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Systolic time intervals: a method to assess cardiovascular drug effects in humans

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Introduction

Investigations in clinical pharmacology require valid and reliable non-invasive methods to detect and describe changes in systolic cardiovascular performance induced by drugs in humans. Such methods should (i) allow valid judgements; (ii) be highly sensitive to avoid false negative results; and (iii) permit easy and repetitive application. In addition, the equipment necessary for these measurements should be inexpensive, thereby encouraging its widespread use. Many non-invasive methods for cardiovascular examinations have been developed during the last decades primarily for diagnostic purposes, some of which are of interest to the clinical pharmacologist.

One method already developed in the first half of this century which clearly fulfills the above-mentioned criteria is based on the measurement of systolic time intervals (STI). Conventional cardiological methods assess cardiac function and changes thereof in terms of the force and length of cardiac muscle contraction and their instantaneous time derivatives [1]. By contrast, the duration of each event in the cardiac cycle is the basic variable of the STI.

STI were originally obtained by a simultaneous registration of an electrocardiogram (ECG), a phonocardiogram (PCG), and a subclavicular pulse tracing [2]. Current methodology using the carotid pulse tracing (CPT) for derivation of the left ventricular ejection time (LVET) was introduced by Blumberger [3], who also published the first extensive studies of drug effects on STI [4]. Extensive systematic studies on STI were then carried out by Weissler and colleagues [5–10], investigating the quantitative influence of heart rate (HR) on STI and devising formulae to correct for rate changes.

Subsequent studies revealed the clinical limitations of the method, which could provide only limited comparative data for diagnostic and therapeutic purposes. The availability of echocardiography, a more powerful diagnostic tool, has now led clinicians to almost completely abandon STI [11]. But the real indication for this method was envisaged by Lewis *et al.* [12] in 1977 who stated: 'Because of the extreme sensitivity of STI, it is ideally suited for studying effects of pharmacological agents upon the heart. Indeed, this may well represent a most useful future application of the technique'.

Investigations in cardiovascular clinical pharmacology performed during the last two decades by our group [13–19] have shown that the use of STI under strictly standardized conditions in healthy volunteers allows precise insight into drug-induced changes of cardiac performance in humans. As interest in pharmacodynamics continues to develop, STI are being successfully used to assess the cardiovascular effects of older drugs and newer drug candidates in humans [20–23].

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Definition of STI

Investigations have been focused on the measurement of three different STI: total electromechanical systole (QS_2); LVET; and the pre-ejection period (PEP). QS_2 lasts from the onset of ventricular depolarization until aortic valve closure and is measured from the onset of the QRS complex (Q) to the start of the high-frequency vibrations of the aortic component of the second heart sound (S_2).

PEP is the interval from the start of ventricular depolarization to the beginning of left ventricular ejection, i.e. the isovolaemic contraction. When intraventricular pressure exceeds the diastolic aortic pressure, the aortic valves open and LVET begins. The ventricle contracts isotonically until the aortic valves close.

LVET is measured from the carotid arterial pulse tracing beginning at the upstroke and ending at the trough of the dicrotic notch. Because of the transmission time of the arterial pulse from the aortic valve to the carotid artery, the incisura of the carotid pulse follows the high-frequency vibrations of the aortic component of the second heart sound by a mean of $18{\cdot}5 \pm 8{\cdot}2$ ms (1 SD) [24]. Consequently, when using the carotid pulse curve, the PEP cannot be measured directly, but is calculated by subtracting the LVET from the QS_2 to eliminate the delay in pulse transmission. Figure 1 is an original registration of ECG, CPT, and PCG for measuring STI at a paper speed of 100 mm s^{-1}. This recording speed allows exact measurements of the time-related events [25].

In the early 1960s, LVET derived from direct aortic pressure curves was compared with those derived from indirect carotid or subclavian pulse tracings and showed a close agreement [5]. Other available

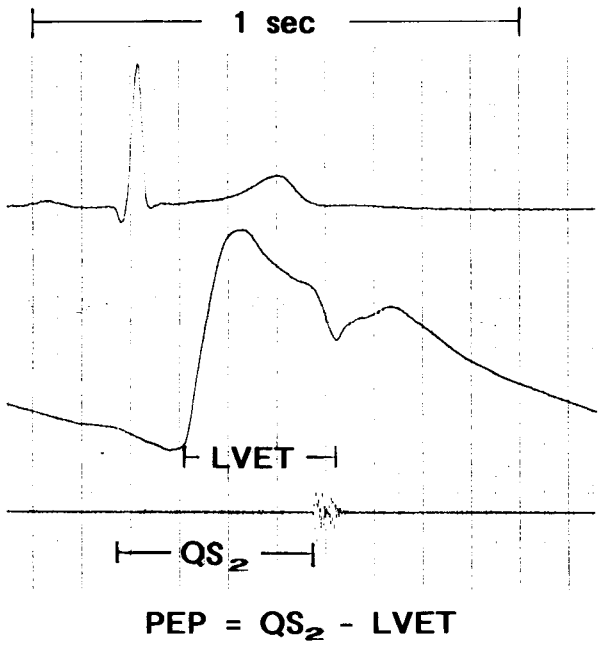

Figure 1. Original registration of electrocardiogram (lead CM_5), carotid pulse curve and phonocardiogram (filter $m_2 = 140$ Hz range) at paper speed of 100 mm s^{-1}. The subintervals of STI are indicated. QS_2, electromechanical systole; LVET, left ventricular ejection time; PEP, pre-ejection period.

evidence also indicates that measurements obtained with external recordings yield accurate STI [26–28].

Technical considerations

Since the LVET is the most variable parameter of the STI, many attempts have been made to record the opening and closing of the aortic valves with other non-invasive techniques such as apex cardiography [29], echocardiography [30], densitography [31], the first derivative of CPT [32], and electrical impedance cardiography [33]. Simultaneous registrations of the echo-, mechano- and electrical impedance cardiograms [33] showed that carotid pulse-derived LVET estimations were about 20 ms shorter than direct observation of the aortic valves via echocardiography. By contrast, LVET values derived from impedance cardiography were about 20 ms longer as compared with those using echocardiography [33]. Combining electrical impedance with PCG to determine LVET correlated well with values from echocardiography [33]. In terms of QS_2 [34], there were no differences between echocardiography and conventional methods (i.e. ECG and PCG).

Although there are technical difficulties, for example in identifying the first high frequency components of S_2 as well as the upstroke and incisural notch on the CPT, a study in 120 healthy young male volunteers under standardized conditions showed that for measuring STI, the evaluation of five consecutive heart cycles obtained by fast-speed recordings (100 mm s^{-1}) of the ECG, PCT, and CPT provides sufficient accuracy for precise evaluation of data [35].

STI measurements are very sensitive to many factors including room temperature and sweating (which decrease preload and consequently shorten $LVET_c$, lengthen PEP_c, but leave QS_{2c} unchanged) [36,37]; food intake (rapid and protracted shortening of PEP, QS_{2c} (Fig. 2) and $LVET_c$ slightly) [14,38–40]; body position [41–44], emotional situations, respiration [45], diurnal effects, etc. Therefore, the optimal standardization of environmental and experimental conditions is most crucial.

Practical aspects

ECG electrodes are positioned according to CM_5 or Nehb A. Repeated CPT are registered on the same side of the neck. The PCG microphone is positioned at the left of the parasternum over the 4th intercostal space, and a frequency filter m_2 [46] is used. Subjects should relax in the supine position for at least 15 min before each recording and remain quiet but awake. Twenty heart cycles are simultaneously registered during normal respiration at a slow paper speed (e.g. 10 mm s^{-1}) to determine the heart rate, and the following 5–10 cycles are recorded during a spontaneous end-cycle expiration at a paper speed of 100 mm s^{-1} for measurement of STI [35]. The recorder should be able to provide a high-frequency response, e.g. photographic system or jet recorder; mechanically direct writing recorders are unlikely to be suitable. STI should be measured by use of electronic digitizing boards connected to a computer. This technique allows estimation of 0·1 mm (= 1 ms) in each cardiac cycle.

Occasionally, it is difficult to identify the beginning of ventricular depolarization if Q waves are flat or absent. In such cases, the onset of the R wave should be used. However, some drugs, such as anti-arrhythmics, may prolong the QRS complex and could alter the interpretation. A bundle-branch block could be missed because the Q wave may comprise 35% of the QRS duration. Spodick *et al.* [25] have shown that the errors made in point measurements were only partially due to incorrect determination of the Q wave. The measurement of points from R (rather than Q) reduce observer variability when dealing with precision of measurement rather than with absolute values.

STI vs. other non-invasive methods

It had long been suspected that STI was more sensitive than other methods in revealing cardiovascular drug effects [12]. Direct evidence for this was established by comparisons of STI (derived from ECG, PCG, and CPG) with 2-D left ventricular echocardiography, dual-beam Doppler echoaortography, and electrical impedance cardiography [47,48]. When detecting the cardiac effects of increasing intravenous doses of isoprenaline vs. placebo, a shortening in the QS_{2c}

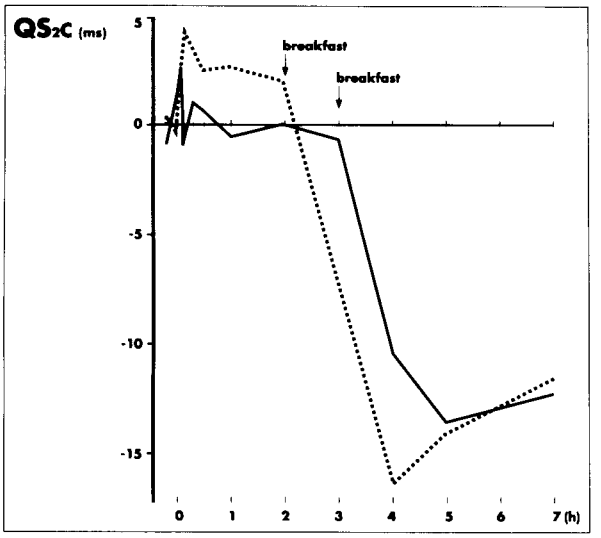

Figure 2. Influence of food on the rate-corrected electromechanical systole (modified from [38]). Mean data of $n = 10$ in each group. Intake of a standard breakfast (no caffeine) induces an intense shortening of QS_{2c}.

and PEP_c permitted an assessment of significant changes in cardiac systolic function at the lowest dose of isoprenaline administered ($0{\cdot}1\ \mu g\,min^{-1}$ i.v. infusion)—effects which increased dose-dependently and linearly. By contrast, twice the dose of isoprenaline was needed to detect significant effects when using electrical impedance cardiography and echoaortography, and no less than a fourfold dose was needed to achieve a statistically significant effect with echocardiography. This study, therefore, clearly indicated that STI is the most sensitive among several existing non-invasive methods to detect changes in cardiac function—at least in detecting inodilatory effects.

Haemodynamic factors and clinical pharmacological relevance

Like most invasive and non-invasive indices of left ventricular function describing ventricular performance, the changes in STI depend not only on myocardial contractility, but also on changes in HR, preload, and afterload [49].

Influence of heart rate on STI

Since the relation between STI and the beat-to-beat interval (RR interval) appears to be linear [50], this implies some non-linearity in the relation between HR and STI. For practical purposes, however, the deviations from linearity for the heart rate correction need not be considered if extreme extrapolations are avoided. HR influences on STI are usually corrected according to equations suggested by Weissler *et al.* [8] and expressed clinically (i) as STI-c or (ii) as STI-i [12]. The STI-c values are calculated from the predicted normal intervals for the observed HR using an appropriate regression equation and subtracting the measured interval from this value (resulting in QS_{2c}, $LVET_c$, and PEP_c). The STI-i indices are calculated as the measured interval length plus the product of the observed HR and the appropriate normal regression slope. The actual indices in fact represent the y-intercepts obtained by use of the regression equations. This index assumes that the HR is zero, which seems unrealistic. Therefore, we prefer the STI-c values.

A series of studies raised questions as to whether Weissler's equations could be generalized [51,52]. Recent investigations with atrial pacing [53] or pharmacological alterations of HR with small bolus doses of atropine [54] gave rise to the expected QS_2-HR and LVET-HR relationships, but with smaller slopes. However, they failed to show a PEP-HR relation. PEP values obtained 'directly' from the aortic valve echocardiogram [55] agreed with these findings. Compared to the other STIs, the influence of HR on PEP in these studies (when present) was relatively small, and the slope of the regression was close to zero. Therefore, the influence of HR on PEP seems negligible and it is acceptable that under most circumstances PEP need not be corrected for HR [55–57]. It can be assumed that the discrepancies between the various results originate from differences in sympathetic stimulation within the various study populations [39]. The PEP/LVET ratio is often used, as it varies within narrow limits and is closely correlated with the ejection fraction and stroke volume [8]. This quotient, despite many suggestions, is not independent of HR [55].

Using STI-HR correction equations with different slopes will lead to different results. Biased results may be obtained if correction formulae from inappropriate populations are applied. Consequently, changes in HR might wrongly suggest or mask changes in cardiac performance. To avoid these problems, bivariate analysis based on the relation between STI and RRI in the specific population can be employed [50,58,59]. Another approach [54] based on Bayes' theorem and the method of maximum likelihood involves predicting individual systolic time interval vs. HR regression equations. Notwithstanding the above, the heart rate corrections devised by Weissler continue to remain the most widely used, offer extensive data concerning many different drugs, and seem to be the best validated approach.

Influence of load and contractility on STI

The contraction–relaxation sequence of the isolated rat left ventricular muscle has been used to document the independent effects of acute changes in preload, afterload, and inotropic state on STI [60]. An isolated rise in preload decreased the preshortening period ($\approx$PEP) and increased both the isotonic contraction time ($\approx$LVET) and electromechanical systole ($\approx QS_2$). An increase in afterload prolonged the preshortening period ($\approx$PEP) and shortened the

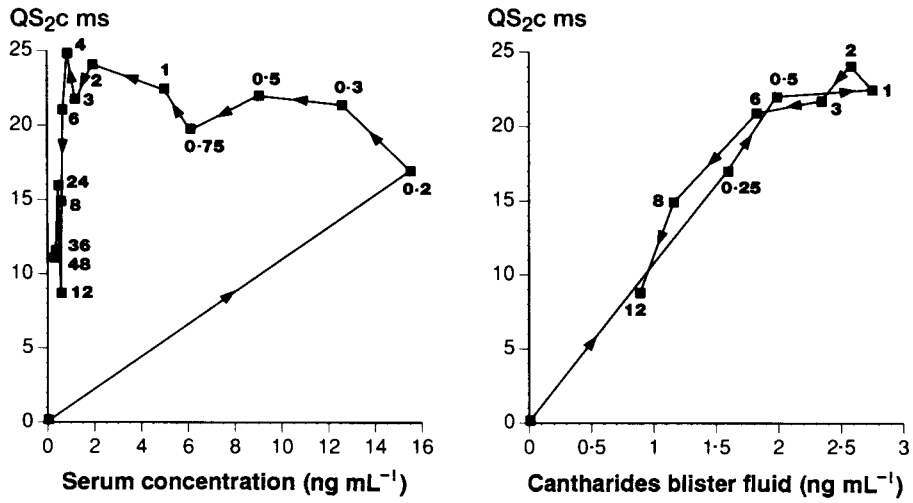

Figure 3. Correlation between digoxin concentration in serum and in cantharides blister fluid vs. shortening of QS_{2c} after a single intravenous dose of 1·0 mg digoxin (modified from [66]). ■, time (h).

isotonic contraction time (≈LVET). However, the electromechanical systole (≈QS_2) showed no significant changes. Under constant load conditions, isoprenaline shortened all three intervals.

In contrast to the clearly defined load conditions of these *in vitro* studies, it is impossible to independently change one haemodynamic variable in humans without inducing changes in one or more of the other determinants of heart performance. One can, however, assess STI and pre- and afterload changes simultaneously using various non-invasive haemodynamic measurements. These can include blood pressure and the echocardiogram of the left ventricle [17]. Additionally, test designs using positive controls with active substances and well known effect profiles can be very helpful. For example, digitalis glycosides with almost pure positive inotropism and negligible influence on load at therapeutic doses produce a concentration- or dose-dependent shortening of QS_{2c} and PEP in humans [4,14,61–66]. The excellent sensitivity of the method in detecting digitalis effects can be seen in the digoxin concentration-effect curves shown in Fig. 3: the relationship between serum digoxin concentration and shortening of QS_{2c} (left panel) is characterized by a marked counterclockwise hysteresis, whereas no hysteresis occurs in the analogous plot of the fluid from cantharides blisters (right panel). Negative inotropic drugs such as anti-arrhythmics or antidepressants cause effects opposite to those of digitalis, i.e. lengthening of the STI [67,68]. Even in the presence of a considerable afterload reduction, the negative inotropic properties of nifedipine were revealed by the lengthening of the QS_{2c} [69]. The inodilatory effects of phosphodiesterase inhibitors were reflected by STI shortening [13,70,71]. After tilting [41,42] or intravenous injection with 40 mg furosemide [72], or profuse sweating [36,37], wherein the reduction of preload is the dominant haemodynamic response, a lengthening of PEP and shortening of QS_{2c} and $LVET_c$ occurred (Fig. 4). Upon infusion of human angiotensin resulting in a nearly exclusive increase in afterload, a dose-dependent lengthening in PEP and QS_{2c} and a shortening in $LVET_c$ were observed [73]. Afterload reduction, obtained by administration of dihydralazine [74,75] produced changes opposite to that of angiotensin on PEP and $LVET_c$; QS_{2c} did not change significantly (Fig. 5). Based on *in vitro* and *in vivo* studies, it is obvious that changes in QS_{2c} mainly reflect inotropic

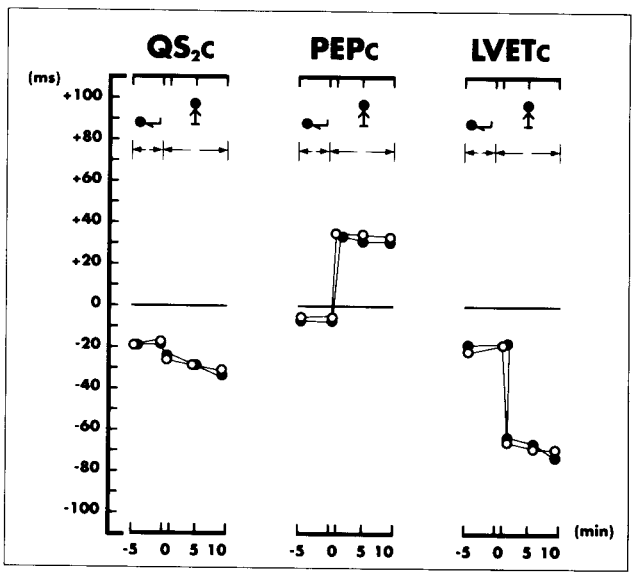

Figure 4. Influence of tilting on STI (modified from [42]). QS_{2c}, electromechanical systole; PEP_c, pre-ejection period; $LVET_c$, left ventricular ejection time. All STI were corrected for heart rate. Results of two different experiments are depicted. ○, experiment 1; ●, experiment 2; means of $n = 11$ volunteers.

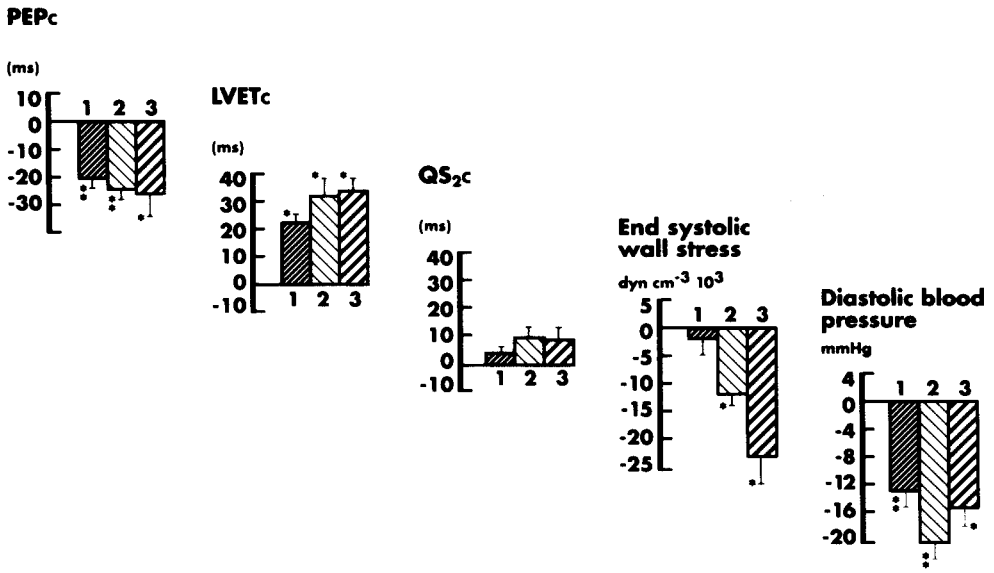

Figure 5. Influence of dihydralazine-induced afterload reduction on STI (modified from [74]). QS_2, electromechanical systole; LVET, left ventricular ejection time; PEP, pre-ejection period. 1, 6 mg dihydralazine i.v.; 2, 12 mg dihydralazine i.v.; 3, 25 mg dihydralazine i.v., mean ± SEM, $n = 6$; * $P < 0{\cdot}01$; ** $P < 0{\cdot}001$.

influences, while load changes have only a relatively weak effect on this interval [12,74,75].

Influence of exercise on STI

Although STI are conventionally evaluated at rest, there have been many attempts to measure STI during exercise [76]. STI are greatly influenced by stress due to changes in HR and contractility induced by increased sympathetic tone. In addition, exercise-related haemodynamic alterations caused by muscle contraction, constriction of subcutaneous arteries, and dilation of skeletal muscle arteries affect STI. An extensive study by van Leeuwen [77] clearly showed the change in the relationship between STI and HR during exercise, indicating that a conventional HR correction would result in relevant bias. One should consequently consider these complexities when analysing data on STI, especially when obtained under non-resting conditions. Finally, the variations in STI according to age, sex, and time of day have been extensively reviewed [78].

Conclusion

HR-corrected STI integrate and reflect changes in ventricular inotropy, preload, and afterload. The measurement of STI represents a global method for the evaluation of cardiovascular performance, provided that well-controlled study designs which include positive and negative controls are adhered to, and that strictly standardized conditions are followed. STI are accurate, economic, reproducible and very sensitive. They represent a very useful non-invasive tool in clinical pharmacology for assessing the influence of drugs, their dose–effect relationships, and the time course of their effects on the cardiovascular system.

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