Measurements of systolic time intervals using a transoesophageal pulsed echo-Doppler

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Measurement of systolic time intervals (STI), an index of left ventricular (LV) systolic function, is usually labour intensive and requires considerable expertise to perform accurately. We have evaluated the accuracy of an automated, continuous and non-invasive STI measurement technique using a descending aortic blood velocity Doppler signal obtained using a transoesophageal echo-Doppler system (TEDS) and an ECG signal. STI were measured in adult pigs using a transoesophageal probe (4\times4 mm pulsed wave Doppler transducer, 5-MHz frequency and a 3\times3 mm echo transducer, 10-MHz frequency) associated with an ECG recorder. Measurements were performed at baseline and after injection of esmolol and dobutamine. TEDS data were compared with those obtained by one-line recordings of the electrocardiogram and the central aortic arterial pressure wave. Similar mean values were observed for pre-ejection period (PEPI), LV ejection time (LVET) and PEP/LVET with the two methods. Agreement between the methods (Bland and Altman’s test) was excellent with 95% confidence intervals for PEP, LVET and PEP/LVET of –7.17 to 1.37 ms, –12.64 to 10.24 ms and –0.033 to +0.028, respectively. We conclude that the combination of descending aorta blood velocity Doppler and ECG signal is an alternative technique for non-invasive and objective measurement of STI, allowing continuous monitoring of LV systolic function.

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The usefulness of systolic time intervals (STI) for the study of systolic performance of the left ventricle has been reported extensively.¹–³ STI, as defined originally, are determined from simultaneous high-speed recordings of the electrocardiogram, phonocardiogram and plethysmographic carotid pulse.¹–⁴ To improve results of STI measurements, a non-invasive method based on simultaneous recordings of the transthoracic M-mode echocardiogram (TTE) of the aortic valve and the electrocardiogram has been developed.⁵ ⁶ However, this method also has limitations. Identification of aortic movements cannot always be recorded satisfactorily⁷ and patients with emphysema and obesity are difficult to study. In addition, this method is not useful during some surgical procedures involving the thorax and neck, it does not provide continuous cardiac monitoring and the need for a trained operator may limit its use.

The possibility of measuring STI based on a transthoracic Doppler signal of aortic blood velocity has been proposed by some authors but it suffers from the same limitations as the TTE method.⁸ Transoesophageal echocardiography (TEE) is an advance in the evaluation of cardiac function in patients who are critically ill or undergoing surgery.⁹ ¹⁰ Although TEE has been used to assess left ventricular function and cardiac output, there are no data on the accuracy of the transoesophageal Doppler technique to determine STI. We have developed a probe, including both a Doppler and an echo transducer, suitable for transoesophageal studies in patients and animals.¹¹ We have shown previously that this oesophageal probe accurately measured aortic blood flow (ABF) over a wide range of body sizes in humans,¹² and was suitable for long-term recordings in various haemodynamic states.¹³ New software has recently been incorporated into this device to calculate STI automatically. In this study, we have compared automated STI measurements performed using the transoesophageal echo-Doppler system associated with an ECG signal with those obtained using a conventional method (aortic arterial pressure wave and ECG) under different inotropic states (after administration of esmolol and dobutamine).
Materials and methods

Animal preparation

The study was approved by the Animal Care Committee of the University of Lyon. We studied eight White adult female pigs, weighing 25 (sd 5) kg. Ketamine 15 mg kg\(^{-1}\) i.m. was given 15–30 min before induction of anaesthesia as premedication. Anaesthesia was induced with propofol 5 mg kg\(^{-1}\) i.v., fentanyl 10 \(\mu\)g kg\(^{-1}\) i.v. and pancuronium 8 mg i.v., and maintained with continuous infusion of propofol 10 mg kg\(^{-1}\) h\(^{-1}\) and repeated injections of pancuronium.

After orotracheal intubation, the lungs were ventilated mechanically with a Modulus CD integrated anaesthetic machine (Ohmeda, Madison, WI, USA) at a tidal volume of 15 ml kg\(^{-1}\) and a frequency of 15 bpm. Ventilatory variables were subsequently adjusted to maintain normocapnia at baseline (end-tidal carbon dioxide partial pressure 5.1–6.0 kPa). An \(F\text{I}_2\) of 0.6 was used in all animals to avoid hypoxaemia during the study.

The left carotid artery and internal jugular vein were exposed. A thin catheter was introduced into the jugular vein for injection of drugs. A 16-gauge Teflon catheter (Vygon, Ecouen, France) was pushed forward via the carotid artery into the left ventricle and then withdrawn into the aortic root above the level of the aortic valve to record aortic arterial pressure (AAP). The position of this catheter was confirmed using TM echo emission of the echo-Doppler device. This catheter was connected to a P23Db Gould Statham transducer zeroed to the mid-chest position.

A special probe, described previously,\(^{11,12}\) was used to measure ABF using a transoesophageal echo-Doppler ultrasound system (TEDS) (Dynemo 3000, Sometec, Suresnes, France). Briefly, the probe includes a 4x4-mm pulsed divergent (\(\pm 20^\circ\)) emission Doppler transducer (5-MHz frequency, maximal velocity speed detected 1.86 m s\(^{-1}\)) and 3x3-mm TM echo transducers (10-MHz frequency, 25 Hz pulse echo repetition rate) allowing continuous automatic measurement of aortic diameter for precise blood flow measurements. Transducers are located at the tip of the probe and are mounted on an epoxy resin bracket produced by moulding. This bracket is mounted in a stainless steel casing connected to a stainless steel flexible hose inserted into a thin polyvinyl sheath (outer diameter 6 mm). A cylindrical latex balloon is mounted around the transducer support and can be inflated with water. This balloon maintains the probe in a fixed position throughout the study, provides good acoustic coupling, avoids air interposition and maintains the angle of incidence of the Doppler beam (60\(^\circ\)) constant. At the other extremity, the probe ends in a head connected to the flexible hose, so when the head of the probe is turned, the transducers rotate into the balloon allowing focalization of the ultrasound beams.

Measurement of STI using the Doppler system

TEDS offers the possibility of measuring STI based on computed analysis of the Doppler descending aorta blood velocity and ECG signals. Opening of the aortic valve can be identified easily at the beginning of systolic acceleration. Detection of closing of the aortic valve was obtained by transforming the velocity signal into its first derivative (acceleration): two systolic deceleration peaks were detected. The second peak corresponds to closing of the aortic valve detected simultaneously with the aortic pulse signal. Software detects the second systolic peak deceleration with a delay less than \(\pm 4\) ms.
wave. We showed that the precision of the method was ±4 ms.

The ECG was monitored continuously using three leads (ITS 104, CGR, Paris, France) and digitized online at a frequency of 250 Hz using an A/D card. The interval from the beginning of the QRS complex on the ECG to the onset of the rapid upstroke of the Doppler curve allows determination of the pre-ejection period (PEP Doppler: PEPd). Left ventricular ejection time (LVET Doppler: LVETd) is represented by the time difference between opening and closing of the aortic valve. For measurement of STI, specialized software was written. Composed of different phases, the software performs the following: integrates the signals coming from the hardware; compresses numerically in groups of 32 consecutive sampling; detects the R wave and identifies the Q wave on the ECG; adapts the time synchronization for both TEDM and ECG recorder used; controls the Q waves identified; accepts or eliminates the sample accordingly; detects opening of the aortic valve by analysing the ascending slope of the velocity signal; detects closing of the aortic valve by analysing the curve of the systolic deceleration; indexes STI values for heart rate (HR) according to the formula of Weissler, Harris and Schoenfeld14; presents the values on a screen table; and renews the values once every 8 s.

Measurement of STI using the conventional method
STI were also determined using the AAP signal and ECG signal (ITS 104, CGR, Paris, France) according to a method reported previously.15 The signal from the aortic root catheter was digitized online and stored for analysis. STI measurements on AAP were obtained as follows: PEPa was measured from the beginning of the ECG Q wave to the beginning of the increase in aortic arterial pressure. LVETA was measured from this last point to the initial part of the dicrotic wave.

The software developed with the TEDS adapts the time synchronization for both Doppler, the imaging system and ECG signals. All recordings from the TEDS, ECG and AAP were stored continuously on hard disk. Recordings were analysed by an independent investigator using specific software (Tetronix Data Acquisition 2510, Beaverton, OR, USA).

Study procedure
All measurements were made with the pig in the supine position. ECG, Doppler and AAP signals were recorded after a 30-min recovery period (baseline T0) after animal preparation. These variables were also recorded continuously after the pigs were allocated randomly to receive one type of cardiovascular drug over two different periods: repeated i.v. bolus of a beta-blocker over 20 s (chlorhydrate of esmolol 1 mg kg⁻¹; Isotec, Saint-Quentin en Yvelines, France) or continuous infusion of dobutamine 5 µg kg⁻¹ min⁻¹ (Lilly France, Saint-Cloud, France) over 15 min. Each drug was administered after a 15-min stabilization period.

Statistical analysis
The methods were compared at baseline and during infusion of the cardiovascular drugs (baseline, dobutamine and esmolol). All data are expressed as mean (SD). Mean (SD and range) normalized differences (difference between the two methods/average of the two methods×100%) were calculated for PEP, LVET and PEP/LVET.

To compare STI obtained by the two techniques, we used the multiple measurements method described by Bland and Altman16, the mean of the differences between each pair of values (bias) was plotted against the average of each pair. The SD of the difference between simultaneous measurements is a measure of the accuracy of the Doppler technique measurement in estimating the AAP technique. For each period, five sequences of 2 min were recorded and analysed in each pig. Least-squares linear regression analysis was also used to correlate the STI values obtained by the two methods.

We also used two-way analysis of variance for repeated measures to evaluate the effect of each drug on STI and to compare STI mean values (Statistica 5.0; Statsoft, Tulsa, OK, USA). When differences were significant, a post hoc test (Newman–Keuls test) was used. Differences were considered statistically significant when P<0.05.

Results
STI were measured successfully using both methods in all animals. Similar mean values were observed for PEP, LVET and PEP/LVET using the two methods (Table 1).

Bias and ‘limits of agreement’ (2 SD) of the pooled data for STI are shown in Figures 2–4. Agreement between PEP measured by the two methods was excellent, with 95% confidence intervals of −7.17 to +1.37 ms. The normalized difference was −2.09% (SD 3.27%; range −8.07 to +5.67 %). This was also observed for LVET values (95% confidence interval −12.64 to +0.24 ms; normalized difference −1.54% (2.57%; −6.63 to +7.70 %) and for PEP/LVET (95% confidence interval −0.033 to +0.028; normalized difference −0.54% (4.45%; −9.50 to +12.77%).

Changes in PEP, LVET and PEP/LVET after administration of esmolol and dobutamine are shown in Table 1. Esmolol produced a significant increase in PEP and PEP/ LVET (P<0.001) and a decrease in heart rate (P<0.001). Dobutamine caused a significant decrease in PEP and PEP/ LVET (P<0.001) and an increase in heart rate (P<0.001). There were no significant changes in LVET with the two techniques.

Discussion
Measurement of STI necessitates identification of opening and closing of the aortic valve and the beginning of
Systolic time intervals

Fig 2 Scatterplot of time differences and mean time for pre-ejection period (PEP) of the transoesophageal Doppler method (TEDM) vs the aortic pressure wave method (APT) according to the technique of Bland and Altman (left). For better representation, each point represents the mean of PEP over 8 s in a given animal. Right: there was a significant correlation between the two methods ($r=0.98$, $P<0.0001$) with a regression equation of: $y=0.95x+2.96$.

Fig 3 Scatterplot of time differences and average time for left ventricular ejection time (LVET) of the transoesophageal Doppler method (TEDM) vs the aortic pressure wave method (APT) according to the technique of Bland and Altman. For better representation, each point represents the mean of LVET over 8 s in a given animal. Right: there was a significant correlation between the two methods ($r=0.94$, $P<0.001$) with a regression equation of: $y=1.01x-14.06$.

Fig 4 Scatterplot of time differences and average time for PEP/LVET (PEP=pre-ejection period; LVET=left ventricular ejection time) of the transoesophageal Doppler method (TEDM) vs the aortic pressure wave method (APT) according to the technique of Bland and Altman. For better representation, each point represents the mean of PEP/LVET over 8 s in a given animal. Right: there was a significant correlation between the two methods ($r=0.97$, $P<0.0001$) with a regression equation of: $y=0.94x+17.65$. 

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ventricular electrical stimulation.\textsuperscript{1} These events are usually recorded by integration of the plethysmographic curve of the carotid pulse, the ECG and phonocardiographic signals. This method has poor reliability, reproducibility and precision because: (1) use of three different systems to measure STI implies three different constants of time (each constant of time is influenced by the characteristics of the patient and by the technical specifications of each measuring device); (2) standard positioning of sensors is difficult to obtain; (3) there is a delay in obtaining results; and (4) the search for the ‘best plethysmographic and phonocardiographic signals’ introduces a subjective bias to the results.

For these reasons, alternative methods have been proposed. Assessment of left ventricular function is now widely performed by echocardiography. In addition, the TTE method allows measurement of STI as closure of the aortic valve can be identified visually. However, this technique has several limitations. Stefadouros and Witham\textsuperscript{5} reported that complete recording of aortic valve events was possible only in 23\% of 36 patients enrolled in their study.

The ultrasound Doppler technique is an alternative method of measuring STI.\textsuperscript{17,18} It requires less equipment than previous methods. Both epicardial and transoesophageal approaches are theoretically practicable. The transthoracic technique requires precise orientation of the transducer, is not useful for continuous monitoring and cannot be used if the transducer cannot be placed on the thorax. The transthoracic approach has been evaluated by Lang-Jansen\textsuperscript{6} The results showed no significant difference between total systolic time (QS\textsubscript{2}) determined by the Doppler transducer placed in the suprasternal notch and the phonocardiographic method. However, the conclusion of the study was limited as the carotid pulse curve was not displayed; PEP and LVET cannot then be calculated and compared with Doppler values.

The transoesophageal technique has been used in an attempt to overcome these problems. In 1975, Daigle and colleagues\textsuperscript{19} measured cardiac output using this method but the probe was difficult to position and did not allow good coupling between the oesophagus and transducer. We have developed a new probe with greater operating simplicity which allows precise measurement of aortic blood flow.\textsuperscript{11,12} Stable positioning of the transducers is ensured using an inflatable latex balloon which also provides good acoustic coupling. Correct positioning of both transducers and their synchronized emission–reception makes it possible to combine the Doppler and echo imaging system. Therefore, automatic positioning of pulsed Doppler sample volume exactly inside the aorta is obtained as a result of the echo guide. The next step was to integrate into this device continuous evaluation of left ventricular systolic performance using measurement of STI, as described previously.

Several clinical studies have shown that interventions which alter LV performance induce similar changes in STI and other invasive and non-invasive indices of LV performance.\textsuperscript{2,19,20} Positive inotropic drugs which shorten isovolumetric contraction shorten STI\textsuperscript{21–24} and negative inotropic drugs which prolong isovolumetric contraction time prolong PEP.\textsuperscript{25,26} LVET generally shortens or remains unchanged, and therefore these changes are more complex to analyse than changes in PEP.\textsuperscript{18} Thus PEP/LVET increases with negative inotropic drugs, decreases with positive inotropic drugs and can provide more precise information on the quality of LV systolic function. Infusion of esmolol and dobutamine exhibited all of these typical changes. ABF, another index of LV performance, showed similar changes. The additional information provided by integration of STI in a haemodynamic profile with ABF included can give valuable information for evaluation of LV systolic performances.

The software integrated with the device corrects PEP for HR according to the formula of Weissler, Harris and Schoenfeld.\textsuperscript{14} Several reports showed that STI varies inversely with HR.\textsuperscript{2} Spodick and colleagues\textsuperscript{27} showed no correlation between PEP and HR, good correlation between LVET and HR and a fair correlation between PEP/LVET and HR. However, their results were limited to the HR range studied (55–110 beat min\textsuperscript{−1}) and must be confirmed in critically ill patients receiving vasoactive drugs or during pharmacological studies where HR could range from 50 to 160 beat min\textsuperscript{−1}. However, these comments do not invalidate the results of our study as the same factor of correction was applied to the two techniques.

In comparison with echocardiography, TEDM does not require complex instrumentation and is easier to use. The main advantage is its use in animal studies, in patients with thorax deformations, during surgery of the upper part of the body, in critically ill and in anaesthetized patients.\textsuperscript{28,29} Therefore, it is possible to consider this device as an alternative to the echocardiographic technique, particularly when long-term monitoring is needed.

Our study demonstrated that automated analysis of the descending aorta transoesophageal Doppler blood velocity and ECG signals accurately estimated STI. This technique was feasible in 100\% of anaesthetized animals undergoing mechanical ventilation. These data indicate that automated STI recording from the transoesophageal method coupled with the ability to determine ABF may be an accurate and

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<th>Baseline</th>
<th>Dobutamine</th>
<th>Esmolol</th>
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<tr>
<td>HR (beat min\textsuperscript{−1})</td>
<td>119 (7)**</td>
<td>119 (7)**</td>
<td>80 (5)***</td>
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<tr>
<td>ABF (litr min\textsuperscript{−1})</td>
<td>2.3 (0.4)</td>
<td>3.0 (0.5)***</td>
<td>1.7 (0.4)***</td>
</tr>
<tr>
<td>LVET\textsubscript{d} (ms)</td>
<td>406.52 (31.22)</td>
<td>418.7 (37.68)</td>
<td>408.15 (28.88)</td>
</tr>
<tr>
<td>LVET\textsubscript{a} (ms)</td>
<td>416.32 (30.27)</td>
<td>425.70 (36.26)</td>
<td>409.95 (22.19)</td>
</tr>
<tr>
<td>PEP\textsubscript{d} (ms)</td>
<td>141.07 (10.66)***</td>
<td>107.8 (9.89)***</td>
<td>164.27 (19.0)***</td>
</tr>
<tr>
<td>PEP\textsubscript{a} (ms)</td>
<td>141.05 (12.02)***</td>
<td>26.0 (0.02)***</td>
<td>0.41 (0.03)***</td>
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<tr>
<td>LVETd (ms)</td>
<td>406.52 (31.22)</td>
<td>418.7 (37.68)</td>
<td>408.15 (28.88)</td>
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<td>LVETa (ms)</td>
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<td>PEPd (ms)</td>
<td>141.07 (12.02)***</td>
<td>26.0 (0.02)***</td>
<td>0.41 (0.03)***</td>
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<tr>
<td>PEPa (ms)</td>
<td>141.05 (12.02)***</td>
<td>26.0 (0.02)***</td>
<td>0.41 (0.03)***</td>
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practical non-invasive method for monitoring LV systolic function.

Limitations of the study and TEDS
The potential limitations of our study should be emphasized. Results from pigs may not be extrapolated directly to humans. Also, STI were not measured at the same anatomical sites. This could be a methodological problem in humans because aortic length could induce systematic overestimation of STI by TEDS. However, in all pigs the TM echo-transducer showed that the two measurement sites were relatively close because aortic length is shorter in pigs. Thus the systematic error between the two methods could be considered negligible. The transoesophageal method cannot be used in patients with major oesophageal malformation and in conscious unco-operative patients. The Doppler technique is limited by the fact that diastolic time intervals are not available simultaneously and by the fact that afterload and preload can affect STI. Systolic and diastolic myocardial dysfunction can produce the haemodynamic characteristic of LV failure and diastolic function can only be assessed accurately using a cardiac echo-Doppler device. Nevertheless, in numerous clinical situations, diastolic function was evaluated using a vascular filling test under the haemodynamic non-invasive profile monitoring proposed. This method is adapted to monitor the evolution of cardiovascular variables for long periods, but contrary to the echo-Doppler device, it does not detect global or regional wall motion abnormalities.

In summary, our results showed that the automated algorithm integrated in this transoesophageal Doppler echocardiographic device could be used accurately to obtain STI. In addition to continuous non-invasive ABF measurement, TEDS may offer an alternative technique to TTE for continuous non-invasive and objective monitoring of LV systolic function under pathological conditions or therapeutic interventions in critical care and anaesthesia.

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