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Estimated preejection period (PEP) based on the detection of the R-wave and dZ/dt-min peaks does not adequately reflect the actual PEP across a wide range of laboratory and ambulatory conditions

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ABSTRACT

The current study evaluates the validity of the PEP computed from a fixed value for the Q-wave onset to R-wave peak (QR) interval and an R-wave peak to B-point (RB) interval that is estimated from the R-peak to dZ/dt-min peak (ISTI) interval. Ninety-one subjects participated in a 90 min laboratory experiment in which a variety of often employed physical and mental stressors were presented and 31 further subjects participated in a structured 2 hour ambulatory recording in which they partook in natural activities that induced large variation in posture and physical activity. PEP, QR interval, and ISTI were scored and rigorously checked by interactive inspection. Across the very diverse laboratory and ambulatory conditions the QR interval could be approximated by a fixed interval of 40 ms but 95% confidence intervals were large (25.5 to 54.5 ms). Multilevel analysis showed that 79% to 81% of the within and between-subject variation in the RB interval could be predicted by the ISTI with a simple linear regression equation. However, the optimal intercept and slope values in this equation varied significantly across subjects and study setting. Bland Altman plots revealed a large discrepancy between the estimated PEP using the R-wave peak and dZ/dt-min peak and the actual PEP based on the Q-wave onset and B-point. We conclude that the PEP estimated from a fixed QR interval and the ISTI could be a useful addition to the psychophysiologist's toolbox, but that it cannot replace the actual PEP to index cardiac sympathetic control.

1. Introduction

Functional disturbances of the autonomic nervous system have been frequently linked to several diseases (Eckberg et al., 1971; Esler et al., 1990; Esler and Kaye, 2000; Huikuri et al., 2003; Kleiger et al., 1987; Langewitz et al., 1994; Nolan et al., 1992, 1998; Palatini and Julius, 2004; Schwartz et al., 1992) and hyperactivity of the sympathetic nervous system (SNS) may be an important cause for the detrimental effects of stress on cardiovascular health (Palatini and Julius, 2004; Schwartz et al., 1992).

Direct recording of action potentials from superficial sympathetic nerves in the muscles and the skin (Wallin et al., 1975, 1981) or the measurement of organ specific spillover of the post-ganglionic neurotransmitter norepinephrine using radioactive tracers (Esler et al., 1988; Esler and Kaye, 2000) is extremely valuable for basic research on the sympathetic nervous system. However, when research moves to an epidemiological scale, the expense and invasiveness of these methods become prohibitive. Furthermore, these invasive measures restrict research to the confines of a hospital or laboratory setting and are stressful for the subject. This precludes examination of individual differences in sympathetic activity in a natural setting, for instance during sleep or during job-related activities with a substantial mental and emotional load. Nonetheless, it is autonomic control during these naturalistic conditions that may have the largest clinical relevance. It is extremely valuable, therefore, to have non-invasive, unobtrusive measures of sympathetic nervous system activity.

At the moment the preejection period (PEP) is the measure of choice to monitor changes in cardiac sympathetic activity non-invasively. Under conditions of stable preload and afterload, changes in PEP reflect changes in contractility (Newlin and Levenson, 1979) which are influenced by sympathetic but not parasympathetic activity in humans. The extant literature supports changes in PEP as a valid measure of changes in β-adrenergic inotropic drive to the left ventricle. Laboratory studies manipulating β-adrenergic tone in within-subject designs by epinephrine infusion (Houtveen et al., 2005) amyl nitrite inhalation (Mezzacappa et al., 1999; Svedenhag et al., 1986; Svedenhag et al., 1991) and adrenoceptor blockade (Nelesen et al., 1999), exercise (Harris et al., 1967; Schachinger et al., 2001; Winzer et al., 1999), emotional stress (Krzeminski et al., 2000; Miyamoto et al., 1983;

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Smith et al., 1989) or monetary reward (Berntson et al., 1994; Newlin and Levenson, 1979; Sherwood et al., 1986) have shown a dose-dependent shortening of the PEP. Between-subject differences in PEP level are stable over time (Richter and Gendolla, 2009), show comparable heritability to plasma catecholamine levels (Goedhart et al., 2006; Vrijkotte et al., 2004), and reliably reflect interindividual differences in cardiac sympathetic activity assessed by dual blockade (Williams et al., 1993; Kupper et al., 2006).

PEP can be obtained by simultaneous recording of the thoracic impedance cardiogram (ICG) and electrocardiogram (ECG) (Willemsen et al., 1996; Riese et al., 2003) and is defined as the interval from the onset of left ventricular depolarization, reflected by the Q-wave onset in the ECG, to the opening of the aortic valve, reflected by the B-point in the ICG signal (Lozano et al., 2007; Sherwood et al., 1990; Willemsen et al., 1996; Labidi et al., 1970). Fig. 1 displays the ECG and ICG signals with the relevant landmarks. Throughout, the term 'actual' PEP is used to refer to the interval between the ECG Q-wave onset and the ICG B-point. To improve signal quality, PEP is usually scored from the ICG waveform after ensemble averaging over multiple beats, time locked to the R-wave peak. This improves automated detection of the crucial landmarks in the ECG and in the ICG but even after ensemble averaging substantial errors in positioning of the Q-wave onset and B-point remain (Lozano et al., 2007; Willemsen et al., 1996; Berntson et al., 2004). For this reason, visual inspection of the automatically detected Q-wave onset and B-point is needed and, to ensure sufficient reliability, scoring is often repeated by multiple raters. The latter visual inspection can be time-consuming and presents an obstacle to the assessment of PEP in epidemiological studies with thousands of subjects or in ambulatory studies collecting data across extended periods of time. In addition, when signal quality of the ICG is compromised, for instance, during unsupervised activities in ambulatory recordings, reliable visual scoring of the B-point is very hard, even when employing multiple raters, leading to the exclusion of a substantial portion of the subjects.

Two practical solutions have been proposed to sidestep the difficult detection of the Q-wave onset. The first is to score the more easily detected R-wave onset and add a fixed value for Q-wave duration of 15 ms (Berntson et al., 2004). The R-wave onset was used by Berntson et al. (2004) in 30 healthy subjects, of which 10 showed no clear Q-wave in a lead II axis ECG derivation. In these subjects scoring of Q-wave onset defaulted to the R-wave onset, and it was shown that using the R-wave onset for *all* subjects significantly reduced the error variance in the individual differences in the PEP. This suggests that a PEP based on the R-wave onset was more reliable than the actual PEP based on the Q-wave onset, although this was established under resting conditions only. The second solution is to extend this reasoning, and use the R-wave peak instead of the R-wave onset as it is an even more sharply defined landmark in the ECG. This makes the further assumption that the R-wave onset to R-wave peak interval is also reasonably constant. Current practice is to estimate the Q-wave onset by subtracting a fixed value of 48 ms from the time of the R-wave peak (Brydon et al., 2008; Willemsen et al., 1996). To our knowledge the validity of this practice has not been verified.

To assist in the detection of the B-point in the ICG the physiological connection between the timing of the B-point and the dZ/dt-min peak can be exploited. The dZ/dt-min peak (in the literature variously called C-point or Z-point) is a maximum defined by a zero-order crossing in the first derivative of the ICG and can be detected with much more fidelity than the B-point, which is often a (subtle)

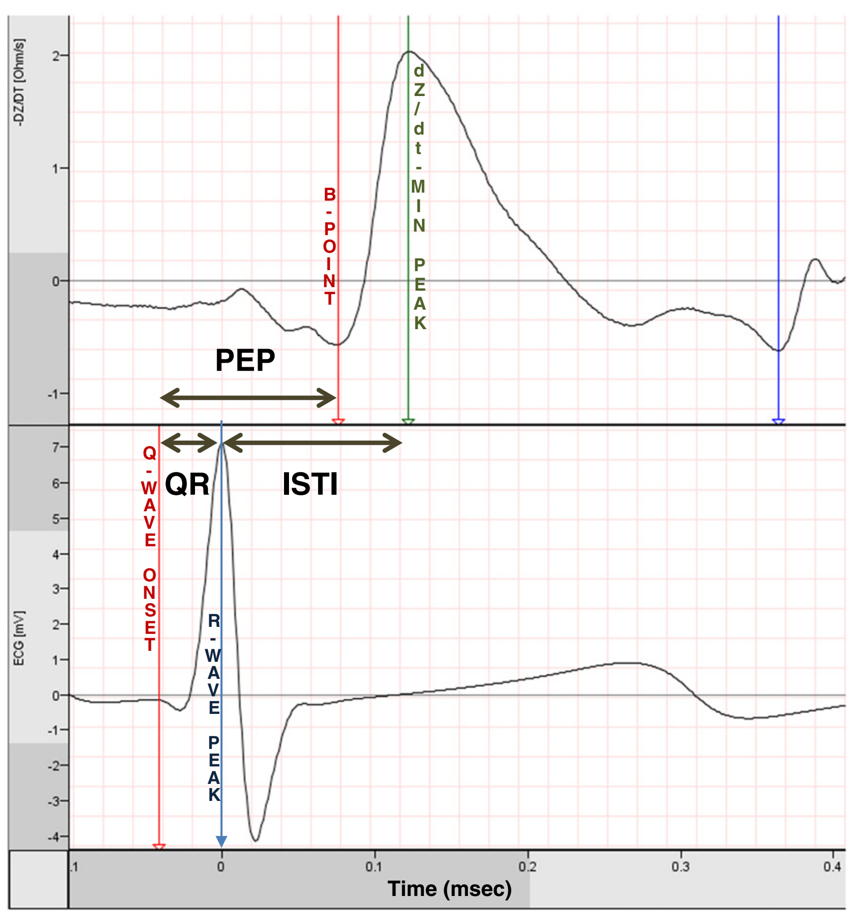

Fig. 1. The impedance cardiogram (top) and the electrocardiogram (bottom) with the four landmarks defining the PEP (Q-wave onset to B-point) and the ISTI (R-peak to dZ/dt-min peak).