Can the left ventricular early diastolic tissue-to-blood time interval be used to identify a normal pulmonary capillary wedge pressure?

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Abstract  The pulsed Doppler early diastolic left ventricular (LV) tissue (e)—blood (E) onset temporal relationship \( e-E \) is suggested to predict pulmonary capillary wedge pressure (PCWP), through the formulas: \( \tau = 32 + 0.7(e-E) \) and \( PCWP = LV \text{ end-systolic pressure} \times e^{-\frac{IVRT}{\tau}} \). Small changes/errors in \( E \) could influence the quotient IVRT/\( \tau \) by oppositely affecting IVRT and \( e-E \). At rest in 50 healthy individuals we noted: \( e-E \): 2 ± 14 ms; IVRT: 89 ± 17 ms; calculated \( \tau \): 33 ± 10 ms; and PCWP: 9 ± 9 mmHg (>12 mmHg in 28%). Non-pharmacological preload alterations in 14 individuals rendered an intraindividual 'PCWP'-fluctuation of up to 40 mmHg. This application may therefore not be clinically robust.

Introduction

To avoid the patient risk and cost of invasive measurements, there is a constant search for non-invasive substitute means to predict invasive parameters. Due to a high sampling rate, the pulsed Doppler, both in its tissue- and blood pool application, possesses an excellent temporal resolution and, recently, there has been some interest taken in the investigation of the left ventricular (LV) tissue-to-blood timing.\cite{1,2} The pulsed Doppler-obtained time interval between the start of the early diastolic LV lengthening, \( e \), and the mitral inflow, \( E \), has been suggested to non-invasively estimate \( \tau \), the time constant of LV relaxation. Furthermore, this time interval \( (e-E) \), when related to the LV isovolumic relaxation time (IVRT), is claimed to be useful in the...
prediction of the pulmonary capillary wedge pressure (PCWP), through the formulas: \( \text{tau} = 32 + 0.7 \times (e-E) \) and \( \text{PCWP} = \text{LV end-systolic pressure} \times e^{-\text{IVRT}/\text{tau}}. \) In order to investigate the clinical validity of this application, we aimed to define its mathematical assumptions and to test it in healthy elderly non-sedentary individuals, at horizontal rest, and, in a sub group, also during simple preload alterations, mediated by changes in body position.

**Methods**

**Study population**

We included 50 healthy elderly (aged 65 ± 10 years, 74% men) non-sedentary individuals, selected from a randomly sampled population within the County Census base. They were all free of cardiovascular, pulmonary, other systemic disease or chest pain or shortness of breath/fatigue and they took no medication. All had a normal electrocardiogram (ECG) and a normal echocardiogram, including a normal LV diastolic filling, as semi-quantitatively assessed by pulsed Doppler echocardiography (for details, please see Echocardiography and Measurements and analysis) according to international recommendations. The study subjects were therefore assumed to have a normal PCWP. Their measured cardiovascular risk-related variables were serum-cholesterol 5.3 ± 0.7 mmol/l, serum-triglycerides 1.0 ± 0.4 mmol/l, blood pressure after 1 h rest; 129 ± 16/73 ± 6 mmHg, body mass index 23.6 ± 3.8 and 60% had never smoked. All the participants gave their informed consent and the regional scientific ethics committee (Göteborg University) approved the protocol. Of these 50 individuals, 14 (aged 73 ± 4 years, 50% men) also underwent a simple non-pharmacological manipulation in loading conditions, following the load alteration protocol described below.

**Mathematical analysis**

Mathematically, the formula PCWP = LV end-systolic pressure \( \times e^{-\text{IVRT}/\text{tau}} \), since it is exponential, will to a large extent depend on the quotient IVRT/tau. A small alteration of the \( \text{E} \) timing could influence this quotient considerably, since it would affect both the IVRT and \( e-E \), but in opposite directions. We therefore explored the quotient IVRT/tau, by performing a transformation of the original formula: \( \text{IVRT}/\text{tau} = -\ln \left( \frac{\text{PCWP}}{\text{systolic blood pressure} \times 0.9} \right) \), and plotting the quotient against a given range of theoretical healthy individual PCWPs and systolic blood pressure values. The systolic blood pressure \( \times 0.9 \) was used as a substitute for LV end-systolic pressure.

**Echocardiography**

The examination was carried out in accordance with the recommendations of the American Society of Echocardiography. In addition, in order to further facilitate optimization of image quality, the subjects were from the left recumbent position facing the examiner, who had an extra monitor opposite and two hands free for the transducer, as an assisting technician mastered the ultrasonic machine. All standard images were registered, including pulsed and continuous wave Doppler. For the general LV filling assessment, we recorded pulsed blood pool Doppler from between the mitral tips; the upper right pulmonary vein and the LV outflow tract. All Doppler registrations were made in relaxed end expiratory apnoea at a sweep rate of 100 mm per second, captured and stored digitally.

For the present objective, we acquired six Doppler images: pulsed tissue Doppler of the septal, lateral, inferior and anterior LV basal walls as well as, again, pulsed blood pool mitral and LV outflow tract Doppler. A clear onset of both \( \text{e} \) and \( \text{E} \) was requested. In the event of an unsharp Doppler envelope at the beginning of the mitral inflow, the sample volume was shifted slightly, from the position between the mitral tips in the direction towards the left atrium. Care was taken to identify the aortic closing click at the end of the sub aortic flow. The ultra sound machine was a Sequoia 512 (Acuson/Siemens, Mountain View, CA) with a 2.5–4 MHz transducer.

**Load alteration protocol**

In each of 14 individuals, these six echocardiographic images were also repeated at eight levels (here called loading steps), according to the following protocol of altogether approximately 90 min, during which the subject remained in the left recumbent position and was fastened by a hip belt (to avoid discomfort, sliding or too much postural or lower limb muscle activation) to a tiltable barrack bed: All changes in body position were carried out slowly and without any reported symptoms or observed signs of the subjects. The eight loading steps were

1. Horizontal position, rest I,
2. Horizontal position, rest II,
3. Tilting to 45 deg, head upwards,
4. Passive standing, 5–8 min,
5. Return to the horizontal position,
6. Horizontal position, 5—8 min,
7. Tilting to −10 deg, head downwards and a two
decimeters of passive leg elevation,
8. Horizontal position, 5—8 min.

All the six pulsed tissue and blood pool Doppler
images, as well as the systemic non-invasive blood
pressure measurement of the right upper arm,
were collected at each level. No invasive data
were obtained and neither transvenous cannulae
nor any drugs were used.

**Measurements and analysis**

The same investigator performed all measure-
ments off-line, utilizing the measurement program
of the same equipment used for the acquisition of
images. The time interval from R in the ECG to the
Doppler-defined aortic valve closure, the time in-
terval from R to the start of the mitral inflow
(E), as well as from R to the onset of the tissue
lengthening (e), of all four LV walls, were mea-
sured. Hence, for the loading alterations, the
data of altogether 14 × 8 × 6 = 672 time interval
measurements were transferred manually to a Mac-
intosh computer and processed using Microsoft
Excel. We defined LV IVRT as the time from the be-
inning of the aortic closing click, to the start of
the pulsed Doppler mitral inflow. The e—E time in-
terval was designated as the tissue-to-blood time
interval for each of the four LV walls; see Fig. 1,
of which the LV mean e—E time interval for each
individual was subsequently calculated.

Prior to these measurements, LV filling had been
semi-quantitatively assessed3–5 and concluded to
be normal in all 50 individuals (no one was ex-
cluded). For the settlement of a normal LV filling
were considered the standard recommended Dop-
pler variables. These were the blood pool peak mitral
E/A ratio, the mitral deceleration time, the IVRT,
the pulmonary venous systolic/diastolic ratio and
the temporal difference between the mitral and
pulmonary venous A-waves at their point of cessa-
tion (with the nearest ECG R-wave as a reference),
diagnostically equivalent to the difference in
mitral-pulmonary venous A-wave duration.5

Likewise, the participants had been evaluated
to have a normal right and LV systolic function,
including a preserved longitudinal motion and
a normal ejection fraction (visually ≥ 60%), no LV
hypertrophy, no valvular disease and a normal sys-
tolic right ventricular pressure (≤30 mmHg).
The latter was estimated from the right ventricu-
lar-right atrial pressure gradient,7,8 with the
addition of the central venous pressure, semi-

![Figure 1](image-url)

Figure 1 Examples of the assessment of (A) The global
isovolumic relaxation time, IVRT: pulsed Doppler of the
left ventricular outflow tract (upper image) shows the
time interval 'R to the aortic valve closure', identified
by its closing click = 392 ms. The pulsed mitral Doppler
(lower image) shows the time interval 'R to the start of
the mitral inflow' = 462 ms. Hence IVRT is calculated
as 462 ms — 392 ms = 70 ms. (B) The e—E time interval: pulsed
mitral Doppler (upper image) shows the time interval
'R to the start of the mitral inflow', E = 462 ms. Pulsed
tissue Doppler of the inferior basal wall (lower image)
shows the time interval 'R to the start of the tissue
lengthening', e = 496 ms. Hence e—E is calculated as
496 ms — 462 ms = 34 ms.

**Statistics**

Values are presented as mean ± SD. Wilcoxon’s
paired signed rank test was applied to analyze
differences between loading steps 2 and 3, for
preload decrease, as well as between steps 4 and 5, for its increase.

Results
Mathematical analysis
For an IVRT/tau quotient above $\approx 5.4$, the calculated PCWP goes asymptotically towards zero, whereas for a quotient below $\approx 2.2$, it goes from $\approx 12$ mmHg and asymptotically towards the LV systolic pressure, see Fig. 2. Due to the inverse exponential relationship between PCWP and IVRT/tau — as defined in the formula (PCWP $=$ LV end-systolic pressure $\times e^{-\text{IVRT/tau}}$), small values of the quotient IVRT/tau will cause PCWP to become very large, and vice versa. Hence, in order to obtain a result of PCWP $\leq 12$ mmHg, the IVRT/tau quotient must exceed a value of $\approx 2.2$. Additionally, the smaller the quotient is, the greater the influence of the end-systolic pressure becomes on the PCWP. Hence, at a low quotient, also the end-systolic pressure will influence the result.

Values in healthy elderly individuals at rest
The mean LV e–E time interval, at horizontal rest in the 50 individuals, was $2 \pm 14$ ms and IVRT was $89 \pm 17$ ms. Applying the formulas resulted in a calculated tau of $33 \pm 10$ ms and a PCWP of $9 \pm 9$ mmHg, with a median of 7 and a range of 0–41 mmHg. In 28% of the individuals, PCWP exceeded 12 mmHg.

Values in healthy elderly individuals at different loading conditions
During non-pharmacological load alterations in the 14 individuals, the IVRT and e–E to a great extent mimickingly diverged from each other, see Fig. 3. Fig. 4 shows a group summary of the effects of a presumed decrease/increase in preload on these variables. Application of the formulas resulted in intrindividually highly variable and sometimes very unlikely values of the calculated PCWP, as illustrated in Fig. 5.

The LV mean maximum early diastolic velocity for the different loading steps was for step 1: $10.6 \pm 1.7$ cm/s, step 2: $10.5 \pm 1.7$ cm/s, step 3: $9.1 \pm 1.7$ cm/s, step 4: $8.7 \pm 1.7$ cm/s, step 5: $10.7 \pm 1.7$ cm/s, step 6: $10.7 \pm 1.9$ cm/s, step 7: $11.3 \pm 1.5$ cm/s, step 8: $10.4 \pm 1.9$ cm/s, step 9: $10.4 \pm 1.5$ cm/s, and step 10: $9.9 \pm 2.0$ cm/s, respectively.

Discussion
In order to reliably predict PCWP by non-invasive estimation, the normal variation in obtained values must be reasonably low, also during different physiological conditions. In the present study, we found a wider normal range of the e–E time interval at rest in healthy elderly individuals, compared to the study by Rivas-Gotz et al., the time interval that was used in the formula $\tau = 32 + 0.7 \times (e–E)$. Additionally, we noted a considerable — and rather inverse — effect of change in preload on the time intervals e–E and IVRT. When applying the formula PCWP $=$ LV end-systolic pressure $\times e^{-\text{IVRT/tau}}$, variable and frequently unlikely values of PCWP were obtained. Since we see no reason to question their data, tentative explanations that may be offered towards the discrepancies in results between the two studies include the selection of individuals, on whom the normal values were based. Their normal ranges of the e–E time interval and the IVRT were derived from 10 healthy dogs and 15 elderly, previously healthy, intensive care unit patients.

One might also consider the effect of preload on these variables. The direction in which the calculated PCWP varied with alterations in preload was an expected finding. However, the quantitative values of PCWP became rather

![Figure 2](image-url)
Figure 3  Effect of the load alteration protocol (numbered 1–8 on horizontal axis), presented as absolute values in each of the 14 individuals, vertical axis representing time (ms), in terms of the global isovolumic relaxation time, IVRT (green lines) and the e–E time interval (red lines). Loading steps: 1 = horizontal rest, 2 = 45 deg of passive stand-up, 3 = remain standing, 5 = return to the horizontal position, 6 = horizontal rest, 7 = position of head down and feet up, 8 = horizontal rest.
Figure 4  A group summary of the alterations in IVRT (upper panel) and LV mean $e-E$ (lower panel) with a presumed preload decrease (steps 2–3: to rise from an horizontal to a half standing position) and a presumed preload increase (steps 4–5: to lie back down again).

Figure 5  Individual values of the quotient IVRT/tau (upper image) and the calculated PCWP (lower image) along the load alteration protocol: 1, 2 = horizontal rest, 3 = 45 deg of passive stand-up, 4 = remain standing, 5 = return to the horizontal position, 6 = horizontal rest, 7 = position of head down and feet up, 8 = horizontal rest. The stippled horizontal red lines represent an IVRT/tau quotient of $\approx 2.2$ (upper image) and a PCWP of 12 mmHg (lower image). The red arrows (lower image) mark where the calculated PCWP tended to fall to normal values, coinciding with a presumed reduction in preload.
exaggerated and unstable. The preload dependency of the time interval \( e-E \) was tested also in the Rivas-Gotz study — by occlusion of the canine inferior vena cava — and concluded to be negligible. This procedure, however, should likely be a test of preload reduction only, if not also registrations at the subsequent reflo are carried out. This study approach appears not to be unexceptional\(^1,10\) even though the preload reduction is more often followed by, for example, a volume loading.\(^{11}\) Among our study subjects, preload reductions, including those of a more relative kind, such as to remain lying flat after having lain down from the half standing position 5 min earlier, resulted in a change towards a normal or near normal calculated PCWP. On the other hand, a preload increase often led to an unlikely high calculated PCWP in the same person.

One might speculate whether this issue could have played a role for the smooth results of the Rivas-Gotz study. Septicemia, a condition with a peripheral vasodilatation and often an increased cardiac output, can be associated with a reduced preload.\(^{12}\) It is usually treated with the support of fluids in order to compensate for this. As much as 80\% (12/15) of their ‘normal’ individuals were in the intensive care unit due to either septicemia (\( n = 6 \)) or pneumonia (\( n = 6 \)), of which septicemia may have occurred in some (since a previously healthy person hardly otherwise would require intensive care) and the remaining three patients were admitted due to bleeding. Their right atrial pressure was measured to be \( 5 \pm 3 \) mmHg, which for a septic condition, depending on what phase of the disease the patient is in, might indicate insufficient treatment of fluids. A preload situation on the short side is possible also in patients with bleeding as the cause for admission.\(^{12}\)

In addition, if the \( e-E \) time interval were to remain constant through preload alterations, it would necessitate, for the formula to be valid, either: the same feature for the IVRT (which is not true), or that all three components (the aortic valve closure, the LV mean early diastolic tissue velocity onset and the start of the mitral inflow) were equally — and unidirectionally — affected, which our results speak against.

A subsequent study failed to register a wider \( e-E \) time interval in patients with an invasively confirmed prolonged tau.\(^{13}\) The extent to which tau is preload dependent is not clear, but some authors claim it to be relatively less so.\(^{14,15}\) If true, it would further support that the \( e-E \) time interval may not, under all circumstances, represent tau.

The choice to investigate intensive care unit patients is comprehensible, since the performance of invasive pressure measurements can be ethically questionable in healthy individuals. Still, not only preload, but also other possible effects of the diagnoses and/or their treatment, might retreat these patients from representing normal individuals. The fact that we did not confirm our data invasively is a major study limitation. However, it is unlikely that the every-day-activities of our carefully preinvestigated-to-be-healthy individuals should raise their PCWPs to up to 30–40 mmHg,\(^{16}\) and this without the causing of any symptoms.

In conclusion, due to the mathematical conditions of the formula \( \text{PCWP} = \text{LV end-systolic pressure} \times e^{-\text{IVRT}/\tau} \), the normal range of the \( e-E \) time interval in healthy elderly individuals (suggested to represent tau through the formula \( \tau = 32 \pm 0.7 \times (e-E) \)), and, finally, the way preload alterations can effect the relationship between IVRT and \( e-E \), this application to non-invasively predict PCWP may not be robust enough for clinical use.

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