UNIVERSITY OF CALIFORNIA, IRVINE

A Close Examination of the Use of Systolic Time Intervals in the Calculation of Impedance Derived Cardiac Autonomic Balance and Regulation

THESIS

submitted in partial satisfaction of the requirements for the degree of

MASTER OF ARTS

in Social Ecology

by

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DEDICATION

To

God, through whom everything is possible, even amidst a global pandemic.

My parents, for providing unconditional love and support at every stage of my life and inspiring the unshakeable faith and courage that serves as the foundation for my success.

My inner circle of friends, Daniel, Brandon, Deyber, Ivan, Kyah, and Walter, for providing much needed laughter and support throughout my personal and professional journeys.

Finally, I would like to thank my legs for always supporting me, my arms for always being by my side, and my hands and toes because I can always count on them.

Whatever you do, strive to do it so well that no man living and no man dead and no man yet to be born could do it any better.

Benjamin E. Mays

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ABSTRACT OF THE THESIS

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Distinguished University Professor Julian F. Thayer, Chair

Traditionally, impedance derived measures of cardiac autonomic balance (CAB) and regulation (CAR) are calculated using indices of heart rate variability (HRV) that primarily reflect parasympathetic nervous system activity (e.g., high-frequency HRV | HF-HRV or HF) and pre-ejection period (PEP; a systolic time interval and measure of sympathetic activity). However, HF-HRV and PEP are considered measures of chronotropic and inotropic cardiac influence, respectively. Left ventricular ejection time (LVET) is a systolic time interval that reflects sympathetic chronotropic influence, and therefore may be a more appropriate measure for calculating CAB and CAR compared to PEP.

Thus, the current study evaluates both PEP and LVET in the calculation of CAB and CAR. Data from 158 healthy participants (mean age = 19.09 years old, SD = 1.84 years) were available for analyses. CAB and CAR values were calculated using both HF-HRV and the root mean square of successive differences (RMSSD), in addition to both PEP and LVET, in accordance with previously established guidelines. Analyses showed that correlations were significantly weaker between CAB and CAR calculated using LVET for both HF ($z = 5.12$, $p < .001$) and RMSSD ($z = 5.26$, $p < .001$) than with PEP.

These data suggest that LVET, compared to PEP, provides better "autonomic space" as evidenced by a lack of correlation between CAB and CAR computed using LVET. We stress that future research consider calculating CAB and CAR using chronotropic measures for both parasympathetic and sympathetic activity, as doing so may yield more accurate and independent measures of cardiac autonomic activity compared to a mixture of inotropic (i.e., PEP) and chronotropic (i.e., HF-HRV) measures.

INTRODUCTION

The dynamic between the parasympathetic and sympathetic branches of the autonomic nervous system is a multifaceted one that is implicated in psychological and physiological processes and health (Sleight, 1997; Thayer, Hansen, Saus-Rose, & Johnson, 2009). Good health is generally marked by a relative equilibrium between the parasympathetic and sympathetic branches, referred to as autonomic balance (Thayer & Friedman, 1997; Malliani, 2005). Conversely, poor health is linked to autonomic imbalance, which is characterized by hyperactive sympathetic activity and hypoactive parasympathetic activity (Malliani, Pagani, & Lombardi, 1994; Thayer, Yamamoto, & Brosschot, 2010). Therefore, examining the association between cardiac autonomic activity, health outcomes, and psychological factors is of interest to psychologists and physicians alike. In this effort, impedance derived measures of cardiac autonomic balance (CAB) and regulation (CAR) have been developed (Berntson, Norman, Hawkley, & Cacioppo, 2008).

Traditionally, both CAB and CAR are calculated using respiratory sinus arrythmia or high frequency heart rate variability (HF-HRV or HF; an index of heart rate variability and measure of parasympathetic activity) and pre-ejection period (PEP; a systolic time interval and measure of sympathetic activity) (Berntson et al., 2008; Singh, Hawkley, McDade, Cacioppo, Masi, 2009; Kreibig, Gendolla, & Scherer, 2012; Bylsma et al., 2015). However, HF is considered a measure of chronotropic influence, defined as control of the heart via the sinoatrial node (Thayer, Hansen, & Johnsen, 2010). In contrast, PEP is considered a measure of inotropic influence, defined as myocardial contractility (Levy, 1997). Thus, it is important to consider the calculation of CAB and CAR using indices of chronotropic influence for both

parasympathetic and sympathetic measures. The left ventricular ejection time (LVET) is a systolic time interval that reflects sympathetic chronotropic influence, and therefore may be a superior measure (compared to PEP) for calculating CAB and CAR (Stemmler, 1993; Uijtdehaage & Thayer, 2000; Thayer & Uijtdehaage, 2001). Thus, the current study investigates both PEP and LVET in the calculation of CAB and CAR and highlights implications for how these differential calculations may impact psychophysiological research.

BACKGROUND

Autonomic Balance: Early Beginnings

Evidence of a link between the central nervous and cardiovascular systems can be traced all the way back to the late 1800s with the work of French physiologist Claude Bernard, whose pioneering research investigated the connections between vital peripheral organs (i.e., the heart) and the brain and how these multisystem interactions influenced physiological responses and health. His research ultimately led him to the conclusion that a reciprocal interaction between the heart and brain exists, such that stimulation of or changes to cardiac activity are reflected in the brain, and in turn the brain reacts via autonomic connections that then influence the heart (Darwin, 1999). While the physiological details of this reciprocal connection were unable to be elucidated due to the empirical and technological limitations of Bernard's time, subsequent research would go on to provide strong evidence in support of this connection by examining particular brain structures and pathways and proposing theoretical frameworks that linked brain activity to cardiovascular functioning.

The Neurovisceral Integration Model proposed by Thayer and Lane (2000) is among the most prominent frameworks that details this physiological relationship. This model proposed that heart rate variability (HRV), or the variation in time between consecutive heartbeats, is regulated by autonomic inputs from Cranial Nerve X (the vagus nerve) and serves as a reliable index of 1) Autonomic control of the heart, 2) Healthy heart function, and 3) Inhibitory control and the self-regulation of cognitive and affective processes (Thayer & Lane, 2000). It was also suggested that a healthy model of the vagus nerve's influence on cardiovascular functioning is characterized by increased activation of the parasympathetic

branch of the autonomic nervous system (which is responsible for "rest and digest" responses), which inhibits activation of the sympathetic branch of the autonomic nervous system (which is responsible for "fight or flight" responses) and represents a state of "autonomic balance" (Thayer et al., 2010b; Thayer & Lane, 2000).

Prior to the proposal of the Neurovisceral Integration Model, autonomic balance had been measured and conceptualized in a variety of ways. Eppinger & Hess (1915) were among the first to suggest that people could be predisposed to have high parasympathetic or sympathetic activity, and that a dominance of either of these systems (reflective of autonomic imbalance) may be linked to a higher risk of developing certain physiological disorders (e.g., hypertension). Years later, Wenger (1941; 1966) surmised that autonomic balance was represented by a reciprocal relationship between the parasympathetic and sympathetic nervous systems, and even derived his own measure of autonomic balance using a factor analysis of nearly 20 physiological measures. However, he was unable to discern differences in autonomic balance among different samples. Additionally, the physiological factors that were used to derive composite measures of PNS activity (e.g., sublingual temperature, palmar conductance) and SNS activity (e.g., salivary output, systolic blood pressure) varied in predictive strength (Wenger, 1966).

Years later, McEwen & Stellar (1993) would revisit the concept of autonomic balance in the context of stress. They not only suggested that the physiological systems of the body fluctuate to meet external demands/challenges (a process known as *allostasis*), but that chronic or heightened activation of these systems can lead to a "wear and tear" on vital organs and biological processes (known as *allostatic load*); limiting one's ability to effectively respond to environmental demands and subsequently increasing their risk for

negative health outcomes via physical and biochemical alterations (McEwen & Stellar, 1993; McEwen 1998). Further exploration of allostatic load would go on to suggest that an imbalance in mediating physiological systems (e.g., the autonomic nervous system) is implicated in the development of physical and mental health maladies, and that this allostatic load can be indexed via several measures of cardiovascular and sympathetic activity (McEwen, 2000; 2004). However, because allostatic load was developed as an umbrella term that encompassed several physiological systems (e.g., cardiovascular, endocrine, inflammatory) and biomarkers (e.g., blood pressure, cortisol, C-reactive protein) involved in the stress experience, less attention was devoted to pure and specific cardiovascular measures of parasympathetic and sympathetic activity or the dynamic between them.

Among the few individuals that sought to further probe this autonomic dynamic from a cardiovascular perspective was Stevo Julius, whose research partly focused on understanding why common hypertension treatments were unsuccessful in effectively reducing cardiac morbidity and mortality. Through both experimental studies (Esler, Zweifler, Randall, Julius, & DeQuattro, 1977; Guzzetti et al., 1988; Julius, Pascual, & London, 1971) and detailed reviews (Brooks & Julius, 2000; Julius, 1991; Palatini & Julius, 2009) Julius and colleagues identified sympathetic hyperactivity paired with parasympathetic hypoactivity (i.e., autonomic imbalance) as a primary mediator of the relationship between hypertension and cardiovascular disease, as this physiological imbalance was shown to have negative implications for the regulation of heart rate, blood pressure, body weight, and hormone levels, which results in the dysfunction of blood vessel walls (i.e., the endothelium) and the hypertrophy of heart chambers that are essential for the circulation of blood (i.e., the left ventricle). However, even within these and other studies that focused on autonomic

imbalance using cardiovascular measures, there remained some inconsistencies in how parasympathetic activity was indexed, with some studies using the spectral analysis of HRV and other studies using pharmacological blockades to induce parasympathetic hypoactivity. Furthermore, studies mainly focused on measures such as heart rate and cardiac output as indices of sympathetic activity.

Overall, despite the lack of a consensus regarding what measures best represented parasympathetic and sympathetic activity (and by extension, autonomic balance), there continued to be a growing amount of evidence suggesting that higher parasympathetic activity was related to better physiological and psychological (e.g., emotion regulation) functioning, whereas higher sympathetic activity (or greater autonomic imbalance) was related to diminished functioning in these domains (Appelhans & Luecken, 2006; Friedman & Thayer, 1998; Thayer et al., 2010b; Thayer & Seigle, 2002).

Cardiovascular Measures of Autonomic Balance

Since the proposal of the Neurovisceral Integration Model, cardiovascular measures of autonomic activity have become more widely used to capture the dynamic between the parasympathetic (Kamath & Fallen, 1993; Shaffer & Ginsberg, 2017; Task Force, 1996) and sympathetic (Levy, 1997; Sherwood et al., 1990; Thayer et al., 2010a) nervous systems due to the non-invasive nature of their collection and the accuracy with which they index pure parasympathetic and sympathetic activity.

Heart Rate Variability. Parasympathetic activity can primarily be indexed via HRV, formally defined as "the oscillation in the interval between consecutive heart beats as well as oscillations between consecutive instantaneous heart rates" (Task Force, 1996, p. 151). It should be noted that despite the nomenclature of "heart rate" variability, HRV refers to

the analysis of the interval between heartbeats (e.g., heart period), not the total number of contractions in a given minute (e.g., heart rate). HRV is measured via electrocardiogram and is typically captured via two domains of measurement: time and frequency.

Frequency-domain measures are used to estimate and classify the distribution of power, or the signal produced from oscillations in a series of heart periods, into four frequency bands via power spectral analysis: Ultra Low Frequency (≤.003 Hz), Very Low Frequency (.003-.04 Hz), Low Frequency (.04-.15 Hz), and High Frequency (.15-.40 Hz) HRV (Task Force, 1996). The low and high frequency bands are the most commonly used in research as they are the easiest to detect. The high frequency band serves as an index of pure parasympathetic activity as well as respiratory activity, while the low frequency band can serve as a surrogate index of sympathetic activity, with higher values representing greater parasympathetic and sympathetic activity, respectively (Task Force, 1996; Thayer et al., 2010). While past research has attempted to index autonomic balance using a ratio of low and high frequency HRV (known as the LF/HF ratio), the use of this measure has since been shown to be less than adequate due to the low frequency band being influenced by other sources outside of the SNS, including the baroreflex as well as the PNS (Billman, 2013; Goldstein, Bentho, Park, & Sharabi, 2011).

Time-domain measures are designed to index the differences between or variability within interbeat intervals, or the time between successive heartbeats, and can be expressed in raw units (typically in ms^2) or log-transformed to achieve a normal distribution (Task Force, 1996; Tarvainen et al., 2014). Examples of common time-domain measures include the standard deviation of the interbeat interval of normal beats (SDNN), the number of adjacent interbeat intervals that differ by more than 50 ms (NN50), and the root mean

square of successive differences between consecutive heartbeats (RMSSD), with RMSSD being the most commonly used time-domain measure to index vagal activity.

Impedance Cardiography. While HRV is concerned with fluctuations in heart period itself, impedance cardiography refers to the mechanical and electrical underpinnings of cardiac functioning and output and how they drive changes in heart period and heart rate (Thayer et al., 2010a). Impedance cardiography is used to measure cardiac output, which is quantified by multiplying heart rate and stroke volume, or the increase in the volume of thoracic blood (in mL) following the contraction of the left ventricle (Sherwood et al., 1990). This ventricular contraction is referred to as the electromechanical systole (or simply the systole) and can be quantified in systolic time intervals (measured in milliseconds) that serve as pure indices of sympathetic activity, known as pre-ejection period (PEP) and left ventricular ejection time (LVET) (Sherwood et al., 1990; Levy, 1997). Unlike vagally-mediated measures of HRV, greater autonomic activity is reflected via *lower* values of PEP and LVET. These systolic time intervals will be explored in greater detail later in this section.

Autonomic Balance and Health

Under normal conditions, autonomic balance (and thus, generally good health) is marked by a dynamic equilibrium between the parasympathetic and sympathetic nervous systems. Due to its importance in health research, there have been several attempts to accurately index the balance and regulation of the two autonomic branches using various cardiovascular measures. Berntson, Norman, Hawkley, & Cacioppo (2008) proposed two indices of cardiac autonomic activity using HRV and impedance cardiography known as Cardiac Autonomic Balance (CAB) and Cardiac Autonomic Regulation (CAR). CAB is defined

as the reciprocal balance between PNS and SNS activity, while CAR is defined as the total activity of both branches. CAB and CAR can be calculated using indices of parasympathetically-mediated HRV (e.g., high frequency HRV) and impedance derived systolic time intervals (i.e., PEP) as an index of sympathetic activity (Berntson et al., 2008; Williams et al., 2017).

Both CAB and CAR have been used as indices of autonomic balance and overall autonomic activity in a myriad of studies, showing associations with affective responses (Kreibig et al., 2012), psychopathologies (Bylsma et al., 2015; Stone, McCormack, & Bylsma, 2020), stress (Gump et al., 2011; Mitchell, Paulson, Cannarozzi, Neer, & Cassisi, 2017), inflammatory markers (Alen, Deer, & Hostinar, 2020; Singh et al., 2009), and physiological health (Berntson et al., 2008; Vrijkotte et al., 2015). More specifically, a history of myocardial infarctions and type 2 diabetes diagnoses are more likely to be linked to low levels of CAR and CAB, respectively (Berntson et al., 2008), while lower CAB has also been shown to be associated with increased levels of inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha (Alen et al., 2020). Autonomic nervous system imbalance, or an increase in sympathetic activity coupled with a decrease in parasympathetic activity, has been associated with poorer physiological health outcomes including metabolic abnormalities (Licht et al., 2013) and cardiovascular disease risk factors (i.e., hypertension, diabetes) (Thayer et al., 2010b), as well as worse psychological outcomes, including anxiety (Friedman & Thayer, 1998), depression (Stone et al., 2020), and increased levels of daily stress (Mitchell et al., 2017).

Chronotropic vs. Inotropic Cardiac Influence

Autonomic influences on the heart can differ based on whether activation occurs at the sinoatrial (SA) node or the atrioventricular (AV) node. Autonomic nervous system activation at the SA node results in control of heart rate, known as chronotropy, which is associated with several cardiac measures including RMSSD (Thayer et al., 2010a). Among these measures is the left ventricular ejection time (LVET), a systolic time interval reflective of sympathetic activity (Stemmler, 1993; Thayer & Uijtdehaage, 2001). LVET is defined as the duration of the left ventricle to eject blood corresponding to the opening and closing of the aortic valve. More specifically, LVET refers to the interval between the B- and X-point on the dZ/dt waveform (Lozano et al., 2007; Sherwood et al., 1990). On the other hand, autonomic stimulation at the AV node results in changes in myocardial contractility, known as inotropy (Levy, 1997). A common inotropic measure is PEP, also a systolic time interval reflective of SNS activity, defined as the duration between initial ventricular depolarization and opening of the aortic valve. More specifically, PEP reflects the interval from the onset of the ECG Q-wave to the onset of left ventricular ejection (the interval preceding LVET) (Berntson, Lozano, Chen, & Cacioppo, 2004; Sherwood et al., 1990).

Whereas both LVET and PEP are systolic time intervals that reflect SNS activity, the physiological foundations of these measures differ significantly. Therefore, a closer examination of the calculation of both CAB and CAR using PEP and LVET is warranted. Berntson and colleagues (1991) even acknowledged this potential issue in an earlier article, stating: “Moreover, in view of the highly specific patterns of autonomic activity that can be seen across organ systems, measures of the two autonomic divisions should be derived from the same organ. Finally, even chronotropic and inotropic influences on the heart, for example, are mediated by separate efferent pathways that may be subject to differential

central control. Consequently, indices should be optimally derived from the same functional dimension of the target organ" (pp. 482-483).

The Autonomic Space Model

Further exploration of the differential autonomic contributions of various cardiovascular measures led to the development of the Autonomic Space Model (Berntson, Cacioppo, & Quigley, 1993), which proposed that chronotropic control of the heart via parasympathetic and sympathetic influence can vary reciprocally, independently, or coactively; laying the foundation for the future development of CAB and CAR. The autonomic "space" in question refers to the transformations that take place between psychophysiological antecedents and autonomic outflows (e.g., reciprocal, independent, or coactive), and between autonomic outflows and functional effects on target organs (i.e., chronotropic and inotropic influences on the heart) (Berntson, Cacioppo, Quigley, & Fabro, 1994a). The varying modes of autonomic control that the Autonomic Space Model describes can be illustrated using a bivariate model where the x-axis represents independent sympathetic control using a normalized sympathetic measure (i.e., z-scores of PEP values) and the y-axis represents independent parasympathetic control using a normalized parasympathetic measure (i.e., z-scores of high frequency HRV). The graphical space within these axes can be divided into four quadrants that represent the modes of autonomic activity (reciprocal sympathetic, reciprocal parasympathetic, coactivation, and co-inhibition; see Figure 1 for an example). Overall, this model provided a more comprehensive conceptualization of the flexibility of the autonomic nervous system and serves as an additional way to examine the influence of different parasympathetic and sympathetic measures on CAB and CAR. Importantly, one piece of such conceptualization, however, is that

CAB and CAR are not significantly related. In other words, these various autonomic states as defined by CAB and CAR values can be *independent* from one another. For example, individuals could conceivably be high in CAB, but not necessarily CAR. This is important, as CAB and CAR are thought to differentially predict cardiac disease states (e.g., myocardial infraction, diabetes; Berntson et al., 2008) and thus, CAB and CAR values should not be related to or dependent on one another.

Present Study

Given the importance of the autonomic nervous system in linking psychological and physiological health, it is crucial that the dynamic between its two branches be conceptualized in a way that optimally and accurately captures pure parasympathetic and sympathetic activity. Taking this into account, the purpose of this paper is to evaluate both PEP and LVET in the calculation of CAB and CAR. Specifically, we aim to determine the differential contributions of PEP and LVET in autonomic space by comparing measures of CAB and CAR that are calculated using each systolic time interval independently (i.e., comparing CAB_PEP to CAR_PEP and comparing CAB_LVET to CAR_LVET). If LVET and HRV measures represent chronotropic cardiac influence, and PEP represents inotropic cardiac influence, then CAB and CAR calculated using LVET should more accurately depict autonomic "space" compared to CAB and CAR calculated using PEP.

Therefore, the following investigation examines the impact different systolic time intervals (PEP and LVET) can have on the association between CAB and CAR. We hypothesize that CAB and CAR calculated using PEP will be more strongly associated compared to CAB and CAR calculated using LVET. Support for these hypotheses would suggest that PEP provides less of a distinction (or less autonomic space) between CAB and CAR compared to

LVET. Thus, the current investigation evaluates the impact of chronotropic (LVET) verses inotropic (PEP) measures in both the calculation and validity of impedance derived measures of CAB and CAR.

A secondary and exploratory purpose of this investigation will also be to examine the association between all calculations of CAB/CAR and difficulties in emotion regulation (as measured by the Difficulties in Emotion Regulation Scale; Gratz & Roemer, 2004) to verify the relationship between cardiac autonomic activity and the self-regulation of emotion. We hypothesize that there will be a negative association between CAB/CAR and total DERS scores, such that lower CAB/CAR (greater autonomic imbalance) will be associated with higher total DERS scores (greater difficulties in emotion regulation).

METHODS

Participants and Procedures

Participants were recruited via two methods: (a) an introductory level psychology course research pool, where students earned class credit for participating; and (b) outside of the research pool, with these individuals being compensated with cash. Data were pooled over three studies (N= 158, 107 females, 57 minorities, Mage = 19.09, SD = 1.84, age range: 18-30). All participants were apparently healthy and did not readily present any mental or physical disorders.

We asked all participants not to smoke, undergo vigorous physical activity, or drink caffeine or alcohol in the six hours prior to the experiment. The methods of each study were approved by the institutional review board at The Ohio State University (IRB Protocol Number: 2012B0580) and followed the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist (Knottnerus & Tugwell, 2008). All participants gave written informed consent. All experimental sessions were conducted between 9am and 5pm. Prior to each session, participants were asked if they wanted to use the restroom and were given the opportunity to do so if necessary. In all studies, participants were placed in a soundproof experimental room that was held at room temperature (70 to 73 degrees Fahrenheit, or 21 to 23 degrees Celsius) and equipped with a camera and microphone for safety and instructional purposes as well as a high-definition TV (for stimuli presentation which did not occur in the present study). Participants were given a detailed explanation of the procedures that would take place without indicating the specific hypotheses underlying the study or the manipulations applied within the study design. Electrocardiogram (ECG) leads were attached to the subjects and while in a

separate control room, the experimenter led the subjects to the initial phases of the experiment. All participants first completed a 5-min baseline resting period, where participants, while spontaneously breathing, sat and viewed a blank, gray screen, and were instructed not to move or fall asleep while their cardiac activity was recorded via ECG. The data for the present study was derived from this baseline period.

Cardiovascular Measures

Cardiac data was recorded continuously throughout each experiment via a three-lead ECG with three additional leads for the ICG signal at a 1000 Hz sampling rate using a Mindware™ 2000D (MW2000D) Impedance Cardiograph package. Electrodes were placed on the clavicle (1), ribs (2), lower back (1), lower sternum (1), notch of the throat (1), and back of the neck (1). Successive R-spikes were obtained from ECG recordings to calculate baseline HR and variability in these R-spikes was employed to calculate baseline HRV. Participants' successive IBIs (in milliseconds) were extracted using Mindware™ HRV Analysis software. IBIs were written in a text file and analyzed using Kubios HRV analysis package 2.0 (Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karialainen, 2014), allowing for the calculation of time- and frequency-domain indices of resting HRV. Artifacts within the R-to-R series were visually detected, and we applied an artifact correction level that would differentiate and remove artifacts (differing abnormal IBIs from the mean IBI). The detrending of time- and frequency-domain HRV measures was accomplished via the smoothness priors approach (see Tarvainen et al., 2014, for review). The root mean square of successive differences (RMSSD), measured in milliseconds, was calculated and is considered to be a stable (Li et al., 2009) and valid (Thayer et al., 2010a), time-domain measure of HRV. Autoregressive estimates were also calculated, yielding high-frequency

power HRV (HF, 0.15– 0.4 Hz; Thayer et al., 2010a). Using Mindware™ Impedance Cardiography Analysis software, mean PEPs and LVETs were also calculated (in milliseconds) in accordance with previously published guidelines (Sherwood et al., 1990).

As previously stated, CAB can be defined as a relative balance between parasympathetic and sympathetic activity. Therefore, it is calculated by subtracting the HRV measure for parasympathetic activity from the impedance measure for sympathetic activity, resulting in the relative difference in control between the two branches (Berntson et al., 2008). Conversely, CAR is defined as the total activity of both branches of the autonomic nervous system. Therefore, it is calculated by adding the HRV measure for sympathetic activity to the HRV measure for parasympathetic activity, resulting in a measure of total autonomic control (Berntson et al., 2008). Berntson and colleagues' (2008) original formulas expressed the dynamics between the PNS and SNS as $CAB = HFz - (-PEPz)$ and $CAR = HFz + (-PEPz)$, which employ a chronotropic frequency-domain measure of parasympathetic activity (HF) and an inotropic impedance-derived measure of sympathetic activity (PEP). However, other research has identified RMSSD as an equally reliable time-domain measure of parasympathetic activity compared to HF (Balocchi et al., 2006; Hill, Siebenbrock, Sollers, & Thayer, 2009; Penttilä et al., 2001; Sollers, Buchanan, Mowrer, Hill, & Thayer, 2007; Williams et al., 2017), while LVET has long been established as an impedance-derived index of SNS activity (Stemmler, 1993; Thayer & Uijtdehaage, 2001). Based on this information, the current conceptualizations of both CAB and CAR use either HF or RMSSD to reflect parasympathetic activity, and either PEP or LVET to reflect sympathetic activity. CAB and CAR were first calculated using the original parasympathetic measure from the Berntson et al. (2008) study, yielding four formulas for CAB and CAR that can be expressed as

CAB_H_PEP = HFz – (-PEPz), *CAR_H_PEP = (HFz) + (-PEPz)*, *CAB_H_LVET = HFz – (-LVETz)*, and *CAR_H_LVET = (HFz) + (-LVETz)*. CAB and CAR were then calculated using a time-domain measure of HRV to reflect parasympathetic activity, yielding four additional formulas that can be expressed as *CAB_R_PEP = RMSSDz – (-PEPz)*, *CAR_R_PEP = (RMSSDz) + (-PEPz)*, *CAB_R_LVET = RMSSDz – (-LVETz)*, and *CAR_R_LVET = (RMSSDz) + (-LVETz)*. In all calculations, z-scores are computed for the parasympathetic and sympathetic measures to account for disparities in their means and units of measurement, while the sympathetic measure is multiplied by -1 to reflect the fact that smaller values are indicative of greater sympathetic activity.

Psychological Measures

Difficulties in Emotion Regulation. Difficulties in emotion regulation were assessed using the Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004), which is comprised of 36 items and six subscales: (a) *Non-acceptance of emotional responses*, (b) *Difficulties engaging in goal-oriented behavior when experiencing negative emotions*, (c) *Difficulties in controlling impulsive behavior when experiencing negative emotions*, (d) *Lack of emotional awareness*, (e) *Lack of strategies to regulate emotions*, and (e) *Lack of emotional clarity.* An example item is "*I experience my emotions as overwhelming and out of control.*" Responses are scaled from 1 (*almost never*) to 5 (*almost always*), with a maximum score of 180.

Statistical Analyses

All statistical tests were conducted using SPSS (ver. 27, IBM Chicago, IL, USA). Zero-order correlations were performed between variables of interest including z-scored variables used to calculate CAB and CAR, as well as log-transformed variables used to

calculate CAB and CAR. Associations between total DERS scores and all calculated measures of CAB and CAR were also examined. Confidence intervals (95%) were obtained for all correlation coefficients and are reported in brackets. Fisher's z-to-r transformation was used to test differences between correlation coefficients. Statistics reported include Pearson's r correlation values, 95% confidence intervals (in square brackets), and *p* values.

Hierarchical regression analyses were also conducted to see whether CAR predicted CAB differentially based on calculations of the measures. Step one included covariates that were sex, age, body mass index, and ethnicity. An individual's ethnicity can determine relative levels of resting HRV (Choi et al., 2006; Hill et al., 2015) and thus, was included as a covariate in applicable analyses (ethnicity coded as 0 = European American, 1 = Other). It is well-known that resting HRV decreases with age (e.g., Choi et al., 2006; Voss, Schroeder, Heitmann, Peters, & Perz, 2015), therefore age was also included as a covariate. Body mass index was also included as previous research has shown that higher body mass index is associated with decreased resting HRV (e.g., Koenig et al., 2014; Molfino et al., 2009). Step two included respiration rate (high frequency Hz; Thayer et al., 2010a). CAR calculated from either PEP (Model 1) or LVET (Model 2) were variables in their respective third step. Statistics reported include, change in R^2 (ΔR^2), unstandardized beta (*b*) coefficients, standard errors (SE), 95% confidence intervals (in square brackets), partial correlation coefficients, and *p* values.

RESULTS

Descriptive Statistics

Extreme outliers (± 2SD) were removed, leaving a total sample of 158 participants (107 females, 57 minorities, $M_{age} = 19.09$, $SD_{age} = 1.84$, $M_{BMI} = 22.96$, $SD_{BMI} = 3.77$). Averages of raw scores for PEP ($M = 118.20$, $SD = 10.71$), LVET ($M = 241.92$, $SD = 36.58$), log-transformed HF ($M = 6.65$, $SD = 0.93$), and log-transformed RMSSD ($M = 3.73$, $SD = 0.45$), were obtained. We also reported averages for variables calculated using HF, which included CAB_H_PEP ($M = 0.02$, $SD = 1.04$), CAR_H_PEP ($M = -0.13$, $SD = 1.02$), CAB_H_LVET ($M = 0.08$, $SD = 1.20$), and CAR_H_LVET ($M = -0.19$, $SD = 1.19$), as well as variables calculated using RMSSD, which included CAB_R_PEP ($M = -0.06$, $SD = 0.92$), CAR_R_PEP ($M = -0.20$, $SD = 0.86$), CAB_R_LVET ($M = 0.00$, $SD = 1.07$), and CAR_R_LVET ($M = -0.26$, $SD = 1.08$). Please see Table 1 for descriptive statistics.

Zero-Order Correlations

Zero-order correlational analyses were conducted (see Tables 2 and 3) and plotted (see Figures 1-4) for measures of HRV, impedance, CAB, and CAR. Results showed that there was a moderate, significant correlation between HFz and RMSSDz ($r = 0.44$, CI [0.31, 0.56], $p < .001$). Importantly, there was a significant strong correlation between *ln*HF and *ln*RMSSD ($r = 0.90$, CI [0.87, 0.93], $p < .001$). Results also showed a significant positive association between -PEPz and -LVETz ($r = 0.36$, CI [0.22, 0.49], $p < .001$).

Results showed that correlations between HFz and -PEPz ($r = -.03$, CI [-0.19, 0.13], $p = .73$) as well as -LVETz ($r = -.01$, CI [-0.17, 0.15], $p = .90$) were not statistically significant. Additionally, correlations between RMSSDz and -PEPz ($r = -.09$, CI [-0.24, 0.07], $p = .28$) as well as -LVETz ($r = .01$, CI [-0.15, 0.17], $p = .91$) were also not significant.

Results revealed that there was a significant relationship between CAR_PEP and CAB_PEP calculated using both HF ($r = 0.69$, CI [0.60, 0.76], $p < .001$) and RMSSD ($r = 0.59$, CI [0.48, 0.68], $p < .001$). There was a significant correlation between CAB_LVET and CAR_LVET calculated using HF ($r = 0.26$, CI [0.11, 0.40], $p < .001$) but not RMSSD ($r = 0.08$, CI [-0.08, 0.23], $p = .28$). The correlation coefficient between CAB_PEP and CAR_PEP was significantly stronger compared to the correlation found between CAB_LVET and CAR_LVET for both HF ($z = 5.12$, $p < .001$) and RMSSD ($z = 5.26$, $p < .001$).

Zero-order correlations were also conducted to examine the relationship between emotion regulation difficulties and the various calculations of CAB and CAR (see Table 4). Results revealed significant, negative correlations between CAB_R_PEP and DERS ($r = -0.19$, CI [-0.35, -0.03], $p = .02$), CAR_R_PEP and DERS ($r = -0.27$, CI [-0.42, -0.12], $p < .01$), CAB_R_LVET and DERS ($r = -0.16$, CI [-0.32, -.002], $p = .05$), and CAR_R_LVET and DERS ($r = -0.21$, CI [-.37, -.06], $p < .01$). When examining the associations between total DERS scores and CAB/CAR values calculated using HF, results revealed negative, but non-significant correlations between CAB_H_PEP and DERS ($r = -0.02$, CI [-0.18, .14], $p = .82$), CAR_H_PEP and DERS ($r = -0.08$, CI [-0.24, 0.08], $p = .33$), CAB_H_LVET and DERS ($r = -0.02$, CI [-0.18, 0.14], $p = .84$), and CAR_H_LVET and DERS ($r = -0.07$, CI [-0.22, .09], $p = .42$).

Regression Analyses

Cardiac Autonomic Balance and Regulation Calculated using HF

Regression analyses (see Table 5) revealed that CAR_PEP significantly predicted 49.9% of the variance in CAB_PEP ($\Delta R^2 = 0.40$, $b = 0.69$, $SE = 0.06$, $r_{partial} = .67$, CI [0.56, 0.81], $p < .001$). In contrast, CAR_LVET significantly predicted 13.0% of the variance in CAB_LVET ($\Delta R^2 = 0.04$, $b = 0.22$, $SE = 0.08$, $r_{partial} = .22$, CI [0.06, 0.38], $p = .01$). The association between

CAR_PEP and CAB_PEP ($r_{partial} = .67$) was significantly stronger ($z = 5.17$, $p < .001$) compared to the association between CAR_LVET and CAB_LVET ($r_{partial} = .22$).

Cardiac Autonomic Balance and Regulation Calculated using RMSSD

For CAR and CAB computed using RMSSD (see Table 6), results showed that CAR_PEP significantly predicted 37.4% of the variance in CAB_PEP ($\Delta R^2 = 0.34$, $b = 0.63$, $SE = 0.07$, $r_{partial} = .59$, CI [0.49, 0.77], $p < .001$). In contrast, CAR_LVET did not significantly predict CAB_LVET ($\Delta R^2 = 0.01$, $b = 0.09$, $SE = 0.08$, $r_{partial} = .10$, CI [-0.06, 0.25], $p = .24$) and only explained 5.5% of the variance in CAB_LVET. The association between CAR_PEP and CAB_PEP ($r_{partial} = .59$) was significantly stronger ($z = 5.08$, $p < .001$) compared to the association between CAR_LVET and CAB_LVET ($r_{partial} = .10$).

DISCUSSION

The purpose of the current investigation was to evaluate PEP and LVET in the calculation of CAB and CAR to determine which systolic time interval provided CAB and CAR with optimal autonomic space. Our results showed the association between z-transformed HRV (HF and RMSSD) and both PEP and LVET to be near zero, however, HRV and LVET appear to show better space given the spread of data points. Importantly, there was a stronger association between CAB and CAR when calculated using PEP compared to LVET, which show little (calculated using HF) to no (calculated using RMSSD) association between CAB and CAR. In other words, when calculated using PEP, individuals higher in CAB are more likely to be higher in CAR. In contrast, when these measures are calculated using LVET, the association between CAB and CAR is significantly lower, and when calculated using RMSSD, the association is negligible. Taken together, these data suggest that LVET provides better autonomic space compared to PEP when paired with HRV in the calculation of CAB and CAR. Furthermore, we highlight that the association between CAB and CAR computed using RMSSD and LVET was not significant. This may further suggest RMSSD as a better measure for the calculation of CAB and CAR. Lastly, our exploratory analyses revealed that CAB and CAR measures calculated using RMSSD are significantly associated with emotion regulation difficulties, but that CAB and CAR measures calculated using HF were not. More interestingly, CAB and CAR measures derived using PEP yielded stronger associations with emotion regulation difficulties compared to CAB and CAR measures derived using LVET. However, Fisher z tests conducted in post hoc analyses revealed that the differences in these correlations were not significant. Therefore, further research is needed to examine whether these differences are practically meaningful.

CAB and CAR are designed to capture opposing modes of autonomic activity, with CAB reflecting a propensity toward the dominance of either the parasympathetic or sympathetic nervous system, and CAR reflecting the co-activation or co-inhibition of both branches. With this in mind, our findings may suggest that CAR and CAB calculated using PEP may not sufficiently reflect these functional differences, as indicated by their strong agreement. Given that the associations seen between PEP-derived CAR and CAB remain strong regardless of which chronotropic HRV measure is used in their calculations, it is likely these associations are the result of PEP failing to provide adequate coverage of autonomic space. One potential reason behind this is that, as previously mentioned, PEP represents an inotropic measure of sympathetic activity, influencing myocardial contractility at the atrioventricular (AV) node of the heart. In contrast, LVET shares a functional foundation with chronotropic measures HF and RMSSD (Stemmler, 1993). When CAB and CAR are calculated using LVET we see that the two measures are in little-to-no association; especially when they are calculated using RMSSD. This suggests that while there may be circumstances under which CAB and CAR may be significantly associated when calculated using LVET (i.e., using HF), it is significantly weaker compared to using PEP, and not significant when calculated using RMSSD. Overall, these results suggest that LVET-derived CAB and CAR represent more distinct patterns of autonomic activity due to LVET providing better autonomic space compared to PEP. Furthermore, these results also suggest that chronotropic time-domain measures of HRV (i.e., RMSSD) and impedance cardiography may be superior indices of parasympathetic and sympathetic activity when calculating CAB and CAR. A potential reason for this pattern may be due to time-domain HRV measures

(especially RMSSD) being more resistant to violations of stationarity compared to frequency domain measures (Tarvainen, Ranta-Aho, & Karjalainen, 2002).

Our finding that greater autonomic imbalance, as indicated by lower CAB values, was associated with greater difficulties in emotion regulation, as indicated by higher DERS total scores, was not surprising given past evidence suggesting that lower HRV (which is typically characteristic of autonomic imbalance) is associated with poorer emotion regulation abilities (Visted et al. 2017; Williams et al., 2015) and the use of maladaptive emotion regulation strategies such as rumination (Cropley et al., 2017; Williams et al., 2017). Research that explicitly examines how CAB and/or CAR relate to affective states and emotion regulation is extremely limited, with only one study implicating CAR in the relationship between goal attainment and emotional responding (Kreibig et al., 2012). Furthermore, there is little to no research exploring the significance of CAR as it relates to psychological factors and processes, and given that this measure reflects total autonomic activity, it is difficult to interpret our finding of higher CAR also being related to greater difficulties in emotion regulation.

Implications

The psychophysiological connection between the autonomic nervous and cardiovascular systems continues to be at the forefront of health research. An imbalance or dysregulation of this relationship is of particular interest, given its association with stress (Wulsin, Herman, & Thayer, 2018), psychopathologies (Thayer & Brosschot, 2005), difficulties in emotion regulation (Williams et al., 2015), cardiovascular disease risk factors (Thayer et al., 2010b), and all-cause mortality (Thayer & Sternberg, 2006). As such, special

attention should be given to the methods and formulas designed to quantify this relationship, especially in regards to the balance and regulation of the parasympathetic and sympathetic branches of the autonomic nervous system. The development of CAB and CAR has proven to be a vital step toward the conceptualization of cardiac autonomic activity, with both serving as valid and reliable indices of the dynamic between the two branches of the autonomic nervous system in several studies examining mental (Kreibig et al., 2012; Bylsma et al., 2015; Gump et al., 2011) and physical (Singh et al., 2009; Berntson et al., 2008; Vrijkotte et al., 2015) health. However, our data suggests that the calculation of these measures can be adjusted to build upon their efficacy as markers of psychophysiological health. Additionally, with research showing that the health-related significance of various states of cardiac autonomic control of the heart can vary across different psychological stressors and pharmacological blockades (Carlsson, Dahlöf, Hedberg, Persson, & Tångstrand, 1977; Stemmler, 1993; Berntson et al., 1994b), calculating CAB and CAR using cardiac autonomic measures with a shared functional foundation may be especially important in accurately classifying individuals and their respective cardiovascular states.

From a methodological perspective, calculating CAB and CAR using LVET may be beneficial for increasing their precision in predicting cardiovascular functioning. As previously mentioned, both parasympathetic and sympathetic influences can have differential effects on the heart depending on the effector tissue involved; even when both systems are active. For example, autonomic influences involved in the control of heart rate at the SA node (i.e., chronotropy) tend to be dependent on the level of background sympathetic nervous system activity, with higher levels of sympathetic activation resulting in greater decreases in heart rate associated with a given PNS stimulus (a phenomenon

known as accentuated antagonism; Levy & Zeiske, 1969). Similarly, autonomic influences involved in cardiac contractility at the AV node (i.e., inotropy) are also dependent on the level of background sympathetic activity. While parasympathetic influence over contractility is negligible with low or no sympathetic activation, increases in sympathetic activity result in marked, non-algebraically additive decreases in contractility (Levy, 1997). Whereas studies tend to calculate CAB and CAR using different chronotropic measures such as HF (Singh et al., 2009), RMSSD (Williams et al., 2017), and respiratory sinus arrythmia (Kreibig et al., 2012), these and other studies almost exclusively use the inotropic measure of PEP to index sympathetic activity as opposed to more appropriate chronotropic sympathetic measures like LVET. Our results suggest that CAB and CAR show dependency when calculated using PEP irrespective of the HRV index used. Of course, this should not be the case, given that these measures reflect different states of cardiovascular functioning, albeit through similar modes of autonomic activity (e.g., coactivation of the parasympathetic and sympathetic nervous systems). Therefore, it is possible that the results of studies that have used PEP-derived measures of CAB and CAR to capture autonomic activity may be limited in their accuracy or interpretation as they relate to cardiac autonomic activity, and our results suggest that using LVET in place of PEP may yield more appropriate results. Indeed, the association between CAB variables and CAR variables derived using different HRV measures and systolic time intervals show considerably high correlations (r's between .6 and .8), however these correlations are far from perfect as one might expect, and thus can have a considerable impact on both data and results.

Limitations & Future Directions

The current study is not without its limitations. The first limitation is that the sample largely consists of college students, and therefore the results may not be generalizable to all age groups. While we are confident that the present relationships seen between the various calculations of CAB and CAR would be present across all ages, future research should collect HRV and impedance data and conduct similar analyses to confirm this. To this end, when using consistent chronotropic measures to compute CAB and CAR in our young and healthy sample of individuals, true variation within autonomic space is revealed. In contrast, the Berntson et al. (2008) report showed similar variation using PEP and HF, however their sample of individuals were significantly older (ranging between 50 and 68 years) and some showed cardiovascular diseases (e.g., diabetes). Thus, it would be important to understand the differential impact of calculating CAB and CAR using LVET/PEP in both older and younger individuals, in addition in those who may show cardiovascular complications.

Additionally, although we did ask participants not to smoke in the hours prior to the study, we did not ask if they were regular smokers, which may or may not have had an influence on general cardiovascular and respiratory functioning in select individuals. In relation to respiratory functioning, another possible limitation is that we did not measure respiration via direct methods (e.g., using a transducer belt or counting thoracoabdominal movements) to ensure that participants had a breathing rate of at least nine respirations per minute, which could have influenced our current results. However, RMSSD has been shown to be resistant to respiratory influence following detrending and thus, results surrounding RMSSD are relatively free of respiratory influence (Laborde et al., 2017; Lewis et al., 2012). Lastly, our results may be limited by a lack of a pharmacological blockade to more accurately verify patterns of autonomic activity. However, as previously stated, sympathetic and

parasympathetic influences on the heart differ based on the effector tissue involved, even when both branches are active. Thus, introducing a blockade to either one of these influences may effectively eliminate an important piece of the physiological puzzle. Additionally, we are not proposing a new method of indexing autonomic activity, but rather offering a more precise method of calculating CAB and CAR, which has already been verified via blockade studies (Berntson et al., 1994a; Cacioppo et al., 1994).

Future research aiming to replicate our research should also attempt to record HRV and impedance data over different or extended time periods, such as comparing CAB and CAR measures during the day and at night. Lastly, it may be beneficial for future studies to examine sex differences in the various calculations of CAB and CAR, as our current sample is predominantly female, and a recent meta-analysis on sex differences in HRV determined that women have higher vagal tone compared to males (Koenig & Thayer, 2016). Moreover, a recent investigation found that the association between HRV and heart rate was not equal between women and men, suggesting a differential influence of autonomic activity on heart chronotropy based on sex (Williams et al., under review).

CONCLUSION

The accurate quantification of cardiac autonomic activity in humans is crucial for psychophysiological health and research, as autonomic imbalance and dysregulation is related to a host of negative health outcomes including cardiovascular disease and all-cause mortality. While the measures of cardiac autonomic balance (CAB) and regulation (CAR) have been developed as reliable indices of autonomic balance and control, they are traditionally derived from parasympathetic and sympathetic measures with differing functional foundations, with high-frequency heart rate variability (HF) serving as a chronotropic measure of cardiac influence and pre-ejection period (PEP) serving as an inotropic measure of cardiac influence. Given that chronotropic measures reflect the control of heart rate and inotropic reflect myocardial contractility, the current calculations of CAB and CAR may be limited in their efficacy as biomarkers of health.

Therefore, we calculated CAB and CAR using two different systolic time intervals, PEP and left ventricular ejection time (LVET; a chronotropic sympathetic nervous system measure), to determine which index of sympathetic activity more accurately delineates the differences between CAB and CAR (e.g., provides better autonomic "space"). Our data showed that measures of CAR calculated from PEP significantly correlate with and predict measures of CAB calculated using PEP. Conversely, computed using LVET, CAR shows a significantly weaker association using HF and no association using RMSSD. The current study provides evidence suggesting that the chronotropic systolic time interval LVET provides better autonomic space compared to the inotropic measure PEP, making it the superior index of sympathetic activity in the calculation of CAB and CAR.

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Table 1. Descriptive Statistics of Variables of Interest

	M	*SD*	*Range (min, max)*
Age	19.09	1.84	18.00, 30.00
BMI	22.96	3.77	14.98, 35.29
Respiration Rate	0.25	0.06	0.15, 0.38
RMSSD	45.90	19.12	9.90, 102.47
HF	36.61	19.08	2.13, 87.74
PEP	118.20	10.71	90.00, 140.00
LVET	241.92	36.58	128.00, 326.00
DERS Total	82.18	19.37	45.00, 146.00
*ln*RMSSD	3.73	0.45	2.29, 4.63
*ln*HF	6.65	0.93	3.96, 8.87
*ln*PEP	4.77	0.09	4.50, 4.94
*ln*LVET	5.48	0.16	4.85, 5.79
*z*RMSSD	-0.13	0.79	-1.63, 2.22
*z*HF	-0.05	0.95	-1.77, 2.49
-*z*PEP	-0.07	0.40	-0.89, 0.99
-*z*LVET	-0.13	0.73	-1.81, 2.14
CAB_HF_PEP	0.02	1.04	-2.44, 2.78
CAR_HF_PEP	-0.13	1.02	-2.46, 2.30
CAB_HF_LVET	0.08	1.20	-2.25, 3.17
CAR_HF_LVET	-0.19	1.19	-2.62, 2.85
CAB_RMSSD_PEP	-0.06	0.92	-2.25, 2.51
CAR_RMSSD_PEP	-0.20	0.86	-2.14, 2.04
CAB_RMSSD_LVET	0.00	1.07	-2.83, 2.90
CAR_RMSSD_LVET	-0.26	1.08	-2.10, 2.80

Note: The table above includes means (M), standard deviations (SD), and the range (minimum, maximum) for raw scores of root mean square of successive differences (RMSSD), high frequency heart rate variability (HF), pre-ejection period (PEP), left ventricular ejection time (LVET), total score on the Difficulties in Emotion Regulation Scale (DERS Total), and log-transformed scores of RMSSD, HF, PEP, LVET, z-scored RMSSD, HF, PEP, LVET. It also includes M, SD and ranges for cardiac autonomic balance (CAB) calculated using HF, RMSSD, PEP, and LVET as well as cardiac autonomic regulation (CAR) using those same variables. *ln* = natural log-transformed; z = z-scored variable; -z = inverse of z-scored variable

Table 2. Zero-Order Correlations Among Variables Used to Calculate Cardiac Autonomic Balance and Cardiac Autonomic Regulation

	1	2	3	4
1. RMSSD*z*	--			
2. HF*z*	**.44****	--		
3. -PEP*z*	-.09	-.03	--	
4. -LVET*z*	.01	-.01	**.36****	--

Note: Zero-order correlations between root mean square of successive differences (RMSSD), high frequency heart rate variability (HF), pre-ejection period (PEP), and left ventricular ejection time (LVET). These variables were used to calculate cardiac autonomic balance and cardiac autonomic regulation variables. Significant correlations are bolded; z = z-scored variable, -z = inverse of z-scored variable, **p < .01.

Table 3. Zero-Order Correlations Among CAB and CAR Variables

Table 3A	1	2	3	4
1. CAB_H_PEP	--			
2. CAR_H_PEP	**.69****	--		
3. CAB_H_LVET	**.82****	**.64****	--	
4. CAR_H_LVET	**.64****	**.81****	**.26****	--

Table 3B	1	2	3	4
1. CAB_R_PEP	--			
2. CAR_R_PEP	**.59****	--		
3. CAB_R_LVET	**.77****	**.53****	--	
4. CAR_R_LVET	**.56****	**.77****	.09	--

Note: Table 3A shows zero-order correlations between cardiac autonomic balance (CAB) and cardiac autonomic regulation (CAR) variables that were calculated using high frequency heart rate variability (denoted as "H") and pre-ejection period (PEP) or left ventricular ejection time (LVET), respectively. Table 3B shows CAB and CAR calculated using the root mean square of successive differences (denoted as "R") and pre-ejection period (PEP) or left ventricular ejection time (LVET), respectively. Statistically significant correlations are bolded, **p < .01.

Table 4. Zero-Order Correlations Among Variables Used to Calculate Cardiac Autonomic Balance/Regulation and Total Difficulties in Emotion Regulation Score

	1	2	3	4	5	6	7	8	9
1. CAB_H_PEP	--								
2. CAR_H_PEP	.72**	--							
3. CAB_H_LVET	.82**	.66**	--						
4. CAR_H_LVET	.66**	.81**	.26**	--					
5. CAB_R_PEP	.58**	.21**	.41**	.26**	--				
6. CAR_R_PEP	.26**	.54**	.23**	.46**	.62**	--			
7. CAB_R_LVET	.45**	.22**	.69**	-.12	.76**	.53**	--		
8. CAR_R_LVET	.25**	.38**	-.15	.69**	.57**	.77**	.07	--	
9. DERS Total	-.02	-.08	-.02	-.07	**-.19***	**-.27****	**-.16***	**-.21****	--

Note: Zero-order correlations between cardiac autonomic balance (CAB) and regulation (CAR) calculated using root mean square of successive differences (R), high frequency heart rate variability (H), pre-ejection period (PEP), and left ventricular ejection time (LVET), and the total score on the Difficulties in Emotion Regulation Scale (DERS). Relevant significant correlations are bolded; *p < .05, **p<.01.

Table 5. Hierarchical Regression Analyses Calculated from HF, PEP, LVET

	Cardiac Autonomic Balance (PEP)						Cardiac Autonomic Balance (LVET)					
Predictor Step	***ΔR²***	***b***	***SE***	***p***	**95%CI**	$r_{partial}$	***ΔR²***	***b***	***SE***	***p***	**95%CI**	$r_{partial}$
R^2		0.50**						0.13**				
Sex					[-0.28,						[-0.19,	
		-0.02	0.13	0.89	0.25]	-.01		0.21	0.20	0.30	0.61]	.09
Age					[-0.06,						[-0.09,	
		0.00	0.03	0.93	0.07]	.01		0.01	0.05	0.91	0.11]	.01
BMI					[-0.05,						[-0.07,	
		-0.02	0.02	0.35	0.02]	-.08		-0.01	0.03	0.57	0.04]	-.05
Race					[-0.19,						[-0.29,	
		0.06	0.13	0.62	0.32]	.04		0.09	0.20	0.63	0.48]	.04
Respiration					[-0.04,							
Rate		1.90	0.98	0.06	3.85]	.16		4.23**	1.48	0.01	[1.30, 7.16]	.23
CAR_HF_PEP	0.40**	0.69**	0.06	<.001	[0.56, 0.81]	.67		--	--	--	--	--
CAR_HF_LVET		--	--	--	--	--	0.04**	0.22**	0.08	.01	[0.06, 0.38]	.22

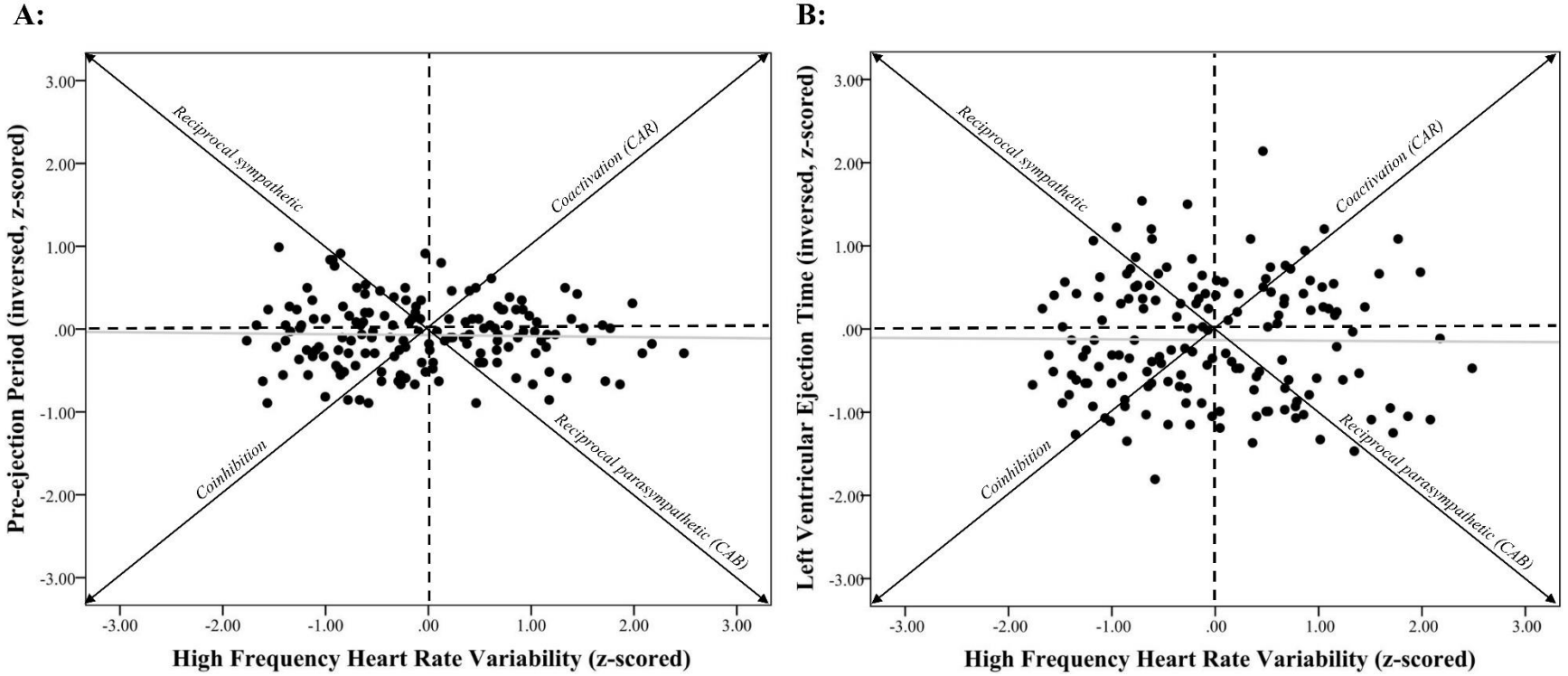
Note: The table above shows the unstandardized beta coefficients (b) with associated significant levels at each step in the regression model. Regression analyses (left) of cardiac autonomic regulation (CAR) calculated from pre-ejection period (PEP) and high frequency heart rate variability (HF) predicting cardiac autonomic balance (CAB) calculated from PEP and HF. Regression analyses (right) of CAR calculated from left ventricular ejection time (LVET) and HF predicting CAB calculated from LVET and HF, **p < .01.

Table 6. Hierarchical Regression Analyses Calculated from RMSSD, PEP, LVET

	Cardiac Autonomic Balance (PEP)						Cardiac Autonomic Balance (LVET)					
Predictor Step	ΔR^2	***b***	***SE***	***p***	**95%CI**	$r_{partial}$	ΔR^2	***b***	***SE***	***p***	**95%CI**	$r_{partial}$
R^2		0.37**						0.0				
Sex		-0.16	0.13	0.22	[-0.42, 0.10]	-.10		-0.15	0.19	0.43	[-0.52, 0.22]	-.06
Age		-0.01	0.03	0.75	[-0.08, 0.06]	-.03		-0.03	0.05	0.57	[-0.12, 0.07]	-.05
BMI		-0.03	0.02	0.10	[-0.06, 0.01]	-.14		-0.04	0.02	0.08	[-0.09, 0.00]	-.14
Race		0.01	0.13	0.91	[-0.23, 0.26]	.01		-0.02	0.18	0.91	[-0.38, 0.34]	-.01
Respiration Rate		1.31	0.96	0.17	[-0.59, 3.21]	.11		2.63	1.37	0.06	[-0.08, 5.34]	.15
CAR_R_PEP	0.34**	0.63**	0.07	<.001	[0.49, 0.77]	.59		--	--	--	--	--
CAR_R_LVET		--	--	--	--	--	0.01	0.09	0.08	.24	[-0.06, 0.25]	.10

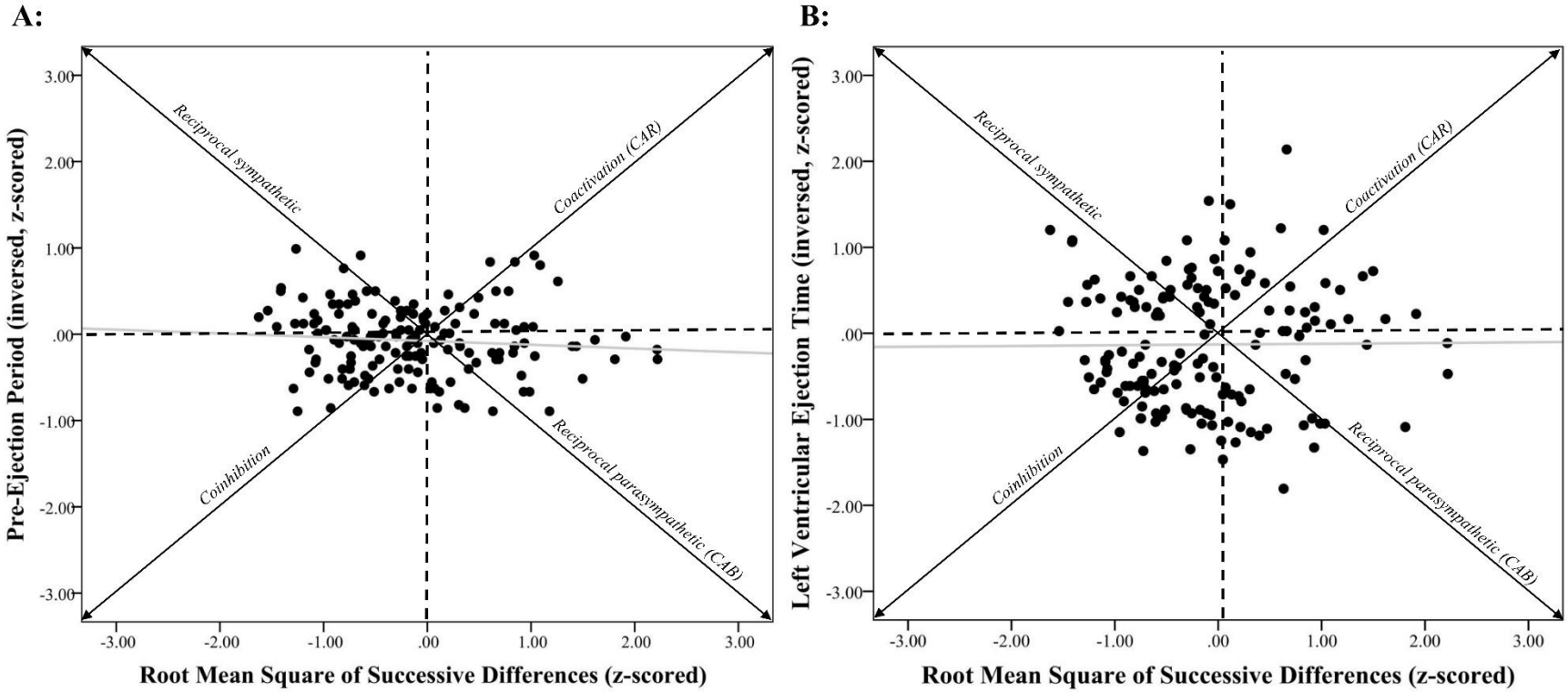
Note: The table above shows the unstandardized beta coefficients (b) with associated significant levels at each step in the regression model. Regression analyses (left) of cardiac autonomic regulation (CAR) calculated from pre-ejection period (PEP) and root mean square of successive differences (RMSSD; denoted as "R") predicting cardiac autonomic balance (CAB) calculated from PEP and RMSSD. Regression analyses (right) of CAR calculated from left ventricular ejection time (LVET) and RMSSD predicting CAB calculated from LVET and RMSSD, **p < .01.

Figure 1. Systolic time intervals and high frequency heart rate variability scatterplots



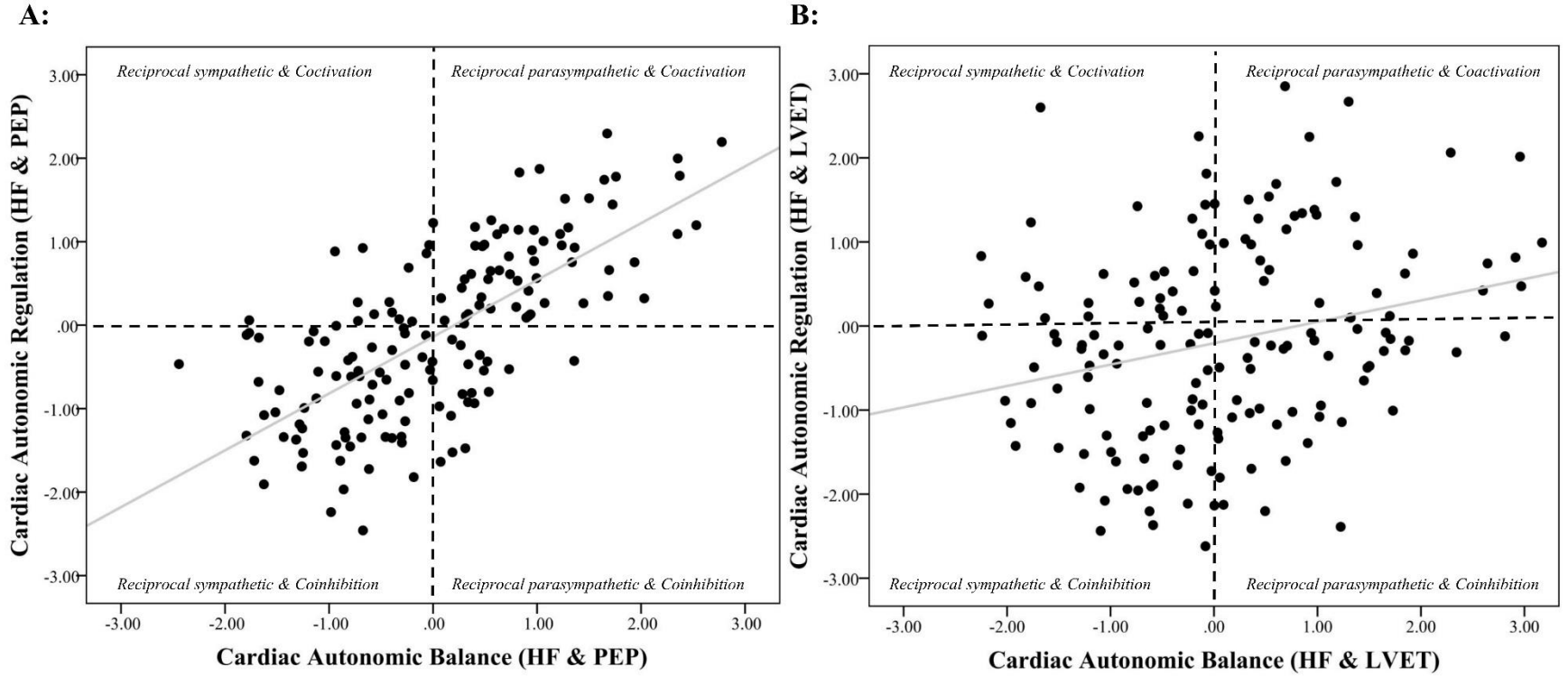
Note. **Figure 1A** shows a scatterplot between pre-ejection periods (PEP z-scored and inversed, *see* Methods and Materials for details) and high frequency heart rate variability (HF-HRV z-scored) (r = -.03, p = .73). **Figure 1B** shows a scatterplot between left ventricular ejection time (LVET inversed and z-scored) and HF-HRV (r = -.01, p = .90). Individuals in the coinhibition quadrant would show lower CAR scores, while individuals in the coactivation quadrant would show higher CAR scores. Individuals in the reciprocal sympathetic quadrant would show lower CAB scores, while individuals in the reciprocal parasympathetic quadrant would show higher CAB scores.

Figure 2. Systolic time intervals and root mean square of successive differences scatterplots



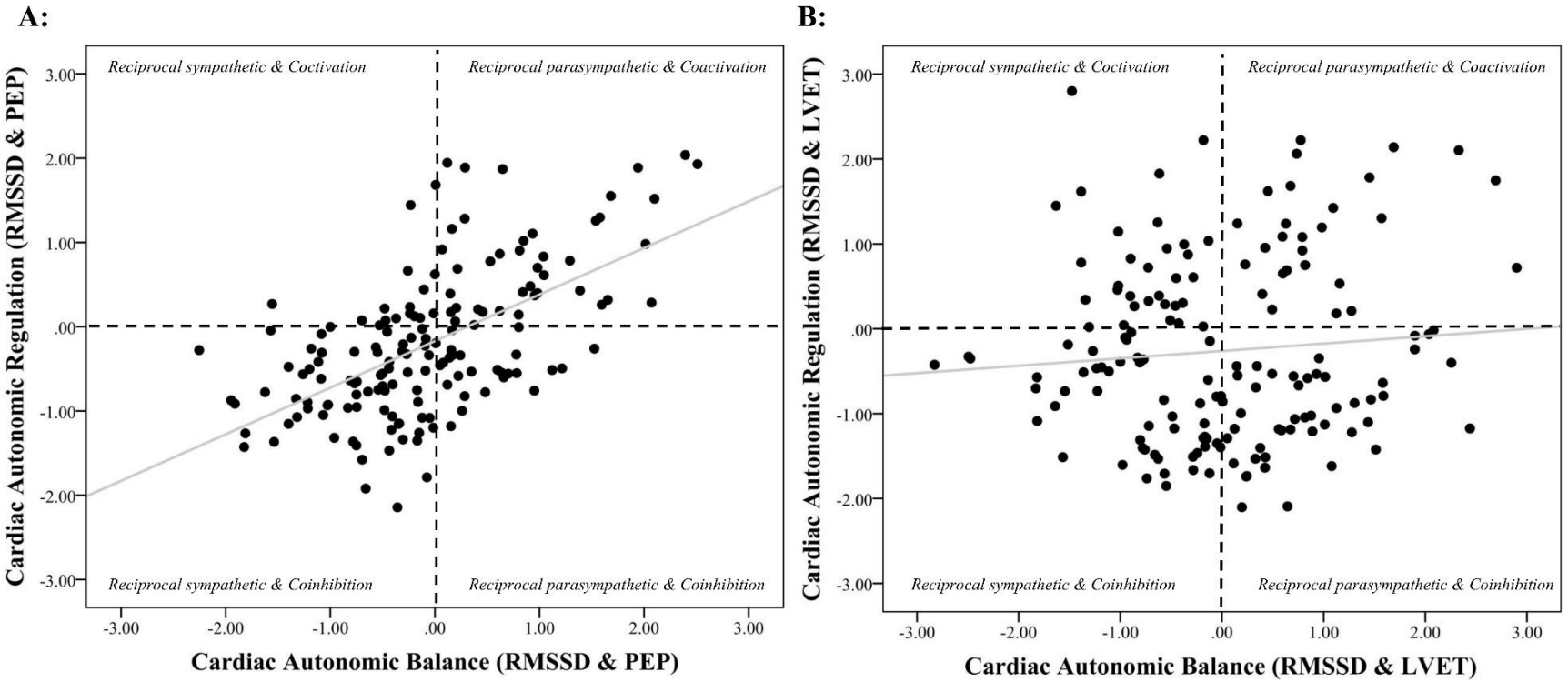
Note. **Figure 2A** shows a scatterplot between pre-ejection periods (PEP z-scored and inversed, *see* Methods and Materials for details) and root mean square of successive differences (RMSSD, z-scored) (r = -.09, p = .28). **Figure 2B** shows a scatterplot between left ventricular ejection time (LVET inversed and z-scored) and RMSSD (r = .01, p = .91). Individuals in the coinhibition quadrant would show lower CAR scores, while individuals in the coactivation quadrant would show higher CAR scores. Individuals in the reciprocal sympathetic quadrant would show lower CAB scores, while individuals in the reciprocal parasympathetic quadrant would show higher CAB scores.

Figure 3. Scatterplots of cardiac autonomic balance and regulation computed using HF-HRV and both PEP and LVET



Note. **Figure 3A** depicts the strong significant association between cardiac autonomic balance (CAB) and regulation (CAR) calculated using high frequency heart rate variability (HF) and pre-ejection periods (PEP) (r = .69, p < .001). **Figure 3B** depicts a significantly weaker association between CAB and CAR calculated using left ventricular ejection time (LVET) (r = .26, p < .001). The correlation coefficient between CAR and CAB computed using PEP was significantly stronger than when computed using LVET (z = 5.12, p < .001).

Figure 4. Scatterplots of cardiac autonomic balance and regulation computed using RMSSD and both PEP and LVET



Note. **Figure 4A** depicts the strong significant association between cardiac autonomic balance (CAB) and regulation (CAR) calculated using high frequency heart rate variability (HF) and pre-ejection periods (PEP) (r = .59, p < .001). **Figure 4B** depicts the lack of an association between CAB and CAR calculated using left ventricular ejection time (LVET) (r = .08, p = .28). The correlation coefficient between CAR and CAB computed using PEP was significantly stronger than when computed using LVET (z = 5.26, p < .001).