van Houwelingen MJ, Merkus D, Hofland J, Bakker J, Tenbrinck R, te Lintel Hekkert M, van Dijk G, Hoeks AP, Duncker DJ. A novel approach to assess hemorrhagic shock severity using the arterially determined left ventricular isovolumic contraction period. Am J Physiol Heart Circ Physiol 305: H1790–H1797, 2013. First published October 11, 2013; doi:10.1152/ajpheart.00504.2013.—Recently, the ventilatory variation in pre-ejection period (ΔPPEP) was found to be useful in the prediction of fluid-responsiveness of patients in shock. In the present study we investigated the behavior of the ventilation-induced variations in the systolic timing intervals in response to a graded hemorrhage protocol. The timing intervals studied included the ventilatory variation in ventricular electromechanical delay (ΔEMD), isovolumic contraction period (determined from the arterial pressure waveform, ΔAIC), pulse travel time (ΔPTT), and ΔPPEP. ΔAIC and ΔPPEP were evaluated in the aorta and carotid artery (annotated by subscripts Ao and CA) and were compared with the responses of pulse pressure variation (ΔPPA) and stroke volume variation (ΔSV). The graded hemorrhage protocol, followed by resuscitation using norepinephrine and autologous blood transfusion, was performed in eight anesthetized Yorkshire X Landrace swine. ΔAIC,Ao, ΔAIC,CA, ΔPPEP,Ao, ΔPPEP,CA, ΔPPA,Ao, ΔPPA,CA, and ΔSV showed significant increases during the graded hemorrhage and significant decreases during the subsequent resuscitation. ΔAIC,Ao, ΔAIC,CA, ΔPPEP,Ao, and ΔPPEP,CA all correlated well with ΔPPA and ΔSV (all r ≥ 0.8, all P < 0.001). ΔEMD and ΔPTT did not significantly change throughout the protocol. In contrast with ΔPPEP,Ao, which was significantly higher than ΔPPEP,CA (P < 0.01), ΔAIC,Ao was not different from ΔAIC,CA. In conclusion, ventilation-induced preload variation principally affects the arterially determined isovolumic contraction period (AIC). Moreover, ΔAIC can be determined solely from the arterial pressure waveform, whereas ΔPPEP also requires ECG measurement. Importantly, ΔAIC determined from either the carotid or aortic pressure waveform are interchangeable, suggesting that, in contrast with ΔPPEP, ΔAIC may be site independent.

graded hemorrhagic shock; resuscitation; heart-lung interactions; systolic timing intervals; ventilatory variation

A REDUCTION IN EFFECTIVE CIRCULATING blood volume, caused either by hemorrhage or vasodilatation, results in a decrease in left ventricular preload and, hence, stroke volume (SV) and cardiac output (CO). An excessive reduction eventually induces systemic hypotension, a situation termed hypovolemic shock (15). Patients in shock are typically treated with fluids and vasoactive agents to increase CO and restore systemic arterial pressure. A patient with hemorrhagic shock requires intravascular administration of fluids, whereas a septic patient may not benefit from a large amount of intravascular fluids and may even experience adverse effects (9, 24, 26, 31, 43, 47). To predict whether patients will be fluid responsive and to determine the optimal quantity of fluids to be infused, several hemodynamic variables have been proposed, including central venous pressure, pulmonary wedge pressure, and pulse pressure variation (2, 12, 13, 27, 34).

Variation in the pulse pressure in the critically ill artificially ventilated patient is a consequence of positive pressure-induced variations in preload which, in turn, cause variations in stroke volume (34, 48) and hence in pulse pressure (25, 28). The amplitude of this variation in stroke volume or pulse pressure reflects the part of the nonlinear Frank-Starling pre-load-stroke volume curve the heart is operating on. Thus, when the steeply sloped part is operated on as a consequence of a low average preload, a small change in preload translates into a large change in stroke volume, involving a fluid responsive patient. Conversely, at normal preload values, when the heart operates on the shallowly sloped part of the Frank-Starling curve, a similar change in preload only results in a small variation in stroke volume (28). In the latter case, a patient is less likely to benefit from intravascular fluid administration. Consequently, variations in ventricular preload produced by positive pressure ventilation have been shown to predict fluid responsiveness better than static variables such as central venous pressure or pulmonary wedge pressure (25, 28). Indeed, the relative variations in stroke volume and pulse pressure over the ventilatory cycle have been shown to be highly predictive of a patient’s fluid-responsiveness (25, 34, 48).

A limitation of the ventilation-induced variations in pulse pressure as an index of filling status is that it requires an invasive blood pressure measurement. Because the variations in preload produced by ventilation also produce variations in systolic timing intervals (1, 10, 44), one could consider pressure waveform timing characteristics, instead of pressure amplitude properties, as a less invasive or even noninvasive assessment of fluid responsiveness (1, 10, 33, 41). Based on the observation that the pre-ejection period (PEP) depends mainly on preload (46), Bendjelid et al. (1) proposed the relative variation in pre-ejection period (ΔPEP) produced by positive pressure ventilation as a predictor of fluid-responsiveness. In
septic patients, these authors showed that the ΔPEP, as measured at the level of the radial artery, was indeed able to predict whether a particular patient would respond to fluid administration (1).

The PEP is composed of two time intervals (Fig. 1). The first interval, the ventricular electro-mechanical delay (EMD), reflects the time between the peak Q wave of the ECG and the mitral valve closure. The second interval is the isovolumic contraction period. Recently we reported the presence of an aortic pressure perturbation before aortic valve opening (41), of which the onset corresponds with the onset of isovolumic contraction (Fig. 1). This arterially detected isovolumic contraction start (AIC\textsubscript{start}) (41) can be used to divide the PEP into the EMD and isovolumic contraction period when assessed in the ascending aorta. The elapsed time between the peak Q wave of the ECG and AIC\textsubscript{start-Ao} equals EMD, whereas the time interval between AIC\textsubscript{start-Ao} and the subsequent systolic foot of the aortic pressure wave reflects the isovolumic contraction period; the latter will be referred to as the arterially determined isovolumic contraction period (AIC\textsubscript{Ao}). When PEP is determined using a peripherally assessed arterial pressure waveform, it will further be confounded by pulse travel time (PTT). Analysis of both the aortic and carotid pressure waveforms will enable us to investigate the contribution to ΔPEP of the variations in isovolumic contraction period, EMD and PTT during shock, and subsequent treatment.

EMD and PTT show relatively little variation on a beat-to-beat basis and appear largely dependent on hemodynamic variables such as heart rate (HR), mean arterial blood pressure, and vascular stiffness and are influenced by sympathetic activity (5, 18, 19). We hypothesized that the ventilation-induced preload variation principally affects the isovolumic contraction period and has little influence on EMD and PTT. Moreover, we hypothesized that the relative ventilation-induced variation in the arterially determined isovolumic contraction period (ΔAIC) is similar for the aortic root and for a peripheral arterial site. If ΔAIC is indeed site independent, it will enable the use of systolic timing intervals in the assessment of severity and treatment of shock, particularly because AIC can be determined noninvasively in peripheral arteries, thereby facilitating clinical application.

To test these hypotheses, we performed a graded hemorrhage protocol in anesthetized swine. In this model, ΔPEP and its individual components ΔAIC, ΔEMD, and ΔPTT were assessed in both the ascending aorta and carotid artery (respectively, annotated by subscripts Ao and CA). Furthermore these were compared with the relative ventilatory variation in both pulse pressure (ΔPP\textsubscript{Ao}, assessed in the ascending aorta) and stroke volume (ΔSV), which are commonly used parameters for the determination of shock and evaluation of its treatment.

**MATERIALS AND METHODS**

**Animals.** Studies were performed in eight 3- to 4-mo-old female Yorkshire X Landrace swine (32 ± 5 kg; means ± SD) in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 85-23, revised 1996) and with approval of the Erasmus University Medical Center Animal Care Committee.

**Surgical procedures.** Swine were sedated with an intramuscular injection of xylazine (2.25 mg/kg), tiletamine (5 mg/kg), and zolazepam (5 mg/kg) (20) and anesthetized with sevoflurane (1.8–2.4% end tidal concentration) (17), in combination with buprenorphine (4 μg kg\(^{-1}\) h\(^{-1}\) iv) (37). This combination suppresses respiratory effort during positive pressure ventilation, a prerequisite for adequate measurement of variables such as ΔPP, ΔSV, and ΔPEP (39). Swine were intubated and mechanically ventilated with a target tidal volume of ~10 ml/kg body wt (range, 10.9 ± 1.6 ml/kg) and with F\textsubscript{O2} set to 0.30. The target tidal volume was maintained during the execution of this study protocol, and ventilation frequency was adjusted to keep blood gases within their physiological range (P\textsubscript{CO2}, 4.0–6.0 kPa; S\textsubscript{O2} > 92%).

After ECG lead connection, a high fidelity double pressure sensor catheter (Millar Instruments, Houston, TX) was inserted into the right carotid artery and advanced into the left ventricle (LV) with the second sensor residing in the aorta. This enabled simultaneous monitoring and recording of both LV and aortic pressure. Parameters derived from the ascending aortic pressure waveform are annotated by subscript Ao. A second single high fidelity pressure sensor catheter was inserted into the left carotid artery to allow recording of the carotid pressure. Parameters derived from the carotid artery pressure
automated postprocessing of the recorded signals. Signal conversion to their proper units before storage as well as for and stored for offline processing. Matlab (Natick, MA) was used for board (National Instruments, Austin, TX; sample frequency 2,000 Hz) flow, airway pressure, and airway flow signals into a data acquisition amplified using a wide-band (1,000 Hz) amplifier system (Experim-

Experimental intravenous infusion of NE was started and titrated (9 /H11006 during the experimental protocol. No fluids were added for volume compensation at any point transfusion of autologous blood at a later stage in the experimental 20 ml/kg was expected to result in severe hemorrhagic shock. All a blood volume of (cumulative 20 ml/kg), again followed by at least 15 min of stabili-

Protocol. After ~30 min of stabilization, baseline measurements of cardiopulmonary signals (i.e., ECG, LV, aortic and carotid pressures, aortic flow, and airway pressure and flow) were recorded simultaneously (BL; Fig. 2). Thereafter, a three-step graded hemorrhage protocol was executed, using a blood extraction rate of 25 ml/min. The first hemorrhage step (H1) consisted of withdrawal of 5 ml/kg blood, followed by at least 15 min of stabilization, and record-

After completion of the three-step hemorrhage protocol, a continu-

Fig. 2. Graded hemorrhage protocol. BL, baseline; H1, hemorrhage –5 ml/kg blood; H2, hemorrhage –10 ml/kg blood; H3, hemorrhage –20 ml/kg blood; NE, norepinephrine; T, transfusion of blood.

RESULTS

Effect of graded hemorrhage and resuscitation on hemody-

PEP was determined as the interval between the Q-top of the ECG and the foot of either the aortic or carotid pressure pulse (PEP Ao and PEP CA, respectively; see Fig. 1 for an example); the feet of the aortic and carotid pressure pulses were determined by means of an intersecting tangent method (6). AIC Ao and AIC CA were determined as the interval between AICstart-Ao or AICstart-CA, identified as a peak in the second derivative of the aortic or carotid pressure wave preceding the onset of systole (41), and the foot of the aortic or carotid pressure pulse, respectively. As aortic pressure was measured just distal (~1 cm) to the aortic valve, the EMD was determined as the interval between the Q-wave peak of the ECG and AICstart-Ao (Fig. 1). PTT was determined by subtracting AICstart-Ao from AICend-CA.

The relative ventilatory variation in PP (ΔPP), SV (ΔSV), PEP (ΔPEP), AIC (ΔAIC), EMD (ΔEMD), and PPT (ΔPPT) in either the ascending aorta (subscript Ao) or carotid artery (subscript CA) were determined using the maximum and minimum value of each parameter during the respiration cycle in the following equation: $\Delta = 100 \times \frac{(\text{maximum} - \text{minimum})}{((\text{maximum} + \text{minimum})/2)}$ (1, 13, 28). To eliminate noise, ensemble averaging of the beat-to-beat values over the ventilation cycle was applied.

Statistical analysis. Statistical analysis of all hemodynamic data was performed by using Excel (Microsoft, Seattle, WA) and SigmaStat (Systat Software, San Jose, CA) software. All data are presented as means ± SD. A repeated-measures ANOVA test followed by a post hoc Student-Newman-Keuls test was used to analyze the extracted parameters. Normality of data was tested using a Kolmogorov Smirnrov test. Pearson’s correlation was used to test correlations between variables. P values < 0.05 (two-tailed) were considered statistically significant.

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in SV and arterial blood pressure. The latter was accompanied by a, probably baroreflex mediated, increase in HR. Nevertheless cardiac output decreased whereas LV \( \frac{dP}{dt} \) at 30 mmHg was not significantly affected by the graded hemorrhage.

Notwithstanding the severe shock produced by the stepwise hemorrhage, all animals survived the entire experimental protocol. Titration of NE infusion restored arterial blood pressure to baseline values by increasing cardiac output and systemic vascular resistance (Fig. 3). The other hemodynamic variables were minimally affected with the exception of an increase in LV \( \frac{dP}{dt} \) at 30 mmHg \( (P < 0.05) \). Washout of NE and transfusion of autologous blood resulted in restoration of all hemodynamic variables toward baseline values.

Figure 4 shows the changes in timing intervals caused by graded hemorrhage. PEPAo, PEPCA, and PTT did not change significantly throughout the graded hemorrhage or resuscitation protocol. As expected, PEPCA was significantly larger than PEPAo \( (P < 0.0001) \) due to the time required for the pulse wave to travel from the aorta to the carotid artery (PTT). In contrast with PEPAo and PEPCA, AICCAo was not significantly different from AICCA, AICCA and AICCA both decreased progressively throughout graded hemorrhage, and only autologous blood transfusion restored these variables to baseline values. EMD progressively increased with increasing hemorrhage severity, whereas both infusion of NE and autologous blood transfusion decreased EMD compared with the last step in the graded hemorrhage protocol (H3). However, only autologous blood transfusion caused a restoration to baseline values.

**Effect graded hemorrhage and resuscitation on \( \Delta AIC \).** Graded hemorrhage resulted in an increase in ventilation-induced variation in most parameters, that is, \( \Delta SV, \Delta PP_{Ao}, \Delta PP_{CA}, \Delta PEP, \Delta Cardiac Output \), and cardiac output LV \( \frac{dP}{dt} \) at 30 mmHg. However, only autologous blood transfusion caused a restoration to baseline values.

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**Fig. 3.** Hemodynamics during graded hemorrhagic shock and resuscitation. *Significant difference from baseline \( (P < 0.05) \); †significant difference from the preceding protocol step \( (P < 0.05) \). In the blood pressure panel, significance indicators refer to maximum systolic arterial blood pressure (SAP) and mean arterial blood pressure (MAP) as well as minimum diastolic arterial blood pressure (DAP), except for DAP at T. LV \( \frac{dP}{dt} \) at 30 mmHg, rate of rise of LV pressure at 30 mmHg.

**Fig. 4.** Systolic timing intervals during graded hemorrhagic shock and resuscitation. PEP, arterially determined isovolumic contraction period (AIC), and pulse travel time (PTT) during graded hemorrhagic shock and resuscitation were determined in the aorta (Ao) and carotid artery (CA), where applicable. *Significant difference from baseline \( (P < 0.05) \); †significant difference from the preceding protocol step \( (P < 0.05) \); ‡significant difference between the aortic and carotid measurement site.


DeltaPEP_Ao, DeltaPEP_CA, DeltaAIC_Ao, and DeltaAIC_CA all increased progressively with graded hemorrhage (Fig. 5). Resuscitation with NE reduced DeltaSV ($P < 0.001$), DeltaPP_Ao ($P < 0.001$), DeltaPEP_Ao ($P = 0.02$), DeltaPEP_CA ($P = 0.02$), and DeltaAIC_Ao ($P < 0.001$) compared with H3, although levels were not fully restored to baseline values (Fig. 5). Autologous blood transfusion (20 ml/kg) during washout of NE fully restored DeltaSV, DeltaPP_Ao, DeltaPP_CA, DeltaPEP_Ao, DeltaPEP_CA, DeltaAIC_Ao, and DeltaAIC_CA to baseline values (all $P = \text{ns} \text{ vs. baseline; Fig. 5}$. Throughout the protocol no significant changes were found in DeltaPTT or DeltaEMD (Fig. 5).

Both DeltaPEP_Ao and DeltaPEP_CA were significantly smaller than DeltaSV, DeltaPP_Ao, DeltaPP_CA, DeltaAIC_Ao, and DeltaAIC_CA (all $P < 0.001$). Moreover, DeltaPEP_CA was significantly smaller than DeltaPEP_Ao ($P < 0.01$), whereas DeltaAIC_Ao was not significantly different from DeltaAIC_CA (Fig. 5).

DeltaPEP_Ao failed to correlate significantly with DeltaEMD. However, DeltaPEP_CA did significantly, but weakly, correlate with DeltaPTT ($r = 0.37$, $P = 0.02$).

Very good correlations were observed between DeltaPP_Ao and DeltaSV ($r = 0.88$, $P < 0.001$). Correlations between DeltaPP_Ao and DeltaSV and DeltaPEP_Ao, DeltaPEP_CA, DeltaAIC_Ao, DeltaAIC_CA, DeltaEMD, and DeltaPTT are summarized in Table 1. The results illustrate that both DeltaPEP and DeltaAIC determined from either the aortic or carotid pressure waveform can be used as substitutes for DeltaPP_Ao and DeltaSV, respectively.

**DISCUSSION**

The main findings of the present study are that 1) the ventilation-induced preload variation principally affected the isovolumic contraction period and has little influence on the ventricular EMD and large artery PTT; 2) both DeltaAIC and DeltaPEP in the aorta and carotid artery (DeltaAIC_Ao, DeltaAIC_CA, DeltaPEP_Ao, and DeltaPEP_CA, respectively) increased with progressive hemorrhagic shock and decreased with subsequent resuscitation and restoration of circulating volume; 3) in contrast, neither DeltaEMD nor DeltaPTT showed any significant changes throughout the experimental protocol; 4) the relative ventilation-induced variation in the isovolumic contraction period (DeltaAIC) determined from the aortic root and carotid pressure waveform were similar and, hence, have an added value in the use of systolic timing intervals in the detection of shock; 5) in contrast, the relative ventilation-induced variation in the pre-ejection period (DeltaPEP) determined from the aortic root pressure waveform was different from DeltaPEP determined from the carotid pressure waveform throughout the hemorrhage and resuscitation protocol within each animal; 6) nonetheless, not only DeltaAIC_Ao and DeltaAIC_CA but also DeltaPEP_Ao and DeltaPEP_CA exhibited a good correlation with both DeltaPP and DeltaSV in swine during graded hemorrhage and subsequent treatment, whereas neither DeltaEMD nor DeltaPTT showed a significant correlation with either DeltaPP and DeltaSV. The implications of these findings will be discussed below.

DeltaSV is able to predict fluid responsiveness (4, 7, 36) but is difficult to obtain directly in the clinical setting (4, 7). Consequently, either approximation of DeltaSV using pulse contour analysis (4, 7, 23) or substitutes like DeltaPP (13, 28) are typically used at the patient’s bedside. In accordance with previous reports we also observed a good correlation between DeltaSV and DeltaPP_Ao (3, 35), which are both known to be good predictors of fluid responsiveness in mechanically ventilated patients (2, 34).

Table 1. Correlations between ventilatory variation parameters

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<th>DeltaPEP_Ao</th>
<th>DeltaPEP_CA</th>
<th>DeltaAIC_Ao</th>
<th>DeltaAIC_CA</th>
<th>DeltaEMD</th>
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<tr>
<td>$r$</td>
<td>0.88</td>
<td>0.88</td>
<td>0.85</td>
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<td>NS</td>
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<tr>
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<td>DeltaSV</td>
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<tr>
<td>$r$</td>
<td>0.84</td>
<td>0.87</td>
<td>0.83</td>
<td>0.80</td>
<td>NS</td>
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<tr>
<td>$P$</td>
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Correlations between the relative ventilatory variation in stroke volume (DeltaSV), pulse pressure (DeltaPP), pre-ejection period (DeltaPEP), arterially determined isovolumic contraction period (DeltaAIC), electromechanical delay (DeltaEMD), and pulse travel time (DeltaPTT). Ao, ascending aorta; CA, carotid artery; NS, not significant.
Furthermore, we found that both ΔPEP$_{Ao}$ and ΔPEP$_{CA}$ correlated well with both ΔPP$_{Ao}$ and ΔSV, which is in line with previous observations in coronary artery bypass graft surgery patients (1) and in a group of septic patients (10).

The PEP can be divided into the EMD and the isovolumic contraction period using the time point at which the mitral valve closes. In previous work we have shown that AIC$_{start}$, when measured close to the aortic valve, is a good estimate for mitral valve closure occurrence and hence for EMD (42). In the present study we showed that the duration of the isovolumic contraction period as determined from the carotid pressure waveform (AIC$_{CA}$) corresponds well to the isovolumic contraction period as determined in the ascending aorta (AIC$_{Ao}$). Additionally, we were able to determine the individual contributions of the isovolumic contraction period (AIC), EMD, and PTT to ΔPEP by measuring simultaneously in the ascending aorta and carotid artery. The latter also enabled us to directly test the site dependency of ΔPEP.

Interestingly, in our study the ΔPEP over the ventilatory cycle at baseline (5%) was slightly larger as compared with the cutoff value between fluid-responders and nonresponders (4%) found by Feissel et al. (10). This may be explained, at least in part, by the ~20% higher tidal volume in combination with a relative low lung compliance in our animals as compared with septic shock patients (21, 22). However, a more likely explanation is offered by the dependency of ΔPEP on pulse travel time. Determination of the PEP in a more distal artery will confound the average of the maximum and minimum PEP with an additional pulse wave travel time. For example, a pulse wave velocity of 10 m/s adds a pulse wave travel time of 60 ms to PEP for a radial artery measurement site at 60 cm from the heart. Quinsac et al. (32) showed that the change in pulse wave velocity as a result of hemorrhagic shock is nonsignificant. Consequently, the ventilatory variation in pulse wave travel time compared with the total pulse wave travel time is likely to be small. The additional pulse wave travel time will reduce ΔPEP. In the example, adding 60 ms travel time to an average PEP of 80 ms reduces the relative variation to 4%, assuming a difference between the maximum and minimum PEP of 7 ms. Indeed the correlation between ΔPTT and ΔPEP$_{CA}$ was weak, indicating that ΔPTT contributes minimally to ΔPEP.

We found no correlation between ΔEMD and either ΔSV or ΔPP$_{Ao}$, suggesting that ΔEMD does not contribute to ΔPEP. Nevertheless, it could be argued that EMD is modulated by ventilation because AIC$_{start}$, which is used in the calculation of EMD, occurs later than the onset of LV pressure increase (42) and hence depends on preload dependent contractile force (38) and the rate of rise of LV pressure (11) in the ventricle. However, we found no significant correlation between LV dP/dt$_{p30}$ and AIC$_{start-Ao}$, which is also confirmed by the lack of correlation between ΔEMD and ΔPEP.

The duration of isovolumic contraction changes with alterations in preload, as was shown 50 years ago by Wallace et al. (45). The present study shows that even small changes in preload produced by positive pressure ventilation can be detected in the duration of AIC. Moreover, we found a good correlation between ΔAIC$_{Ao}$ and ΔAIC$_{CA}$ and either ΔSV or ΔPP$_{Ao}$, which was as good as the correlations between ΔPEP$_{Ao}$ and ΔPEP$_{CA}$ and either ΔSV or ΔPP$_{Ao}$. ΔAIC is not confounded by EMD (which changes minimally over the ventilatory cycle) and, if assessed in the carotid artery, by pulse travel time. This shows that, contrary with ΔPEP, ΔAIC derived from either the carotid or the aortic pressure waveform is interchangeable.

It could be argued that AIC changes due to alterations in pulse wave velocity. However, because the change in pressure over the AIC interval preceding the systolic foot of the arterial pressure waveform is small, the influence of a changing pulse wave velocity on AIC can be considered negligible compared with the influence of a changing preload. This assumption is supported by our results that show that AIC changes during the hemorrhage and resuscitation protocol with no significant difference between AIC$_{Ao}$ and AIC$_{CA}$ responses (Fig. 4). Consequently, it is unlikely that there is a causal relationship between changes in pulse wave velocity and ΔAIC, which suggests that ΔAIC may be site independent. However, we cannot exclude that due to wave dispersion (which increases with an increasing travel path of the pulse wave) the low amplitude pressure perturbation may be obscured in more distal arteries. As a result, the determination of AIC may become less accurate when assessed in more distal arteries. In the present study there was no significant difference in variance between the data from the aorta and carotid artery, but it should be noted that the path length between the aorta and carotid artery is relatively small. Clearly the ability to detect, and the accuracy of, AIC at more distal measurement sites should be the subject of future studies.

Whereas both ΔAIC and ΔPEP require an arterial pressure waveform (or a noninvasive substitute like a distension waveform) (41), ΔAIC does not require an ECG for synchronization. Consequently, errors due to possible measurement delays, introduced by equipment characteristics and interfacing that could occur in the determination of PEP, are circumvented with the use of ΔAIC.

A high temporal sample resolution is required to reliably detect changes in both ΔPEP and ΔAIC. The radial pressure waveform assessed by Bendjelid et al. (1) had a temporal sample resolution of 10 ms, which is low compared with the absolute ventilatory variation in PEP that we found (~7 ms, data not shown), and likely explains their lower accuracy of the remotely assessed ΔPEP in the prediction of fluid responsiveness as compared with radial ΔPP (1). Indeed, Feissel et al. (10), recording radial artery pressure with a temporal sample resolution of 2 ms, found that the radial ΔPEP predicted fluid responsiveness as accurate as radial ΔPP. Using a temporal sample resolution of 0.5 ms, we found good correlations between ΔPP$_{Ao}$ and ΔPEP$_{Ao}$, ΔPEP$_{CA}$, ΔAIC$_{Ao}$, and ΔAIC$_{CA}$.

**Methodological considerations.** To eliminate the effects of anesthesia on hemodynamic responses the present study would ideally have been executed in awake animals (16). Based on the drop in blood pressure and the modest reflex-tachycardia it could be argued that the baroreflex-mediated response to the decrease in circulating blood volume was impaired (8), which is a known effect of most anesthetics including sevofluran (29). Interestingly, the lack of increases in cardiac contractility despite significant increases in HR during the graded hemorrhage protocol was likely due to the opposing effects of the staircase phenomenon (Bowditch) and a negative Frank-Starling effect. Thus the hemorrhage-induced reduction in cardiac filling, reflected in a lower LVEDP (Fig. 3), will likely have decreased length-dependent force development (11). In addition, the use of sevoflurane, which has been shown to depress cardiac contractile force (29, 30) and blunt baroreceptor-re-
flexes (29), may have further contributed to the absence of an increase in cardiac contractility.

In the present animal study we used the carotid artery as peripheral artery. We have shown in a previous study that AIC can be determined noninvasively from the carotid artery distension waveform in healthy test subjects (41). Whether AIC can be determined from the pressure waveform (or substitute) assessed in more peripheral arteries in patients is subject to future studies.

Conclusions

The present study shows that the ventilation-induced preload variation principally affects the isovolumic contraction period and has little influence on the ventricular EMD and large artery PTT. The relative ventilation-induced variation in the arterially obtained AIC correlates well with the gold standards for the prediction of fluid-responsiveness reported in mechanically ventilated patients, i.e., pulse pressure variation and stroke volume variation (4, 28, 34). In light of these findings taken together, AIC may be of added value in the use of systolic timing intervals in the detection of shock.

REFERENCES


