were used in this analysis. The median number of data pairs per patient was 11 (interquartile range: IQR, 7–26). The baseline characteristics are shown in Table 1. None of the patients required inotropic agents or mechanical cardiopulmonary support before CPB.

The values of the incident wave travel time to the foot (t1) and the end of the ejection travel time to the dicrotic notch (t2) were 120.7 ± 14.4 ms and 174.5 ± 25.7 ms, respectively. t2 was significantly longer than t1 ($P < 0.0001$) (Figure 1a). The difference between t2 and t1 ($\Delta t1$) was 53.8 ± 20.8 ms and $\Delta t1n\%$ was 45.2 ± 17.9%.

The values of the centrally measured ejection time via CW Doppler across the aortic valve (t3) and the peripherally measured ejection time from the foot of the wave to the dicrotic notch on the arterial waveform (t4) were 314.8 ± 35.4 ms and 367.8 ± 35.9 ms, respectively. t4 was significantly longer than t3 ($P < 0.0001$) (Figure 1b). The difference between t4 and t3 ($\Delta t2$) was 53.0 ± 22.4 ms, with a normalized difference $\Delta t2n\%$ of 17.4 ± 8.7%.

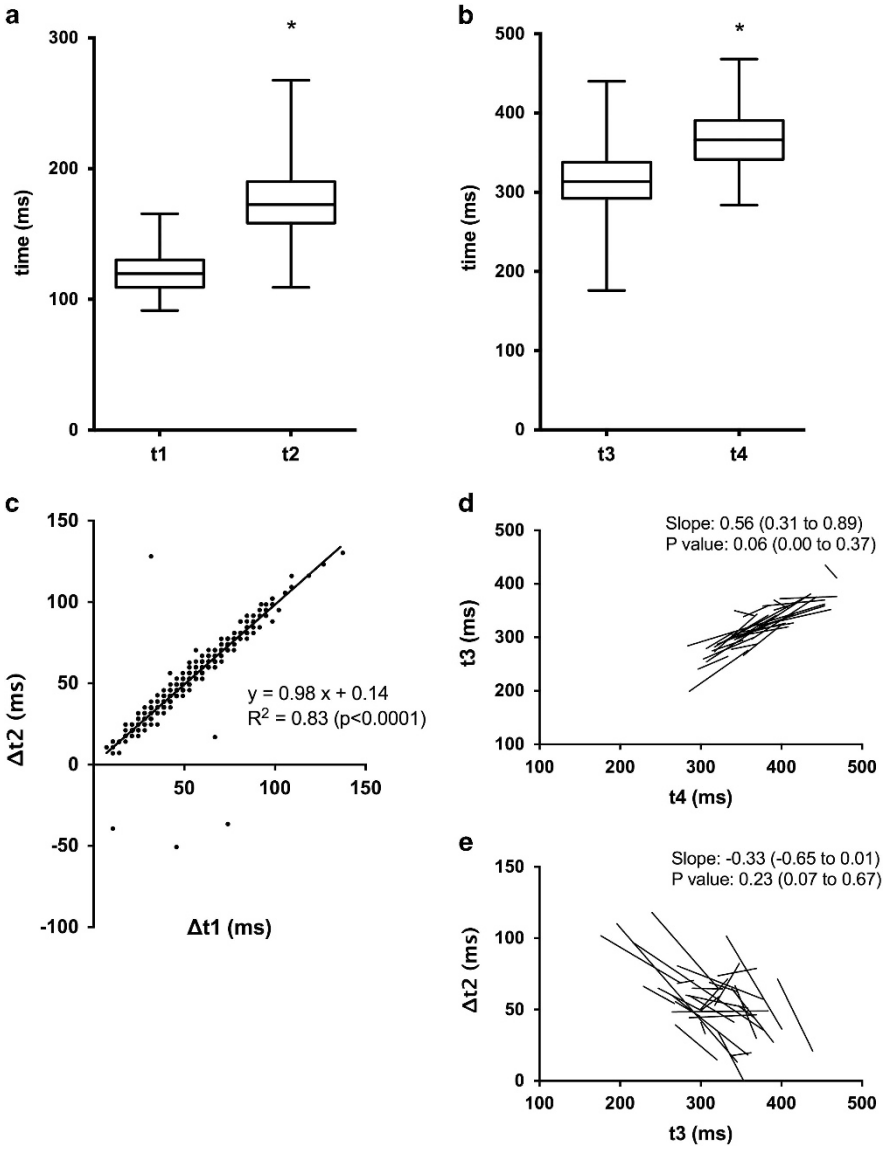

Figure 1 Comparison between time arrivals, central and peripheral ejection times, and difference between them (t1, t2, t3, t4, Δt1, Δt2). Box plots showing the distribution of t1, t2, t3, t4. The top of each box in the box plots indicates the 75th percentile, the bottom of each box indicates the 25th percentile and the bar inside the box is the median. Whiskers above and below the box indicate the maximum and minimum values. (**a**) Box plot of t1 compared to that of t2. (**b**) Box plot of t3 compared to that of t4. (*$P<0.0001$) (**c**) Scatter plots for relationship between Δt1 and Δt2. The function of regression line, the coefficient determination (R^2), and *P*-value are presented. (**d**) The relationship between t3 and t4 within patient, (**e**) the relationship between Δt2 and t3 within patient. The median (IQR) slope and the median (IQR) *P*-value are presented in upper right corners. IQR, interquartile range.

The range of the 90% confidence interval to assess the equivalence between Δt1 and Δt2 ranged from −1.46 to −0.10 ms. This range lay within 5% of Δt2 (±2.7 ms), which we defined as the zone of indifference. Figure 1c illustrates the equivalence between them.

The relationship between t3 and t4, Δt2 and t3 within patients are shown in Figures 1d and 1e. Although each patient had a different simple linear regression line and a different P-value, the overall trend of each individual regression line was estimated by a linear mixed model. (Table 2) A positive association was observed between t3 and t4 (slope: 0.72, $P<0.0001$). In addition, Δt2 was inversely related with t3 (slope: −0.29, $P<0.0001$).

The linear regression lines demonstrating a relationship between t3 and MAP, t4 and MAP, and Δt2 and MAP in each individual patient are depicted in Figures 2a–c. The estimated slopes showing relationships between t3 and MAP was −0.13 ($P<0.01$), t4 and MAP was −0.35 ($P<0.0001$), and Δt2 and MAP was −0.44. (Table 2) Δt2 was more likely to vary with MAP than t3 and t4. And all relationships between Δt2 and blood pressure (MAP, SBP, DBP and PP) were negative (Slope: −0.44, −0.30, −0.55 and −0.50, respectively). Hence, increasing BPs significantly associated with decreasing Δt2.

The relationships between t3 and HR, t4 and HR, and Δt2 and HR are shown in Figures 3a–c. It was observed that both t3 and t4 became longer as HR decreased. The slope of the linear mixed model of t3 *vs.* HR was −1.39 ($P<0.0001$) and the slope of t4 *vs.* HR was −1.78 ($P<0.0001$,). Δt2 *vs.* HR was also explained by a linear mixed model ($P<0.001$); however, the slope was relatively small (−0.35). Individual patient linear regression lines showed substantial variability (slope median −0.41 and IQR −1.02 to 0.11) (Figure 3c).

Table 2 Estimated intercept and slopes for the dependent variable – independent variable after using linear mixed model

Linear mixed models

Variables	Intercept	95%CI (intercept)	Slope	95%CI (slope)
t3 – t4	51.20***	26.14, 75.82	0.72***	0.65, 0.78
Δt2 – t3	147.0***	126.39, 167.43	−0.29***	−0.35, −0.23
t3 – MAP	306.1***	290.6, 321.3	−0.13*	−0.32, −0.06
t4 – MAP	400.2***	384.1, 416.3	−0.35***	−0.48, −0.22
Δt2 – MAP	89.17***	78.38, 97.95	−0.44***	−0.54, −0.35
Δt2 – SBP	88.45***	78.81, 98.08	−0.30***	−0.36, −0.23
Δt2 – DBP	86.92***	77.01, 96.84	−0.55***	−0.68, −0.43
Δt2 – PP	81.90***	72.81, 91.00	−0.50***	−0.61, −0.39
t3 – HR	405.8***	386.89, 424.82	−1.39***	−1.65, −1.13
t4 – HR	482.1***	464.83, 499.32	−1.78***	−2.01, −1.54
Δt2 – HR	74.52***	59.52, 89.46	−0.35**	−0.56, −0.13
t3 – PWV	344.1***	319.6, 368.6	−4.60*	−8.45, −0.75
t4 – PWV	423.4***	399.8, 446.9	−9.71***	−13.4, −5.97
Δt2 – PWV	78.25***	61.36, 95.08	−4.85**	−7.79, −1.88

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
*P-value <0.01; **P-value <0.001; ***P-value <0.0001.

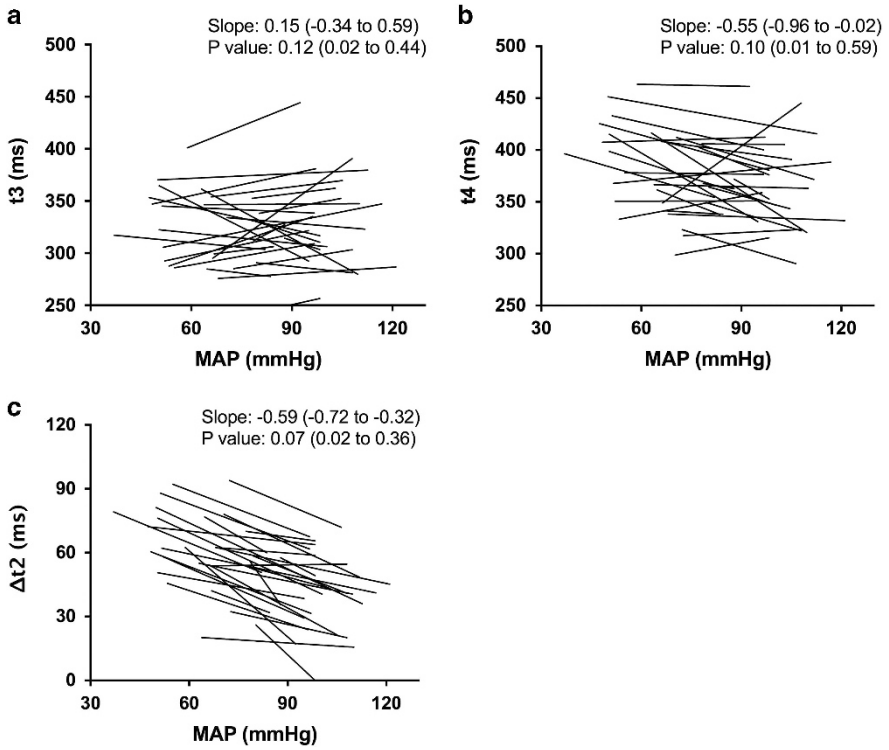

Figure 2 Relationships between central and peripheral ejection times and MAP. Each line indicates a simple linear regression line in each individual patient. (**a**) The relationship between central ejection time (t3) and MAP, (**b**) the relationship between peripheral ejection time (t4) and MAP, (**c**) the relationship between difference in peripheral–central ejection times (Δt2) and MAP. The median (IQR) slope and the median (IQR) *P*-value are presented in each graph. IQR, interquartile range; MAP, mean arterial pressure.

The relationships between t3 and PWV, t4 and PWV, and Δt2 and PWV are shown in Figures 4a–c. The negative slopes presented at the right top corner of each graph means that the dependent parameters (t3, t4 and Δt2) decrease as PWV increases. The range of *P*-values presented in the figure represent *P*-values for each individual patient. The increase in PWV was significantly associated with shortening of t3, t4 and Δt2 (slope: −4.60, $P<0.01$, slope: −9.71, $P<0.0001$, slope: −4.85, $P<0.001$).

After accounting for multiple variables in the mixed model, Δt2 decreases with increases in MAP (coefficient: −0.46, 95% confidence interval (CI): −0.56 to −0.35, $P<0.001$) and Δt2 increases with increases in BMI (coefficient: 1.08, 95% CI: 0.08 to 2.08,

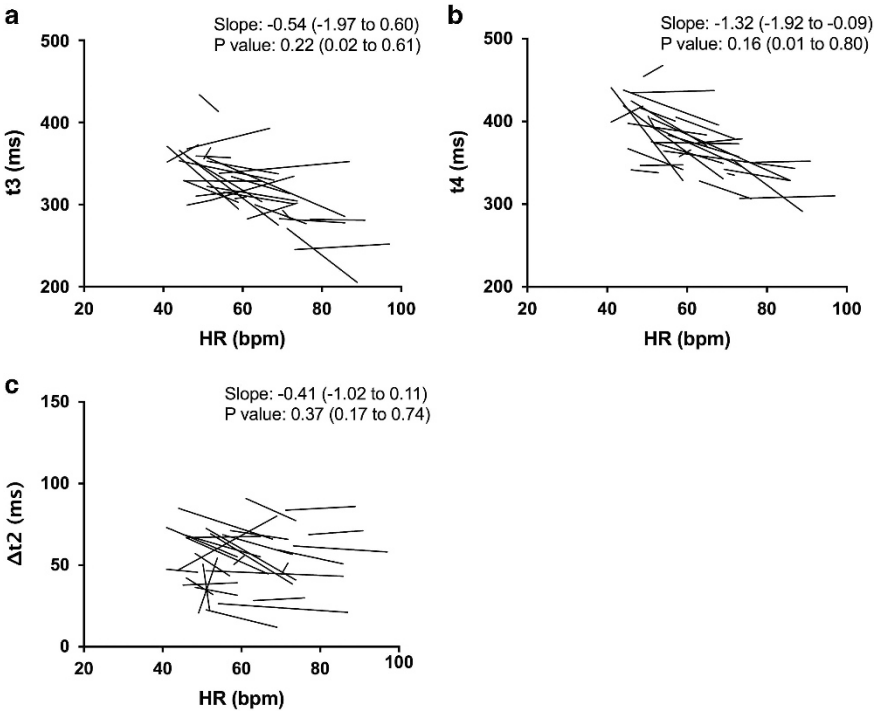

Figure 3 Relationships between central and peripheral ejection times and HR. Each line indicates a relationships between central ejection time (t3) and HR (**a**), peripheral ejection time (t4) and HR (**b**), and difference between peripheral and central ejection times (Δt2) and HR (**c**) in each individual patient. The median (IQR) slope and the median (IQR) *P*-value are presented in each graph. IQR, interquartile range; HR, heart rate.

$P=0.04$). Age and HR were not significantly associated with Δt2 (coefficient: 0.10, 95% CI: −0.37 to 0.59, $P=0.66$, coefficient: 0.07, 95% CI: −0.15 to 0.29, $P=0.56$, respectively).

DISCUSSION

The most important finding of the present study is that the ejection time measured from the radial artery waveform is significantly longer compared to the centrally measured ejection time. This prolongation of the ejection time at the peripheral artery is different in each individual and also depends on BP, HR and PWV, such that low blood pressures, low heart rates and low pulse wave velocities result in a more pronounced prolongation of the peripherally measured ejection time. We consider our study as a proof of principle study focusing on the dependence of the peripherally measured ET on the site of measurement and hemodynamics, given that the technical setup utilized in our study is not practical to be routinely used in other settings since it requires TEE and an invasive arterial line. Our finding that the central ejection time (t3), as measured by Doppler ultrasound through the aortic valve, is shorter than the peripherally measured ejection time (t4) has several explanations. It could be that there is a time delay between the end of ejection and aortic valve closure (Supplementary Figure 2-(1)). Physiologically this is consistent with the notion that following the end of ejection on CW Doppler, there exists an interval before the LV pressure falls below the aortic pressure with aortic valve closure and the associated dicrotic notch is seen on the arterial trace. Moreover, the aortic valve does not close instantaneously, rather it takes a finite time for complete aortic valve closure. From this perspective any ejection time measurement based on the aortic valve closure will overestimate 'true' ejection time as measured by Doppler ultrasound across the aortic valve. Two prior studies support this mechanism. Aase *et al.*[13] demonstrated that end systole occurred significantly earlier than aortic valve closure in healthy human subjects (by 26.7 ± 6.2 ms). Duan *et al.* investigated different methodologies of measuring ejection times utilizing Doppler and M mode ultrasound, thoracic impedance cardiography, and peripheral photoplethysmography in young healthy subjects. In their study, the central ejection time measured by M mode utilizing aortic valve opening and closing was longer than central ejection time directly measured by Doppler through the LVOT and the aortic valve (328 *vs.* 309 ms, respectively). In addition and consistent with our findings they reported differences between the central ejection time from Doppler ultrasound and peripheral ejection time from photoplethysmography. The average peripheral ejection time was 348 ms, a 12.6% prolongation of the peripherally measured ejection time compared to the central ejection time. This is in good agreement with our results showing an average of 17.8% prolongation.[4] However, neither of the above studies performed simultaneous hemodynamic measurements. They therefore do not report the hemodynamics at the time of ET measurement, nor do they propose a mechanism(s) for the observed difference.

A second potential mechanism for the observed time delay might reside at the level of the aortic root, due to retrograde flow in the aorta after aortic valve closure. (Supplementary Figure 2-(2)) This mechanism was proposed in an elegant animal study by MacCanon *et al* in 1964.[14] They simultaneously recorded the central aortic pressure waveform and aortic valve closure in 11 dogs. They showed that aortic valve closure precedes the incisura on the central aortic pressure tracing by at least 5–13 ms.

A third possibility could be that the arterial waveform undergoes significant transformation during transmission across the vascular tree. (Supplementary Figure 2-(3)) The waveform at the site of the peripheral muscular arteries is dramatically different from the one in the elastic central aorta, in part, due to the existence of a central to peripheral arterial stiffness gradient.[1,15,16] It has been proposed that

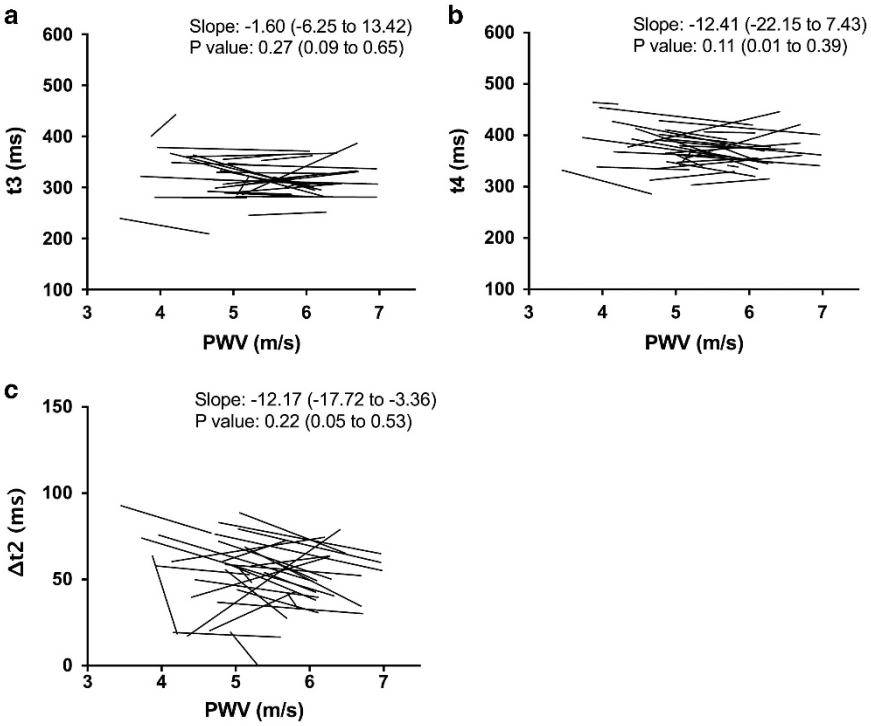

Figure 4 Relationship between central and peripheral ejection times and PWV. Each simple linear regression line indicates a relationship between central ejection time (t3) and PWV (**a**), peripheral ejection times (t4) and PWV (**b**), and difference between peripheral and central ejection times (Δt2) and PWV (**c**) within patient. The median (IQR) slope and the median *P*-value are presented in each graph. IQR, interquartile range; PWV, pulse wave velocity.

during propagation from the aorta to the radial artery the forward wave is transformed by resonant responses of the peripheral artery such that the location of the dicrotic notch at the level of radial artery mainly depends on the natural frequency of the radial artery rather than the transmission of the aortic incisura.[17] This shift in the location of the dicrotic notch in comparison to the aortic incisura might explain our observed differences in centrally *vs.* peripherally measured ejection times. In an elegant simulation study, Schwid *et al.*[18] showed how various factors such as aortic compliance, peripheral resistance and HR could affect the position of the dicrotic notch. A high aortic compliance, low peripheral resistance and low HR may shift the dicrotic notch rightward on the downslope of the arterial waveform. However, they did not measure the ejection time. The fact that the dicrotic notch shifts does not automatically mean that the ejection time becomes longer. From a numerical vascular tree simulations study, Politi *et al.*[19] suggested that reflected waves might be the major contributors to the time-position and the amplitude of the dicrotic notch.

Our results have important implications for certain clinical devices. Several prior studies investigated the brachial ET (bET) measured by a clinical device ABI-form (Colin VP1000, Komaki, Japan).[20–23] The bET is automatically measured from the foot of the waveform to the dicrotic notch of the brachial artery pulse waveform. The brachial pre-ejection period (bPEP) is also automatically calculated by subtracting the bET from the QS2 interval (time from the onset of the QRS complex on the ECG to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram). These studies demonstrated that the ratio of the bPEP to bET was associated with fluid overload in diabetic chronic kidney disease (CKD),[20] adverse renal outcomes in patients with advanced CKD,[21] impaired left ventricular ejection fraction[22] and left ventricular diastolic dysfunction.[23] However, the underlying assumption is that the peripherally measured ET (bET) accurately represents true central ejection time, which as shown by our data and others is only an approximation of the central ejection time.

The Cardio-Ankle Vascular Index (CAVI) has been developed as a BP-independent arterial stiffness indicator measured by VaSera (Fukuda Denshi, Tokyo, Japan).[5] However, recent studies reported that the CAVI does depend on BP.[24,25] Given that calculation of the CAVI depends on measurements of the duration from the end of ejection to the dicrotic notch of the peripheral blood pressure waveform (diastolic pulse transit time), our results might provide an explanation why the CAVI is indeed significantly associated with BP and peripheral resistance. On the basis of the formula to calculate the CAVI, we predict that the observed average of a 45% increase in pulse wave travel time (Δt1) would correspond to a 17% change in ejection time, which will decrease the CAVI by 50%, which is clinically significant. In addition, several algorithms used for noninvasive cardiac output monitors rely on the discrimination of systolic and diastolic phases. This distinction is made using the ET of the peripheral arterial waveform, hence inaccuracies in estimating the peripheral ET would affect the clinically important calculation of cardiac output.

We found only two studies that do not directly support our findings. Chan *et al* compared the automatic beat-to-beat detection of left ventricular ejection time measured in the central aorta by Doppler flow velocity waveform and peripherally using finger photoplethysmographic pulse oximetry.[26] Interestingly, the ejection time measured in the central aorta was longer than at the peripheral site on average by 14 ms. This is in contrast to our findings. However, they measured central ejection time in the aorta and not true ejection time across aortic valve. They also didn't measure central and peripheral ejection time simultaneously. In another study, Su *et al.*[27] reported that the ejection time derived from the pulse wave Doppler waveform in

the LVOT is longer than the brachial pulse volume waveform. However, they used pulse volume measurements to obtain peripheral ejection times with an ABI-form device (Colin VP1000). Moreover, they used a brachial site for peripheral measurements of ejection time. It is unclear if the pulse volume methodology at the brachial artery site and the resultant waveform correlate with the invasive blood pressure waveforms. Moreover, they didn't measure central and peripheral ejection times simultaneously. This limits the ability to accurately assess the effect of different hemodynamic parameters. Focusing on the cardiac surgical population, subjects in our study already had images of the radial arterial waveforms superimposed onto the CWD waveforms through the aortic valve. This provided us with the ability to simultaneous record the parameters of interest.

Our study has several limitations. Firstly, the subjects represented a very heterogeneous group of patients who underwent cardiothoracic surgery. Moreover, these patients usually have multiple cardiovascular risk factors. These patient characteristics are known to affect vascular function and stiffness.[28,29] Second, the data was collected on anesthetized and intubated patients during cardiac surgery. Surgical stimulation, mechanical ventilation, changes in volume status as well as effects of anesthesia medication all modulate vascular tone, peripheral resistance, stroke volume, dP/dt, BP and HR. The observed prolongation of the peripherally measured ejection time might be confounded by those factors. Nevertheless, they allowed us to investigate effects of changes in HR, MAP and PWV on the ejection time. And we compared central and peripheral ejection times at the same heartbeat to minimize the effect of ejection time variation for each heartbeat. It should also be noted that the radial artery waveform is significantly dampened when peripheral resistance becomes extremely low, which we did not measure. In our analysis, we used only the data collected prior to initiation of CPB to minimize the effect of post CPB variables. Third, due to technical limitations we used a calculated MAP instead of a MAP that was calculated from the area under the curve for each arterial waveform.[30] Fourth, the precise time interval measurements on a spectral analysis of Doppler flow requires Fourier transformation. We did not use any mathematical transformation of the original waveforms. Instead, we performed measurements manually and hence our results dependent on the individual observer's judgment. The advantage of this was that mathematical transformation generally generates a moderate amount of broadening of the flow waveform, which we avoided by analyzing the original waveform. Also, there are timing and bandwidth issues that arise when comparing disparate types of waveforms (flow and pressure). There is a potential for hardware-related temporal lags on the two data streams (flow and pressure), which were not measured in our study. Another potential for a hardware-related confounding issue would be the presence of bubbles in the manometer tubing, which could have damped the signal and distorted the waveform. Even if significant hardware-related time delays exist, they should equally affect t1 and t2, hence delta $\Delta t1 = t2 - t1$ will cancel out such time delay. However, since PWV is calculated based on t1, any hardware-related temporal lags could greatly affect the absolute value of PWV. Finally, we did not obtain central aortic blood pressure waveforms and hence we do not know its relative contribution to the observed prolongation of the peripherally measured ejection time. Overall, however, our results are consistent with the concept that low blood pressure, low PWV and hence low resistance against ejection causes a quicker ejection of the stroke volume, slower aortic valve closure and a larger distortion of the arterial waveform during transmission across the arterial tree resulting in the observed time prolongation of the peripherally measured ejection time.

In conclusion, ejection time measured peripherally from the arterial BP waveform is significantly longer than the central ejection time in patients under anesthesia undergoing cardiothoracic surgery. This time difference is more pronounced at low BPs, low HRs and low PWV. These findings suggest that ejection time measured from the peripheral arterial waveform should not be substituted unadjusted for the central ejection time when used by clinical devices. Further studies are required to confirm our findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the Clinical Research Core of the Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine.

1 Nichols W, O'Rourke MF, Vlachopoulos C. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles* 6th edn, Hodder Arnold: London, UK. 2011, 570.
2 Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension* 2009; **54**: 375–383.
3 Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; **18**: 3S–10S.
4 Duan W, Zheng D, Eggett C, Langley P, Murray A. Development of techniques for measurement of left ventricular ejection time. *Comput Cardiol* 2014; **41**: 241–244.
5 Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J Atheroscler Thromb* 2006; **13**: 101–107.
6 Asamoto M, Orii R, Otsuji M, Bougaki M, Imai Y, Yamada Y. Reliability of cardiac output measurements using LiDCOrapid™ and FloTrac/Vigileo™ across broad ranges of cardiac output values. *J Clin Monit Comput*. e-pub ahead of print 14 June 2016; doi:10.1007/s10877-016-9896-7.
7 Hirani V, Aresu M. Development of new demi-span equations from a nationally representative sample of older people to estimate adult height. *J Am Geriatr Soc* 2012; **60**: 550–554.
8 Guerra RS, Fonseca I, Pichel F, Restivo MT. Hand length as an alternative measurement of height. *Eur J Clin Nutr* 2014; **68**: 229–233.
9 Walker E, Nowacki AS. Understanding Equivalence and Noninferiority Testing. *J Gen Intern Med* 2011; **26**: 192–196.
10 Barker LE, Luman ET, McCauley MM, Chu SY. Assessing equivalence: an alternative to the use of difference tests for measuring disparities in vaccination coverage. *Am J Epidemiol* 2002; **156**: 1056–1061.
11 Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982; **38**: 963–974.
12 R: The R Project for Statistical Computing. R-project.org http://www.R-project.org/. Accessed on 7 April 2016.
13 Aase SA, Torp H, Stoylen A. Aortic valve closure: relation to tissue velocities by Doppler and speckle tracking in normal subjects. *Eur J Echocardiogr* 2008; **9**: 555–559.
14 Maccanon DM, Arevalo F, Meyer EC. Direct detection and timing of aortic valve closure. *Circ Res* 1964; **14**: 387–391.
15 Hickson SS, Nichols WW, Yasmin, McDonnell BJ, Cockcroft JR, Wilkinson IB, McEniery CM. Influence of the central-to-peripheral arterial stiffness gradient on the timing and amplitude of wave reflections. *Hypertens Res* 2016; **39**: 723–729.
16 Ye C, Pan Y, Xu X, Su S, Snieder H, Treiber F, Kapuku G, Wang X. Pulse wave velocity in elastic and muscular arteries: tracking stability and association with anthropometric and hemodynamic measurements. *Hypertens Res* 2016; **39**: 786–791.
17 WARNER HR. A study of the mechanism of pressure wave distortion by arterial walls using an electrical analog. *Circ Res* 1957; **5**: 79–84.
18 Schwid HA, Taylor LA, Smith NT. Computer model analysis of the radial artery pressure waveform. *J Clin Monit* 1987; **3**: 220–228.
19 Politi MT, Ghigo A, Fernández JM, Khelifa I, Gaudric J, Fullana JM, Lagrée P-Y. The dicrotic notch analyzed by a numerical model. *Comput Biol Med* 2016; **72**: 54–64.
20 Tsai Y-C, Chiu Y-W, Kuo H-T, Chen S-C, Hwang S-J, Chen T-H, Kuo M-C, Chen H-C. Fluid overload, pulse wave velocity, and ratio of brachial pre-ejection period to ejection time in diabetic and non-diabetic chronic kidney disease. *PLoS ONE* 2014; **9**: e111000.
21 Chen S-C, Chang J-M, Tsai Y-C, Su H-M, Chen H-C. Brachial-ankle pulse wave velocity and brachial pre-ejection period to ejection time ratio with renal outcomes in chronic kidney disease. *Hypertens Res* 2012; **35**: 1159–1163.

22 Su H-M, Lin T-H, Lee C-S, Lee H-C, Chu C-Y, Hsu P-C, Voon W-C, Lai W-T, Sheu S-H. Myocardial performance index derived from brachial-ankle pulse wave velocity: a novel and feasible parameter in evaluation of cardiac performance. *Am J Hypertens* 2009; **22**: 871–876.
23 Hsu P-C, Lin T-H, Lee C-S, Chu C-Y, Su H-M, Voon W-C, Lai W-T, Sheu S-H. Impact of a systolic parameter, defined as the ratio of right brachial pre-ejection period to ejection time, on the relationship between brachial-ankle pulse wave velocity and left ventricular diastolic function. *Hypertens Res* 2011; **34**: 462–467.
24 Steppan J, Sikka G, Hori D, Nyhan D, Berkowitz DE, Gottschalk A, Barodka V. Seeking a blood pressure-independent measure of vascular properties. *Hypertens Res* 2016; **39**: 27–38.
25 Lim J, Pearman ME, Park W, Alkatan M, Machin DR, Tanaka H. Impact of blood pressure perturbations on arterial stiffness. *Am J Physiol Regul Integr Comp Physiol* 2015; **309**: R1540–R1545.
26 Chan GSH, Middleton PM, Celler BG, Wang L, Lovell NH. Automatic detection of left ventricular ejection time from a finger photoplethysmographic pulse oximetry waveform: comparison with Doppler aortic measurement. *Physiol Meas* 2007; **28**: 439–452.
27 Su H-M, Lin T-H, Hsu P-C, Chu C-Y, Lee W-H, Chen S-C, Lee C-S, Voon W-C, Lai W-T, Sheu S-H. A comparison between brachial and echocardiographic systolic time intervals. *PLoS ONE* 2013; **8**: e55840.
28 Orr JS, Gentile CL, Davy BM, Davy KP. Large artery stiffening with weight gain in humans: role of visceral fat accumulation. *Hypertension* 2008; **51**: 1519–1524.
29 Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989; **80**: 1652–1659.
30 Razminia M, Trivedi A, Molnar J, Elbzour M, Guerrero M, Salem Y, Ahmed A, Khosla S, Lubell DL. Validation of a new formula for mean arterial pressure calculation: the new formula is superior to the standard formula. *Catheter Cardiovasc Interv* 2004; **63**: 419–425.

Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)