Estimated preejection period (PEP) based on the detection of the R-wave and dZ/dt-min peaks in ECG and ICG

René van Lien¹, Nienke M Schutte¹, Jan H Meijer², Eco J C de Geus¹

¹ Department of Biological Psychology, VU University Amsterdam
² Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, the Netherlands

E-mail: R.van.lien@vu.nl

Abstract. The validity of estimating the PEP from a fixed value for the Q-wave onset to the R-wave peak (QR) interval and from the R-wave peak to the dZ/dt-min peak (ISTI) interval is evaluated. Ninety-one subjects participated in a laboratory experiment in which a variety of physical and mental stressors were presented and 31 further subjects participated in a sequence of structured ambulatory activities in which large variation in posture and physical activity was induced. PEP, QR interval, and ISTI were scored. Across the 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 to 54 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. However, the optimal intercept and slope values varied significantly across subjects and study setting. Bland-Altman plots revealed a large discrepancy between the estimated PEP and the actual PEP based on the Q-wave onset and B-point. It is concluded that the estimated PEP can be a useful tool but cannot replace the actual PEP to index cardiac sympathetic control.

1. Introduction
The preejection period (PEP) is currently 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 [1] which are influenced by sympathetic but not parasympathetic activity. PEP can be obtained from the thoracic impedance cardiogram (ICG) and electrocardiogram (ECG) [2] 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 [2, 3, 4]. Figure 1 shows the ECG and ICG signals with the relevant landmarks.

PEP is usually scored from the ICG waveform after ensemble averaging over multiple beats, time locked to the R-wave peak to reduce noise. However, substantial problems in detection of the Q-wave onset and B-point remain [2, 3, 5]. 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 [2, 6]. The validity of this practice has not been verified to date. To assist in the detection of the B-point in the ICG the dZ/dt-min peak can be exploited. The dZ/dt-min peak (also called C-point or Z-point) can be detected with much more fidelity than the B-point. Changes in cardiac contractility, the main concept that PEP aims to assess, are reflected in the time it takes the left ventricle to build up sufficient force to open the aortic valve (B-point) but also in the time it takes to reach peak ventricular ejection (dZ/dt-min). Previously, two groups have reported that the time interval between the R-wave peak and the dZ/dt-min, called the Initial Systolic Time Interval (ISTI), is a significant predictor of both the R-wave peak to B-point (RB) interval as well as the actual PEP [3, 7]. This suggests that an adequate estimation of the PEP could be achieved by the detection of the two most prominent features in the ECG or ICG, the R-wave peak and the dZ/dt-min peak respectively. An estimated PEP can be defined as the sum of a fixed QR interval and an estimated RB interval derived from the ISTI by a regression relationship. As this bypasses the detection of the Q-wave onset and the B-point, PEP estimation could be achieved in automated way.
The current paper reports on two studies that evaluated the estimated and actual PEP in subjects undergoing a wide variety of stress manipulations in a laboratory setting, and in subjects who underwent a protocol resembling daily activities with a large variance in posture and physical activity. Firstly, it was explored whether the QR interval can be approximated by a fixed interval even in very diverse laboratory and ambulatory conditions. Secondly, multilevel regression analysis was used to derive an equation to estimate the RB interval from the ISTI in both laboratory and ambulatory recordings. It was tested whether this analysis resulted in a set of fixed regression coefficients that can be applied to all subjects as was suggested by Lozano et al. [3]. Finally, Bland and Altman plots were used to investigate whether the estimated PEP from the R-wave and dZ/dt-min peaks and fixed QR interval adequately predicts the actual PEP across this set of subjects and a wide range of conditions.

2. Methods

2.1. Subjects
In the laboratory study 91 young, healthy volunteers (20 male, 71 female) with a mean age of 21.7 years (SD = 3.2) and a mean Body Mass Index (BMI) of 22.2 (SD = 2.9) participated. The participants in the ambulatory study were 31 young, healthy volunteers (11 male, 20 female) having a mean age of 22.0 (SD = 1.9) and a mean BMI of 23.4 (SD = 4.3). Participants in both studies did not report any psychiatric diseases or cardiovascular problems and none were using cardio-active medication (e.g. antihypertensives). All gave their written, informed consent prior to participation.

2.2. General Procedures
Laboratory study: The subjects were seated in front of a 19" monitor in a dimly lighted, electrically-shielded, sound-attenuated cabin. The experimental session commenced with general instructions and a brief period of rest. To induce variation in SNS activity, various experimental physical and mental stressors were presented in a fixed order. Ambulatory study: A sequence of protocolized, supervised ambulatory activities was performed in the lab, outdoors, and in a sports centre to create variations in posture and intensity of physical and mental activity in close resembling normal daily activities.

2.3. Physiological recordings
ECG and ICG leads were attached to the participants using pregelled Ag/AgCl spot electrodes. The electrodes were attached as described by Goedhart et al. [8]. The ECG and ICG signals in the laboratory study were continuously recorded at a sample rate of 1000HZ with use of the ECG100C and NIC01000C modules of the BioPac data-acquisition system (BioPac systems INC, Santa Barbara, CA). The electrocardiogram (ECG) and the impedance cardiogram (ICG) of the ambulatory study were recorded continuously with the VU-AMS5fs device (VU University, Amsterdam).
2.4. Signal Analyses and Data Reduction

The mean QR interval was computed per condition across all valid beats in the laboratory data. For detection of the Q-wave onset in the ambulatory data, the ECG was imported into the VU-AMS5fs software. For each experimental condition the interbeat interval (IBI, ms) was scored from the R-wave peaks. Poor ECG signal fragments were removed. The mean Q-wave onset for each ambulatory condition was visually scored. The procedures to score the ISTI were identical for both studies: After obtaining the IBI time series, visual scoring from all valid beats was used to mark the B-point and the dZ/dt-min peak (see figure 1 for an example). The actual PEP was computed as the interval from the Q-wave onset in the ECG to the B-point in the ICG signal. The ISTI was computed as the time interval between the R-wave peak and the dZ/dt-min peak [7].

2.5. Statistical Analyses

The grand averaged QR interval across all subjects and all laboratory and ambulatory conditions was used to compute a weighted average QR across both studies to be used as a fixed QR interval. To test whether the QR interval can be approximated by a fixed interval the actual QR values were compared to the grand weighted average to determine the absolute agreement and its error values across both studies. Multilevel regression was applied to establish the optimal regression equation to predict the RB interval from the ISTI for both studies separately. Previous research suggested that a fixed single equation can be used for all subjects [3], which would mean that models with a random slope and intercept should not provide a significant better fit than a model with a fixed intercept and slope. Finally, the estimated PEP was computed for each individual in every condition in both studies by summing the weighted grand averaged QR interval across both studies to the RB interval estimated from the ISTI using the slope and intercept parameters from the best fitting model of the laboratory study, with the ambulatory data acting as the confirmatory set. A Bland-Altman analysis was used to test the absolute agreement between the estimated PEP and the actual PEP for both studies.

![Figure 2](image2.png)

Figure 2. Bland-Altman plots of the difference between the actual PEP based on the ECG Q-wave onset and the ICG B-point and the estimated PEP based on the ECG R-wave and ICG dZ/dt-min peaks. The difference is plotted as a function of the absolute value of the actual PEP for the laboratory study (left) and the ambulatory study (right). Dotted lines represent the 95% confidence intervals around the mean difference.

3. Results

3.1. QR interval

The mean QR interval across all conditions was 39 ms (sd = 8 ms) in the laboratory study and 42 ms (sd = 6 ms) in the ambulatory study. To obtain the best possible value for a fixed QR interval the weighted grand average of both studies of ((39 * 91) + (42 * 31))/122 = 40 ms was computed. The 95% confidence interval (-14.5 ms – +14.5 ms) was found to be substantial.
3.2. Estimation of the R-wave peak to B-point interval using the ISTI
The multilevel analysis showed that the best model to describe the relationship between the RB interval and the ISTI in the laboratory study was the extended linear model with a random intercept and a random slope, RB = -46 + (0.9 * ISTI) ms. The model explained 79 % of the total variance in the RB interval. The same was true for the ambulatory study where the linear model with a random intercept and a random slope explained 81 % of the variance in RB. However, the slope and intercept were significantly different from the laboratory study: RB = -15 + (0.7*ISTI) ms.

3.3. Absolute agreement between actual PEP and estimated PEP
Figure 2 depicts the crucial test whether the estimated PEP adequately reflects the actual PEP across a wide range of laboratory and ambulatory conditions. PEP was estimated as: 40 + (-46 + (0.9 * ISTI)). The mean difference between the actual PEP and the estimated PEP in the laboratory study was +8 ms, and in the ambulatory study -4 ms. The 95% confidence intervals were very large, ranging from -20 to +36 ms for the laboratory study and from -25 to +18 ms in the ambulatory study.

4. Discussion and conclusions
Two studies in different samples and settings found substantial discrepancies between the estimated PEP and the actual PEP based on the Q-wave onset and B-point. In the laboratory study, at least 84% of the differences between the estimated PEP and the actual PEP exceeded 3.5 ms, which is the mean reactivity found to two often used tasks in laboratory stress studies. About half of the error is due to the use of a fixed QR interval. The mean value of QR interval across both settings was 40 ms which is in agreement with previous studies. For instance, Goldberger and Bhargava [9] reported a QR interval of around 37 ms at rest which decreased by a few ms during exercise. Apart from the QR interval, the estimation of the RB interval from the ISTI also strongly contributed to the difference between estimated and actual PEP. These findings are in contrast to previous reports showing the ISTI to be a significant predictor of both the R-wave peak to B-point (RB) interval as well as the actual PEP [3]. Specially, Lozano et. al [3] found that the equation RB = -31.59 + (1.233 * ISTI) + (0.0032 * ISTI²) accounted for 95% of the variance in the actual RB interval during rest, a mental arithmetic task and a speech preparation task. The present study, with a wider range of conditions, shows that a single regression equation relating ISTI to RB is not adequate.

It is concluded that for valid PEP scoring the detection of the Q-wave onset and B-point remains mandatory. PEP estimated from the R-wave and dZ/dt-min peaks should not be used to replace the actual PEP, but could be a useful in helping to locate the Q-wave and B-points. Focusing the detection algorithms in a window around these expected locations can assist automated detection and reduce the effort of visual inspection.

References
[1] Newlin D B and Levenson R W 1979 Psychophysiology 16 546-53
[2] Willemsen G H, de Geus E J, Klaver C H, van Doornen L J and Carroll D 1996 Psychophysiology 33 184-93
[3] Lozano D L, Norman G, Knox D, Wood B L, Miller B D, Emery C F and Berntson G G 2007 Psychophysiology 44 113-9
[4] Sherwood A, Allen M T, Fahrenberg J, Kelsey R M, Lovatto W R and van Doornen L J 1990 Psychophysiology 27 1-23
[5] Berntson G G, Lozano D L, Chen Y J and Cacioppo J T 2004 Psychophysiology 41 333-7
[6] Brydon L, O'Donnell K, Wright C E, Wawrzyniak A J, Wardle J and Steptoe A 2008 Obesity 16 2642-7
[7] Meijer J H, Boesveldt S, Elbertse E and Berendse H W 2008 Physiol. Meas. 29 S383-91
[8] Goedhart A D, Kupper N, Willemsen G, Boomsma D I and de Geus E J 2006 Biol. Psychol. 72 110-7
[9] Goldberger A L and Bhargava V 1983 J. App. Physiol. 54 1083-8