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Mathematical detection of aortic valve opening (B point) in impedance cardiography: A comparison of three popular algorithms

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Abstract

The preejection period (PEP) is an index of left ventricle contractility widely used in psychophysiological research. Its computation requires detecting the moment when the aortic valve opens, which coincides with the B point in the first derivative of impedance cardiogram (ICG). Although this operation has been traditionally made via visual inspection, several algorithms based on derivative calculations have been developed to enable an automatic performance of the task. However, despite their popularity, data about their empirical validation are not always available. The present study analyzes the performance in the estimation of the aortic valve opening of three popular algorithms, by comparing their performance with the visual detection of the B point made by two independent scorers. Algorithm 1 is based on the first derivative of the ICG, Algorithm 2 on the second derivative, and Algorithm 3 on the third derivative. Algorithm 3 showed the highest accuracy rate (78.77%), followed by Algorithm 1 (24.57%) and Algorithm 2 (13.82%). In the automatic computation of PEP, Algorithm 2 resulted in significantly more missed cycles (48.57%) than Algorithm 1 (6.3%) and Algorithm 3 (3.5%). Algorithm 2 also estimated a significantly lower average PEP (70 ms), compared with the values obtained by Algorithm 1 (119 ms) and Algorithm 3 (113 ms). Our findings indicate that the algorithm based on the third derivative of the ICG performs significantly better. Nevertheless, a visual inspection of the signal proves indispensable, and this article provides a novel visual guide to facilitate the manual detection of the B point.

Descriptors: Preejection period, Isoelectric crossings, Second derivative classification, Third derivative classification

The autonomic space theory (Berntson, Cacioppo, & Quigley, 1991) marked an inflection point in the scientific understanding of the functioning of the autonomic nervous system. The possibility of coactivation, coinhibition, reciprocal activity, and uncoupled activation of the two autonomic branches (sympathetic and parasympathetic) made it necessary to include specific autonomic indexes in psychophysiological research. Among these, the preejection period (PEP) is of high relevance as a reliable index of left ventricular contractility, showing widespread acceptance in recent literature (see Figure 1).

The PEP is one of the two components of electromechanical systole, and comprises the time from the onset of ventricular depolarization until the onset of left ventricular ejection, when the aortic valve opens to let the oxygenated blood flux enter the systemic circulation (Sherwood et al., 1990). Therefore, in order to calculate the PEP for a cardiac cycle, it is necessary to identify the precise moment when those two physiological events occur. As a bioelectrical phenomenon, the onset of ventricular depolarization can be directly observed in the shape of the Q wave onset in the electrocardiogram (ECG) (Berntson, Lozano, Chen, & Cacioppo, 2004). The opening of the aortic valve, in contrast, is a mechanical event that cannot be directly detected with the noninvasive techniques available for psychophysiological research. However, it can be derived by changes in thoracic electrical impedance (ICG), easily measurable in laboratory settings (Kubicek, Karnegis, Patterson, Witsoe, & Mattson, 1966). In a study carried out in 1970, Lababidi, Ehmke, Durnin, Leaverton, and Lauer (1970) found a temporal coincidence between the appearance of a notch in the graph of the first derivative of the impedance cardiogram (dZ/dt) and the second deflection of the first noise in the phonocardiogram. Since this deflection is associated with the opening of the aortic valve, an indirect correlation could be established between this physiological event and the function derived from thoracic impedance. Hence, the distinctive notch observed in dZ/dt was labeled as B point and was suggested as an indicator of the onset of left ventricular ejection.

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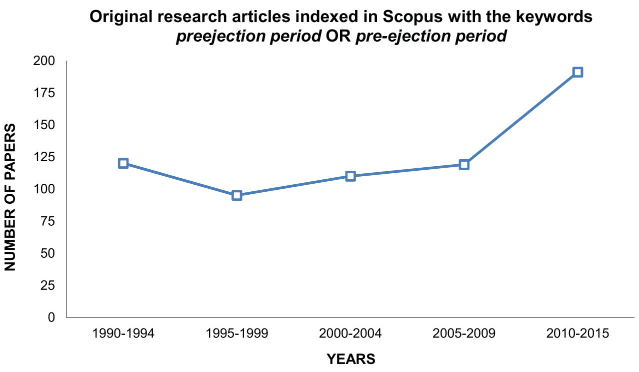

Figure 1. Growth of the research works indexed in Scopus with the keywords "preejection period" OR "pre-ejection period" since year 1990. The results have been grouped by 5-year intervals.

The Problem of B Point Detection

The possibility of determining the exact moment when the aortic valve uncloses by means of a precise and noninvasive technique signifies an important advantage for psychophysiological research. However, there is a major disadvantage: Although the aortic valve opening is a physiological event that occurs in every single cardiac cycle (at least in healthy subjects), the notch reported by Lababidi et al. (1970) is not always clearly identifiable. This idiosyncrasy extends beyond individual differences: Even within the same experimental session of a single person, the notch may become impossible to detect by visual inspection in some sections of the data set (Nagel et al., 1989). To account for the variability observed in the cardiac impedance waveform, Sherwood et al. (1990) modified in their methodological guidelines for impedance cardiography the classical description of the B point as a "notch," defining it as "the onset of the rapid upslope of dZ/dt as it rises to its peak value," and establishing the current operationalization of the term.

Following this definition, several mathematical algorithms were developed for its automatic estimation. Most of these algorithms aim to localize the upstroke of dZ/dt based on the calculation of the second (dZ^2/dt^2) or third (dZ^3/dt^3) derivative of the impedance cardiogram (Debski, Zhang, Jennings, & Kamarck, 1993). Alternatively, Lozano et al. (2007) proposed an indirect polynomial method that does not require identifying the B point for the estimation of PEP, but is rather based on the correlation between PEP and the time interval between the R peak of the ECG and the C point of the ICG (both easily identifiable marks in their respective graphs). However, Van Lien, Schutte, Meijer, and de Geus (2013) found substantial discrepancies in different experimental conditions between the PEP estimated with this last method and the traditional one. They concluded that, even being a helpful tool, it should not be considered as a substitute for the actual PEP obtained by aortic valve opening detection.

A literature review (with the search terms: preejection period, pre-ejection period, and PEP in full text) of the original research articles reporting estimates of PEP (72 articles), published in the journals *Psychophysiology* (26), *Biological Psychology* (26), and *International Journal of Psychophysiology* (20) during 2010–2015, revealed that in 39 articles (54%) an automatic B point detection method was used, in 15 articles (21%) authors employed only and exclusively manual detection, while 18 articles (25%) did not report the methodology used. It is important to know that, out of the 39 articles using an automatic detection method, only 11 (28%) inform about the algorithm applied to detect the B point: 9 (23%) report that they used the Lozano's polynomial method, one reports having employed the maximum of the second derivative, and one relates that they utilized the B15% methodology (Kubicek, Patterson, & Witsoe, 1970; Ono et al., 2004), while the remaining 28 (72%) do not mention which algorithm was employed (see online supporting information Table S1). This lack of information raises an important reproducibility issue, unless we have compelling evidence that all B point detection algorithms described in the literature and available at popular data analysis software packages are equally reliable and produce identical results.

The only study that, to our knowledge, has assessed the reliability of two different B point detection algorithms based in upstroke identification by means of derivative calculations is the one where Debski et al. (1993) compared the average values of five physiological indexes that required B point estimation. The first algorithm located the B point at the reversal point of the second derivative, while the second located the B point at the maximum of the third derivative. In a third experimental condition, a human operator placed the B point employing visual detection following the operationalization of Sherwood et al. (1990). Although the average value of the indexes did vary depending on the method used to detect the B point, the statistical analysis did not reveal significant differences in the average variability of the three detection methods. The authors also reported high between-subjects Pearson correlation coefficients in the scores obtained by the two algorithms when compared to those obtained by means of visual detection. An analysis of PEP was not included in the study.

The aim of the present study was to test the performance of three different B point detection algorithms provided by common data analysis software programs. The three algorithms we tested were (1) the cycle-by-cycle isoelectric crossings, (2) the maximum of the second derivative, and (3) the maximum of the third derivative. We compared the average PEP estimate obtained by means of each algorithm, as well as the respective error rates in the computation of the index. Furthermore, we tested the level of coincidence of each algorithm with the placement of the B point made manually by two independent scorers, following the methodological guidelines for impedance cardiography (Sherwood et al., 1990).

Method

Data Set

The data set comprised 100 consecutive cardiac cycles by 30 subjects (15 women, 15 men; *M*age = 22.11; *SD* = 4.65) obtained during a baseline resting period. The participants were seated in a comfortable armchair during the complete duration of the recording session. All experimental procedures were designed according to the Declaration of Helsinki and received approval by the Ethics Committee in Human Research (CEIH) of the University of Granada. Prior to data collection, an informed consent form was filled out and signed by all the participants, who voluntarily took part in the study. The cardiac impedance dZ/dt signal was obtained by means of an impedance cardiography module NICO100C (Biopac Systems Inc., Goleta, CA), wired to a Biopac MP150 polygraph and using a 1 kHz sampling rate. The ICG signal was obtained following the classical tetrapolar array with band electrodes described in Kubicek et al. (1966), placing one of the two voltage electrodes around the base of the neck and the other one around the chest 3 cm below the xiphisternal junction. The corresponding current electrodes were placed 3 cm distal of their respective voltage electrodes. The alternating current injected was set at 400 μA intensity and 50 kHz frequency. The ECG signal was obtained by means of an ECG100C module (Biopac Systems Inc.), wired to a Biopac MP150 polygraph using a 1 kHz sampling rate and a couple of disposable electrodes following Einthoven's Lead II array: The two active electrodes were placed on the right wrist and on the left ankle. The ground electrode was placed on the right leg. The software used to record and process the psychophysiological signals was Acqknowledge 4.2 (Biopac Systems Inc.).

Algorithms

Three different algorithms were evaluated, all based on derivative calculations, with the aim to localize the B point defined as the initiation of the rapid upstroke of the dZ/dt wave (Sherwood et al., 1990).

Algorithm 1 is known as *cycle-by-cycle isoelectric crossings*. This algorithm obtains the mean value of the dZ/dt wave for a given cycle. Then, it places the B point in the last crossing of the mean value before the dZ/dt peak.

Algorithm 2 is known as *second derivative classification*. It first establishes a 50-ms time window starting 150 ms before the C point (the maximum of the dZ/dt at each cardiac cycle). It subsequently calculates the second derivative of the impedance cardiogram (dZ^2/dt^2) and places the B point at its maximum value within the established time window.

Algorithm 3 is known as *third derivative classification*. It calculates the third derivative of the impedance cardiogram (dZ^3/dt^3) and places the B point at the local maximum found within 300 ms previous to the C point.

Scoring Procedure for B Point Visual Detection

The reference for the visual detection of the B point was the definition established in the methodological guidelines for impedance cardiography: The onset of the rapid upslope of dZ/dt as it rises to its peak value (Sherwood et al., 1990). In regular subjects, the location of that upstroke is restricted to a time window comprised between two easily identifiable marks: the R peak of the ECG and the C point of the dZ/dt. This constrains the possible placement of the B point to a time window of approximately 150 ms prior to the C point. Within that time window, the onset of the rapid upslope is sometimes preceded by a clear notch (Lababidi et al., 1970). Examining a vast set of impedance cardiography data, however, reveals that the notch is not always present, different shapes of the dZ/dt wave can be found, and such variance in the morphology of the wave may cause confusion when proceeding to a visual detection of the B point (Nagel et al., 1989). Although a certain degree of variability in the shape of the dZ/dt concerning the B point area is reported in the literature, a precise description of this variability is usually omitted. In the current study, we developed a decision tree (see Figure 2) following the description of the dZ/dt morphology found in Nagel et al. (1989), in order to facilitate a more objective manual placement of the B point by the two scorers. The decision tree indicates where to localize the onset of the rapid upslope, depending on the shape of the wave, and takes into consideration that it may be preceded by an incisive notch, by a plateau, by an inflection point, by a sharp change in the gradient of the graph, or even the lack of any identifiable mark.

The visual detection of the B point was made by two independent scorers (Kelsey et al., 1998; Riese et al., 2003), under a single-blind manipulation: They did not know which algorithm was being used for the computational detection of the B point in each case. One of the scorers had broad experience in impedance cardiogram analysis, while the second had no previous experience. The data of the 30 participants were independently checked, cycle by cycle, by both scorers under each one of the three experimental conditions (algorithms). After the algorithm had made its automatic detection, the B point was manually placed, cycle by cycle, by the scorers, following the criteria depicted in the decision tree. Subsequently, the two scorers registered the number of cycles where the placement of the B point by the algorithm coincided with their own decision. That score indicated the number of cycles that did not need manual edition after the application of the algorithm, and was taken as an index of each algorithm's accuracy.

Data Analysis

The PEP was computed as the time interval from the Q onset to the B point detected by the respective algorithm, and was subsequently averaged for all subjects under each of the three different experimental conditions. The number of cycles where the computational detection of the B point failed (missed cycles) was registered as well. A univariate analysis of variance (ANOVA) was used to test significant differences in the PEP values depending on the algorithm used.

We also checked whether the average PEP obtained by each algorithm was found within the normal physiological limits of the index in resting conditions (Hodges, Halpern, Friesinger, & Dagenais, 1972; Weissler, Harris, & Schoenfeld, 1968). If an average PEP value was below 70 ms or above 175 ms, it was classified as abnormal.

The accuracy score (coincidence with visual detection) was averaged for all the participants in the three experimental conditions. A 3×2 ANOVA with the factors algorithm and scorer was used to test the differences between experimental conditions and between the performance of the two scorers. The Bonferroni test was applied for all post hoc paired comparisons.

Finally, we tested the interscorer reliability in terms of absolute agreement in single measures by means of the intraclass correlation coefficient (ICC) based on a random effects model (Model 2, Shrout & Fleiss, 1979). Given that exactly 100 cycles were analyzed for each subject, in the results the absolute count of missed cycles and accurate detections is directly expressed as a percentage.

Results

Algorithm 1 obtained an average PEP value of 119 ms ($SD = 23$), Algorithm 2 averaged 70 ms ($SD = 26$), and the average value for Algorithm 3 was 113 ms ($SD = 16$; see Figure 3 and Table 1). These differences were statistically significant, $F(2,8997) = 1749.7$, $p < .0001$. The Bonferroni test showed significant differences between Algorithms 1 and 2 ($p < .0001$), 2 and 3 ($p < .0001$), and 3 and 1 ($p < .0001$). The average percentage of missed cycles per subject due to an error of the algorithm was 6.3% ($SD = 9.4$) for Algorithm 1, 48.57% ($SD = 36.25$) for Algorithm 2, and 3.5% ($SD = 5.69$) for Algorithm 3 (see Figure 4). The difference in errors between the three algorithms was also significant, $F(2,87) = 39.961$, $p < .0001$. The post hoc analysis showed that only the differences between Algorithms 2 and 1 ($p < .0001$) and Algorithms 2 and 3 ($p < .0001$) were significant. In addition, Algorithm 2 provided an abnormal average PEP value for 13

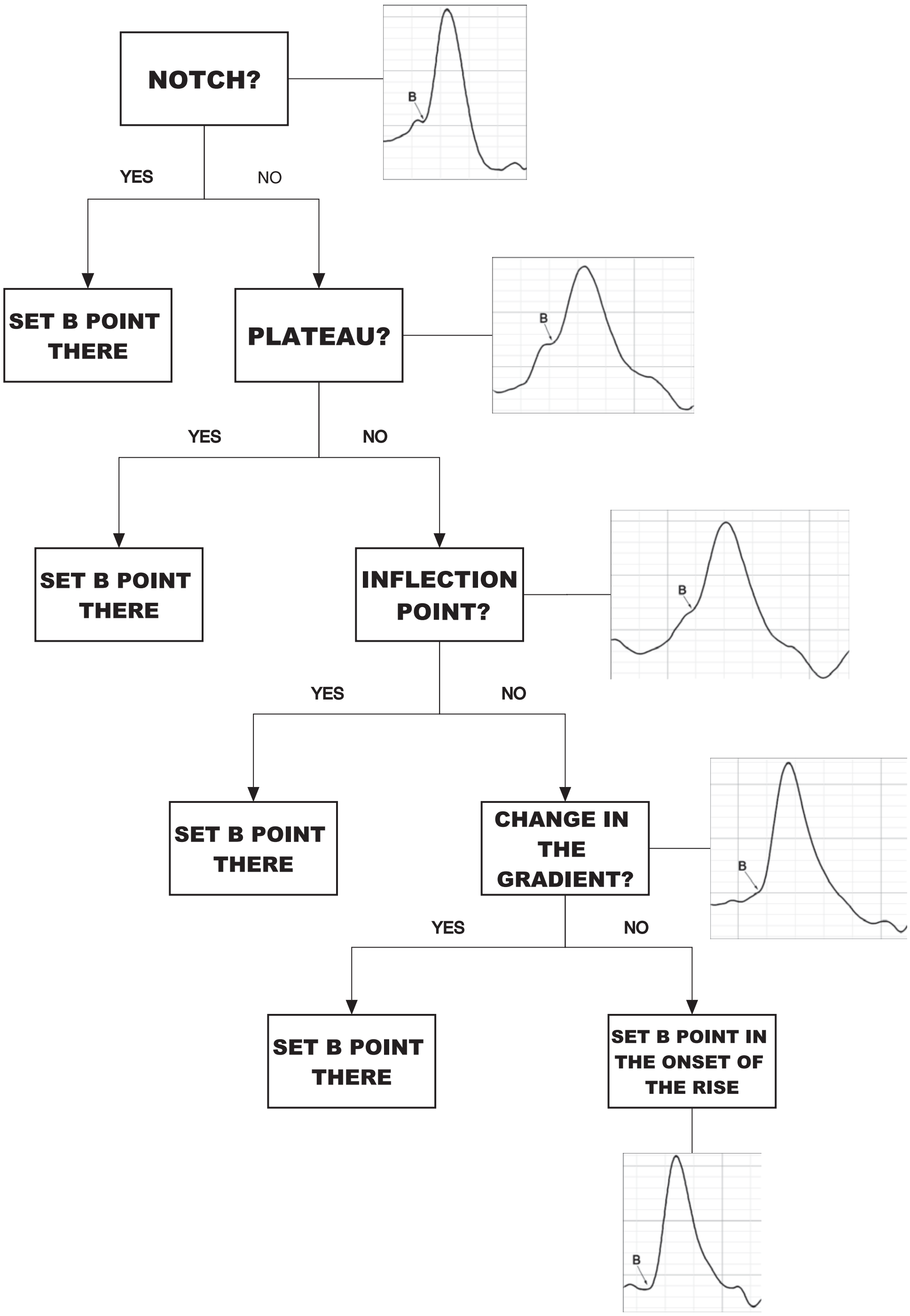

Figure 2. Decision tree for visual B point detection in dZ/dt, based on Sherwood et al. (1990) and Nagel et al. (1989).

subjects (43%), while no abnormal values were obtained by Algorithms 1 and 3.

Regarding the comparison with the visual detection procedure, the average percentage of cycles with accurate detection was 24.57% ($SD = 16.76$) for Algorithm 1, 13.82% ($SD = 14.42$) for Algorithm 2, and 78.77% ($SD = 25.37$) for Algorithm 3 (see Figure 5). These differences were statistically significant as reflected by the significant main effect of the algorithm factor, $F(2,174) = 190.39$, $p < .0001$. The post hoc analysis showed significant differences between Algorithms 1 and 2 ($p < .01$), 3 and 1 ($p < .0001$), and 3 and 2 ($p < .0001$). No significant effect was found for the scorer factor nor for the interaction (both ps > 0.3; see Figure 6). The ICC between scorers was 0.968, similar to the value found by Kelsey et al. (1998).

Discussion

Our findings revealed a significant difference both in the accuracy and the performance of three algorithms commonly used for the mathematical detection of the B point (aortic valve opening) in impedance cardiogram. Specifically, Algorithm 2, which performs a B point detection based on the second derivative of the cardiac

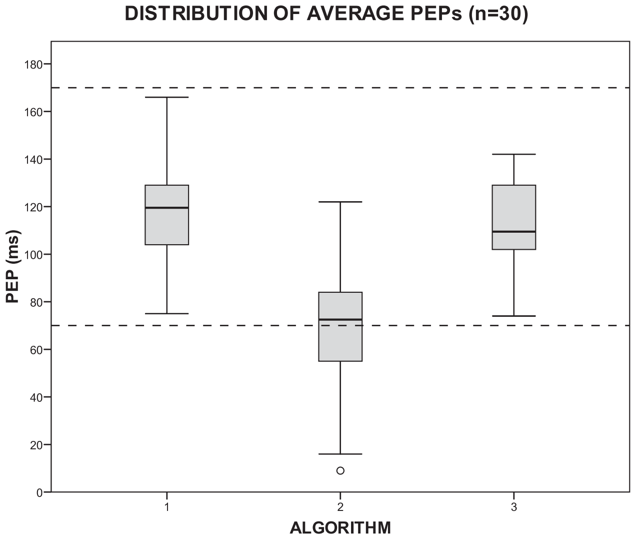

Figure 3. Distribution of the average PEP obtained depending on the algorithm used to estimate the B point. Vertical bars denote maximum and minimum values, horizontal bars denote the mean, and circles identify outliers. Horizontal discontinuous lines signalize the normal physiological limits of PEP in resting conditions.

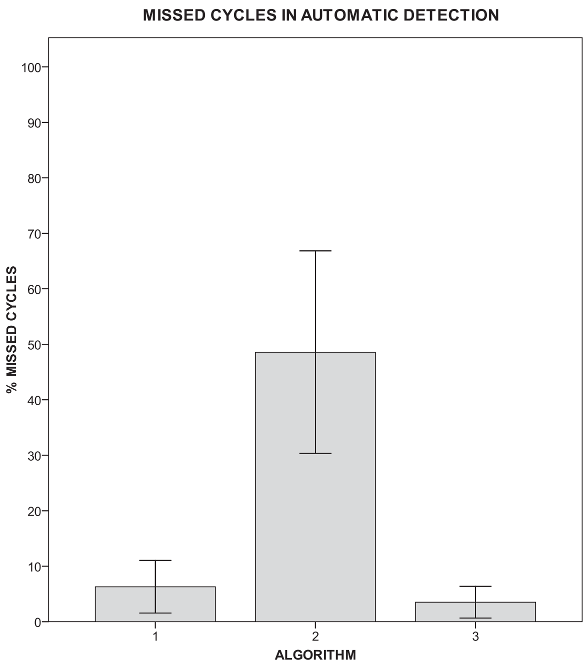

Figure 4. Error rates of the three different algorithms in the automatic detection of the B point, depicted by missed cycles in PEP estimation. Vertical bars denote 0.99 confidence intervals.

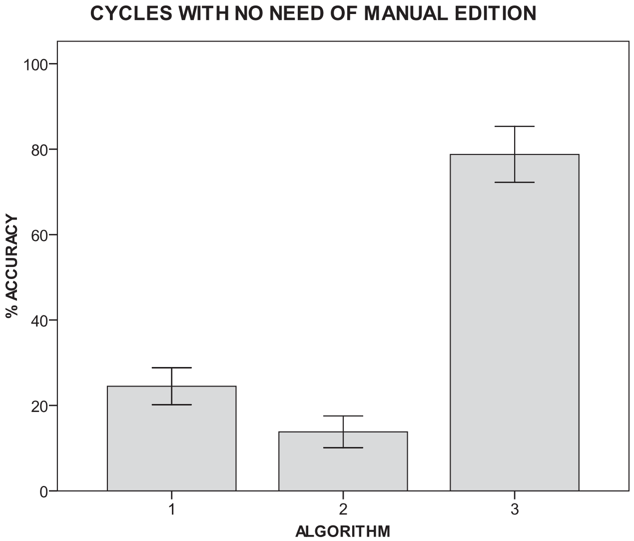

Figure 5. Percentage of cycles with no need of manual edition after applying automatic detection of the B point. Vertical bars denote ± 2 standard errors of the mean.

impedance waveform, proved to be particularly inaccurate (13.82% hits) and to result in a large number of missed cycles and abnormal PEP values. It is not clear whether these poor results relate to the choice of the second derivative for B point detection, to the restricted time window used for the calculation (50 ms), or to both factors. Interestingly, Algorithm 1, which is based on the first derivative of the cardiac impedance waveform and does not define a concrete time window for the detection of the B point, also proved to be dramatically inaccurate. Algorithm 3, based on the third derivative and using a less restrictive time window of 300 ms, was the most accurate of the three (see Figure 5).

Importantly, apart from the striking differences in accuracy, the three algorithms also resulted in significantly different average PEP values. PEP estimation based on Algorithm 2 was more than 40 ms shorter than the one obtained by using Algorithms 1 and 3. This is a remarkably large difference if we consider the normal variability of the PEP in resting conditions, a parameter that usually ranges between 70 ms and 170 ms (Hodges et al., 1972; Weissler et al., 1968). The difference between Algorithms 1 and 3 was smaller (6 ms), but still statistically significant (see Figure 3).

The fact that these three algorithms are provided as standard options for B point detection by widely used commercial software, and that 72% of published articles using algorithmic B point detection for the estimation of the PEP parameter do not explicitly report which algorithm has been used, raises a serious methodological concern with significant implications for the reliability of already published research. Furthermore, these findings signal a reproducibility issue, since even when the raw electrophysiological data

Table 1. *Performance of the Algorithms: Summary of Results*

	Algorithm 1			Algorithm 2			Algorithm 3		
	M	SD	SE	M	SD	SE	M	SD	SE
Average PEP (ms)	119	23	11	70	26	12	113	16	8
Missed cycles (%)	6.3	9.4	1.72	48.57	36.25	6.62	3.5	5.69	1.04
Coincidence with visual inspection (%)	24.5	16.76	2.17	13.82	14.42	1.86	78.77	25.37	3.27

Note. M = mean; *SD* = standard deviation; *SE* = standard error of the mean.

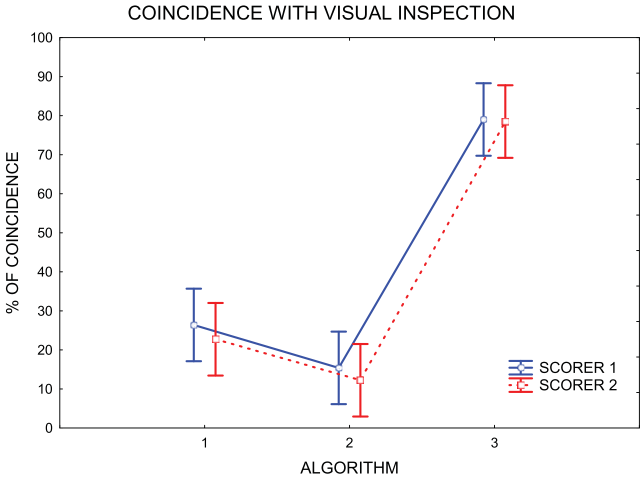

Figure 6. Level of coincidence of automatic B point detection with the visual inspection by the two different scorers. Vertical bars denote 0.99 confidence intervals.

become available, results cannot be independently replicated without any knowledge of the specific algorithms used for B point detection.

Our results, aside from identifying these two crucial issues, provide evidence in favor of using the third derivative classification method (Algorithm 3). This algorithm significantly outperforms the other two in terms of accuracy in B point detection. Although our findings indicate that, disregarding the algorithm employed, a visual cycle-by-cycle inspection to correct misplaced B points is essential and unavoidable, the use of Algorithm 3 can significantly save time and help optimize human resources, especially in studies that do not make use of ensemble average techniques (Kelsey & Guethlein, 1990). Considering that in our study each scorer examined 3,000 cardiac cycles per condition, Algorithm 1 required a manual edition of 2,250 cycles, Algorithm 2 an edition of 2,580 cycles, and Algorithm 3 an edition of 630 cycles.

Nevertheless, it is important to point out that our results were obtained from a data set taken in resting conditions. Thus, given the morphological differences in the cardiac impedance signal depending on age, heart disease, and experimental conditions (Ermishkin, Kolesnikov, & Lukoshkova, 2014; Ono et al., 2004), further research is required before we can generalize these findings.

Another contribution of this paper is the development of a visual guide for correctly identifying the B point in the cardiac impedance waveform by visual inspection (see Figure 2). This guide was developed in the form of a decision tree that takes into consideration the variability in the morphology of dZ/dt waves reported by Nagel et al. (1989), as well as the operationalization of the B point as the onset of the rapid upslope of dZ/dt as it rises to its peak value (Sherwood et al., 1990). Specifically, it indicates which different characteristic marks in the dZ/dt waveform may signalize the onset of the rapid upslope, which is taken as an indicator of the aortic valve opening. This visual guide aims to minimize the subjective weight of the decisions on where exactly to locate the B point in each cardiac cycle. The agreement between scorers, depicted by the high ICC obtained, suggests that this aid can prove a valuable scoring instrument, especially for researchers with little or no previous experience in ICG analysis.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Review of recent papers published in Psychophysiology, Biological Psychology, and International Journal of Psychophysiology (2010–2015) that use PEP as a variable (N = 72).