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Autonomic cardiac control in depressed adolescents

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Abstract

Background—The aim of this study was to identify the aspects of cardiac physiology associated with depressive disorder early in life by examining measures of autonomic cardiac control in a community-based sample of depressed adolescents at an early phase of illness, and matched on a number of demographic factors with a non-depressed comparison group.

Methods—Participants were 127 adolescents (44 boys), ages 14–18, who formed two demographically matched groups of clinically depressed and non-depressed participants. Adolescents were excluded if they evidenced comorbid externalizing or substance-dependence disorders, were taking medications with known cardiac effects, or reported regular nicotine use. Resting measures of heart rate, respiratory sinus arrhythmia, skin conductance level, blood pressure, and pre-ejection period were collected.

Results—Depressed adolescents had resting heart rates significantly higher than those of healthy adolescents. No other measure of autonomic functioning differentiated the groups. Post-hoc analyses were conducted to examine the influence of illness chronicity, severity, comorbidity and sex on cardiac psychophysiology. These variables did not appear to exert a significant influence on the findings.

Conclusions—Our findings suggest that neither autonomic cardiac control, illness chronicity or severity, nor medication effects fully explain resting heart rate differences between depressed and non-depressed adolescents. Future research on depression and heart rate should consider mechanisms other than sympathetic or parasympathetic control as potential explanations of heart rate differences, including blood-clotting mechanisms, vascular and endothelial dysfunction of the coronary arteries, and inflammatory immune system response.

Keywords

Heart Rate; Autonomic Nervous System; Major Depressive Disorder; Cardiovascular Diseases

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Introduction

Depression is a strong independent predictor of coronary heart disease (CHD) [1]. Strikingly, the magnitude of the association has been found to be on par with that of known behavioral and biological risk factors such as smoking or high cholesterol [2]. Despite the clear associations between depressive and cardiac conditions, the mechanisms underlying the association are not yet well understood [3].

To date, most of the research on the association between depressive disorder and cardiac functioning has been conducted in adults, presumably because cardiac disease is typically of adult onset. However, depression is very frequently an adolescent-onset disorder [4]. The examination of cardiac functioning in depressed adolescents may be particularly beneficial in that, relative to adults, there is less heterogeneity with regard to disease and treatment history- factors which have been hypothesized to obscure previous research findings [5–6]. If cardiac irregularities known to predict subsequent cardiac disease are experienced disproportionately by depressed adolescents, then this knowledge would have significant public health implications. First, it would suggest that depressed youth may be a population at risk for subsequent cardiac disease and hence, an important population target for prevention efforts. This approach would build on preliminary evidence regarding the efficacy of preventive efforts aimed at unselected samples of children and adolescents as well as at those selected on the basis of biological risk factors [7–8]. Second, it would suggest that the examination of potential mechanisms to explain the comorbidity, including the identification of shared risk factors, should focus on those that are present early in the life span, well before cardiac illnesses typically emerge.

One plausible mechanism for the association between depression and CHD is dysregulation of the autonomic nervous system, characterized by greater sympathetic and/or weaker parasympathetic activity. Consistent with this model is evidence that depressed persons without known cardiac disease demonstrate higher resting heart rates than do non-depressed persons [5, 9–12]. Given that elevated heart rate is a predictor of subsequent cardiac events (e.g.,[13–14]), elevated heart rate in depressed persons may be relevant to understanding the association between cardiac and depressive disorders.

Heart rate, however, is a rather blunt index of autonomic activity as it is influenced by the heart's autonomous rate as well as by innervations from both the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Hence, increasing attention has been directed to comparing more specific indices of autonomic cardiac control in depressed patients. Most research has focused on respiratory sinus arrhythmia (RSA) as an index of vagal tone, and therefore of parasympathetic functioning [15–16]. Because vagal tone has been associated with a wide array of physical and mental health outcomes, including both cardiac disease and difficulties in emotion regulation [6], it has been considered a promising candidate for investigation.

Overall, this body of research has yielded mixed results. Some research has reported lower vagal tone in people suffering from Major Depressive Disorder [17], whereas other studies have failed to find such differences [5, 11, 18]. In a recent meta-analysis, Rottenberg [6] concluded that the association between depression and cardiac vagal control was modest, noting that heterogeneity in symptoms, comorbidity, and severity could obscure relationships.

A smaller body of research has examined indices of sympathetic activity. For example, plasma norepinephrine has been found to be elevated in patients with major depression, suggesting increased sympathetic tone [12]. Again, however, findings have not been

consistent. Studies examining other indices of sympathetic activation, such as systolic blood pressure, have not found between-group differences[5].

As suggested above, one notable limitation of the research to date has been the use of adult patient samples, especially inpatient samples, whose depressive conditions are likely of unusual severity and chronicity. Thus even in regard to the well-replicated effect of elevated heart rate, it is difficult to discern the extent to which the effect is inherent to depressive disorder versus a consequence of either lifestyle factors associated with chronic disorder or treatment effects [5]. Indeed, there are many potentially confounding variables affecting autonomic tone in studies of depressed adult patients. In particular, it appears that medication effects may account for observed associations between autonomic function and depression [11, 18–19], as controlling for antidepressant use appears to significantly attenuate associations especially as regards indices of heart rate variability. Notably, medicated depressed persons have been found to differ from both non-medicated depressed persons and non-depressed controls [11, 19].

To our knowledge, no studies have examined whether there are disturbances in cardiac physiology associated with depressive disorder during adolescence. However, a few studies have revealed associations between cardiac physiology and anxiety disorders and internalizing symptoms in children and adolescents [20–21]. For example, findings from a small sample of youth presenting for treatment of anxiety disorders indicated that they had higher heart rates and lower heart rate variability relative to nonanxious youth [22]. As well, self-reports of depressive symptoms in community samples of children have been associated with resting RSA [23], although this effect has not been obtained consistently [24], even with other autonomic measures such as heart rate variability and baroreflex sensitivity [25]. Though these findings suggest that aspects of cardiac physiology associated with internalizing symptoms and disorder are identifiable in youth, decades before the comorbidity between depression and cardiac illness or events would be evident, the associations have not been examined in samples of youth with case-level depressive disorder.

In this investigation, we examined aspects of cardiac physiology hypothesized to be associated with depressive disorder in a community-based sample of adolescents. We strove to provide a precise characterization of the nature of potential autonomic dysregulation by examining a wide range of measures, including those that provide presumptively pure indices of sympathetic and parasympathetic activation. In this way, we sought to both examine whether associations between cardiac functioning and depression were evident in youth, and to provide preliminary data regarding the extent to which one potential explanation for comorbidity, excessive sympathetic as compared to parasympathetic activation, might be responsible for these effects.

Materials and Methods

Participants

Participants were 127 adolescents (44 boys) between the ages of 14 and 18 participating in a larger study of emotion processes associated with unipolar depression. Adolescents had to meet research criteria for placement in one of two groups (Depressed, n = 54 or Healthy, n= 73). Depressed adolescents evidenced elevated scores on the Center for Epidemiological Studies-Depression Scale (CES-D, [26], ≥ 31 for males and ≥ 38 for females) during a school-based screening and subsequently met DSM IV [27] diagnostic criteria for a current unipolar depressive disorder during a diagnostic interview. Consistent with guidelines for establishing the offset of depressive episodes, a diagnosis was considered current if it was ongoing or had an offset within two months preceding the diagnostic interview [27]. Twelve

of the depressed adolescents had one or more comborbid psychiatric disorders, including four participants with comorbid anxiety disorders. Healthy adolescents scored below an adolescent-appropriate cut-off on the CES-D (< 21 for males and < 24 for females), had no current or lifetime history of psychopathology, and no history of mental health treatment.

Exclusion criteria—Adolescents were excluded if they evidenced comorbid externalizing disorders, were regularly taking medications with known cardiac effects (e.g., antidepressants, oral contraceptives, benzodiazepines), reported regular nicotine use, or reported marijuana use on the day of testing. Allowable medications were: asthma medication (6 participants), antibiotics (1 participant), acne medication (1 participant) and antihistamines (1 participant). Three potential participants whose physiological data were missing or unusable were also excluded. Demographic data are presented in Table 1.

Recruitment and Assessment Procedures

The research was approved by the Institutional Review Board of the Oregon Research Institute. Informed consent was obtained from the participants and guardians after each procedure was explained. Adolescents were recruited and selected using a two-gate procedure consisting of an in-school screening and an in-home diagnostic interview.

School Screening—Students (N=4182) from 10 area high schools participated in the school screening which was conducted during class time. Approximately 70% of eligible students participated, 12% declined or had parents who declined their participation and 18% were absent on the day of the assessment. Participating students completed the CES-D, a demographic information form, and a contact form.

Diagnostic Assessment—Interviewers conducted the Schedule of Affective Disorders and Schizophrenia-Children's Version (K-SADS,[28]) with adolescents who demonstrated elevated CES-D scores. Subsequent to the interviews, adolescents who met diagnostic criteria for a unipolar depressive disorder were invited to participate in a lab-based assessment. A healthy comparison participant, demographically matched to the depressed student, was recruited from the pool of students who scored within the normal range on the CES-D and invited to participate. Of adolescents invited to participate in the diagnostic assessment, approximately 26% declined or had parents decline their participation. Rates of decline did not vary as a function of pre-interview group status (i.e., elevated or healthy CES-D score), age, or race. Rates of decline were higher for males than females (31.6% vs. 23%), $\chi^2(1,n=498)=4.57$, $p<.05$.

Lab Assessment—Approximately 4% of adolescents and parents invited to participate in the lab assessment declined. The decline rate did not vary as a function of group status, age, race, or gender. The assessment consisted of a battery of questionnaire, family interaction, and interview tasks designed to obtain measures of emotional functioning, including indices of cardiac and respiratory physiology. Data for the current report were obtained during a three-minute quiet baseline, which occurred after the questionnaires and interviews and before the family interaction tasks. During the baseline assessment, participants were seated and instructed to remain still and quiet. Participants were asked to abstain from coffee, tea, alcohol, and illicit drugs for at least two hours before the assessment. Compliance with this instruction was confirmed on the day of the assessment via self report.

Measures

Depression Screener—The CES-D is a self-report measure of depressive symptomatology that has acceptable psychometric properties for use with adolescents

(e.g., [29–30]). It has a well-established record of use as a screener for depressive symptomatology in adolescent samples (e.g., [31–33]).

Diagnostic Interview—The K-SADS interview was conducted with the adolescents only to obtain current and lifetime diagnoses. Adolescent-only diagnostic interviews have been used successfully in past research [34–35]. Interviewers, who were bachelor and masters level research staff, participated in a rigorous training program and demonstrated agreement with a senior interviewer ($\kappa \geq .80$) on at least two interviews before conducting independent interviews. All interview-derived diagnoses were confirmed by supervisors who reviewed both item-endorsement and interviewers' notes. Reliability ratings were obtained on approximately 20% of the interviews, chosen at random. The average agreement was $\kappa =$. 94.

Brief Health Status Assessment—Height and weight measurements were completed by research staff at the time of the lab appointment[1]. Adolescents reported on their intake of caffeinated beverages, nicotine, medications, alcohol and illicit substances on the day of the assessment as well as of their average use of caffeinated beverages and nicotine during the last 12 months.

Physiological Measures and Procedures—All data were acquired using software and equipment from the James Long Company (www.jameslong.net) except where otherwise noted. Electrocardiograph (ECG), skin conductance, and respiratory signals were input to an isolated bioelectric amplifier custom built for research ("Bioamp"). Impedance cardiogram (ICG) signals were amplified and processed by a Hutchinson Impedance Cardiograph model HIC-2000 produced by Bio-Impedance Technology Inc. (Chapel Hill, NC, USA). Blood pressure was monitored via a Portapres portable continuous blood pressure monitor produced by Finapres Medical Systems (Amsterdam, The Netherlands).

The ECG and ICG signals were recorded using Ag-AgCl electrodes. To record the ECG signal, we used a three-lead system to maximize the r-wave amplitude and minimize movement artifact and t-wave amplitude. The ECG signals were amplified with the Bioamp, with a gain of 250 and bandpass of frequencies between 0.1 – 1000 Hz. ICG signals were produced using two current electrodes placed on the back at thoracic vertabra T9 and on the neck at cervical vertabra C4[25] through which a 2 mA RMS current was passed. The basal thorax impedance (Z_0) was measured (in ohms) by two electrodes placed between the current electrodes between the shoulder blades and in the mid back, and the rate of change in impedance waveform (dZ/dt) was calculated.

The Portapres blood pressure monitor measured systolic and diastolic blood pressures, and over time calculated the mean blood pressure (MBP) from the aggregate blood pressure waveform.

Respiration signal was detected by a pneumo-bellows chestband and recorded as input into the Bioamp. Skin conductance level (SCL) was measured with a 10mA constant AC current passed through two Ag-AgCl electrodes attached to the palmar surfaces of the medial phalanges of first and second fingers of the participant's left hand. The SCL signal was also amplified by the Bioamp.

[1]Data from 40 participants were collected before we began taking height and weight measurements. All participants provided self-reports of height and weight. Self- and lab-assessed height and weight were highly correlated for participants on which we had both (rs =.97 & .97). There were no differences between self-report and lab-assessed height. On average, self-reported weight was 2.75 and 6.5 lbs less than lab-assessed weight for boys and girls, respectively These amounts did not differ as a function of group. Hence, in participants missing lab-assessed data, we used self-reported height data and self-reported weight plus 2.75 or 6.5 lbs, for boys and girls, respectively

The ECGRWAVE program from the James Long Company identified r-waves from the ECG signal with an automated, multiple-pass, self-scaling algorithm. These signals were then visually inspected to see if the program identified the morphology of the r-wave correctly and manually corrected for missed or misrepresented r-waves. Sections of movement, noise artifact or flat line artifact were removed. Overall, this accounted for only 0.5% (in seconds) of the total data that had to be marked and removed as artifact. Other physiological data such as skin conductance, respiration, and blood pressure were visually inspected to ensure signal quality, and quantitative data were examined to ensure that values fell within a biologically plausible range (e.g., values of 0 in any signal were removed as artifact).

Respiratory sinus arrhythmia (RSA) reflects the variation in heart rate due to changes in respiration. We calculated a "time-domain" RSA variable by measuring the difference in milliseconds between the maximum inter-beat interval (IBI, or r-r interval) during expiration and the minimum IBI during inspiration (peak-to-trough method[2]). Because the RSA variable had a non-normal distribution, we transformed it to log(RSA). Log(RSA) has been used as a time-domain measure of respiratory sinus arrhythmia in previous research [5, 11].

Preejection period (PEP) estimates the period of time commencing with onset of ventricular depolarization as represented by the ECG Q wave and ending with the onset of left ventricular ejection as indicated by the B point of the dZ/dt signal [36]. The positions in time of the Q peak in the ECG and the B point in the dZ/dt signal were detected automatically and were subsequently checked visually and edited where the detection was incorrect.

We considered RSA to be a measure of vagal tone, and therefore of parasympathetic nervous system functioning. We used blood pressure, SCL, and PEP as indicators of sympathetic nervous system functioning [36].

Results

Preliminary Analyses

We conducted preliminary analyses to assess the equivalence of the depressed and healthy groups. Participants in the depressed and healthy groups were similar on demographic variables, with the exception of income, which was somewhat higher in families of healthy adolescents (see Table 1). They were also equivalent with regard to body mass index (BMI), and caffeine use (see Table 2). Finally, as assessments were done at all times of the day, and some autonomic processes can be more active in the morning [37], we conducted a Pearson Chi-Square test that showed no between group difference in the time of day that the laboratory protocol was conducted (see Table 2).

Between Group Differences in Cardiac Control

Between-group tests on measures of heart rate and autonomic nervous system activity are presented in Table 3. Consistent with hypotheses, depressed adolescents had resting heart rates significantly higher than those of healthy adolescents. Contrary to expectations, no other measure of autonomic functioning differentiated depressed from healthy adolescents.

[2]We used the peak-to-trough method (time-domain) of measuring RSA instead of the spectral analysis method (frequency-domain) because we only had time-domain RSA separately for each task. However, we also had a frequency-domain RSA value for the entire two-hour session. When we ran t-tests by diagnostic group to look for differences in frequency-domain RSA across the entire session, no group differences emerged [$t(127) = -0.513$, $p = 0.609$]. Therefore, the time-domain RSA reported for the quiet baseline would be similar to frequency-domain RSA for the quiet baseline.

Because as described earlier, clinical characteristics of disorder may influence findings [5], post-hoc analyses were conducted to examine the influence of illness chronicity, severity, and comorbidity on cardiac psychophysiology. Overall, these variables did not appear to exert a significant influence on the findings. Analyses conducted within the depressed group indicated that there were no significant correlations between either the total duration of MDD episodes (past and current) or the age of the onset of the first MDD episode and any autonomic measure (r_s = −0.06 to 0.12, p = 0.40 to 0.91). Similarly, analyses comparing adolescents experiencing mild episodes/episodes in partial remission to those with moderate to severe episodes indicated no group differences for any autonomic measure (t = −1.88 to 1.32, p = 0.07 to 0.83). Our depressed sample included only four participants who had current comorbid anxiety disorders. This number was too low to run any statistical analyses to control for anxiety. However, we re-ran the t-tests without these four participants and the pattern of findings was unchanged. Therefore, we conclude that the presence of comorbid anxiety disorders did not account for the significant difference in heart rate nor the absence of significant differences in other autonomic measures between the depressed and healthy groups.

Finally, given evidence that sex can moderate the relations between depression and cardiac control (e.g., [38]), we examined group by sex interactions for all dependent variables. No significant interactions emerged (Fs = 0.15 to 3.28, p = 0.07 to 0.70).

Discussion

Our findings replicate, in an adolescent community sample, the association between higher heart rate and depression that has been well-established in adult samples. Contrary to our hypothesis, however, no differences in measures of sympathetic or parasympathetic activation during rest emerged between the depressed and healthy groups, despite the higher heart rate in the depressed group. Furthermore, the association between depressive status and higher heart rate was not significantly moderated by sex, depressive severity, or illness duration as assessed by length of current episode or age of first onset. Given the importance of these null findings it is worth noting that the current study has adequate power (>0.80) to detect medium effect sizes (i.e., Cohen's =0.45, critical t = 1.66) at the conventional significance level. Further, the observed effect sizes of the null findings for these variables were generally very small, suggesting that additional statistical power would be unlikely to reveal non-null effects. The significance of these findings are twofold and lie primarily in demonstrating that: 1) community-based depressed adolescents who are young, physically healthy, and free from the effects of cardioactive substances had higher resting heart rates than demographically matched, non-depressed controls; and 2) this difference in heart rates does not appear to be associated with concomitant differences in sympathetic or parasympathetic cardiac control.

The lack of difference in RSA between groups is consistent with other research [11]. For example, Licht and colleagues [11] concluded that associations between HRV and depression were largely attributable to medication effects.

Previous research has suggested that if there are no differences in parasympathetic activation, then the higher heart rate in depressed patients may be due to differences in sympathetic activation [11]. However, our findings show no difference between depressed and healthy participants in sympathetic activation as measured by baseline PEP, BP, and SCL, and as such is consistent with the negative findings of Moser and colleagues [5] regarding sympathetic arousal and depression. Some research has noted that higher resting heart rate in depressed patients could be attributable to medication effects [18] or lifestyle changes [5]. Data from participants who were taking medication or substances that could

affect autonomic parameters were removed, as was that of participants who reported regular nicotine use. Given the young age of our sample, any lifestyle changes due to depressive symptoms would likely be less pervasive and long standing than those observed in adults, especially patient- as opposed to community- based samples. As noted earlier, preliminary analyses to compare possible fitness and lifestyle differences, indicated no differences in BMI, or in caffeine use between the depressed and healthy groups. Moreover, indices of illness severity or chronicity did not appear to influence findings.

Limitations

It is important to note that we have only examined between group differences in the tonic levels of these measures, which does not rule out the possibility that there are between group differences in their reactivity. Some research has shown that differences in parasympathetic functioning between depressed and non-depressed groups may occur in the presence of stressors [6, 39–40]. It is conceivable that depressed adolescents display autonomic dysregulation only in response to stress, and that baseline autonomic functioning is similar to controls.

However, given that a robust difference in resting heart rate was observed, our findings suggest that differences in resting parasympathetic and sympathetic enervation of the heart cannot explain the observed heart rate difference between depressed and non-depressed participants.

Another limitation of this study is that it is not based on a clinical sample, and data is not included from patients taking antidepressant medication (which may have influenced cardiovascular factors). Therefore, our sample may be biased in that it only includes adolescents with depression not severe enough to require pharmacological treatment or is not generally representative of adolescents requiring clinical treatment. Finally, the study design does not allow us to tease apart the specificity of the observed effects of depression from those associated with other symptom dimension that are correlated or comorbid with depression. Future studies would be enhanced by the inclusion of non-depression psychiatric control groups, especially anxiety and conduct disorders groups, in order to address this issue.

Conclusion

Consistent with some previous research [5], our findings suggest that autonomic cardiac control cannot explain resting heart rate differences between depressed and non-depressed groups and that perhaps the autonomous heart rate (or “intrinsic” heart rate) of depressed patients is inherently higher. Bernardi and colleagues [41] suggested that the heart is capable of maintaining a heart rate independent of autonomic functioning based on a study of denervated transplanted human hearts. Given the strong test of whether higher heart rate is characteristic of depression provided by the current study (i.e., by controlling for potentially confounding factors) it seems that future research on depression and heart rate should consider mechanisms other than sympathetic or parasympathetic control as potential explanations of heart rate differences. A range of biological mechanisms have been hypothesized to explain the association between depression and heart disease, including disturbances in blood clotting mechanisms, vascular and endothelial dysfunction of the coronary arteries, and inflammatory immune system response [2]. Investigating the links between these mechanisms and higher heart rate in depression may reveal critical aspects of the pathophysiology of depression, potentially including those that confer increased risk for cardiovascular disease.

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Table 1

Demographic Data

Demographic Category	Depressed (N=54)	Healthy (N=73)	Test Statistic
Sex			χ^2 (1)= 1.04, p= 0.31
Male	16	28	
Female	38	45	
Mean Age (SD)	16.06 (1.08)	16.17 (1.06)	t(125)= −0.51, p=0.61
Md Income	$45K	$53K	$\chi^2(1)=4.06$, p<.05
Race & Ethnicity			$\chi^2(1)=0.01$, n.s.[a]
Caucasian	37	53	
African American	2	2	
Asian	0	1	
Native American	1	0	
More than one race	10	15	
Unknown	4	2	

[a] χ^2 is based on analysis of Caucasian - non-Caucasian dichotomy due to limited frequencies in specific non-Caucasian racial groups

Table 2

Assessment and Subject Differences

	Depressed (N=54)	Healthy (N=73)	Test statistic
Assessment differences			
Time of day			$\chi^2(2)= 0.19$, p=0.91
Morning	21	28	
Afternoon	20	26	
Evening	12	19	
Subject differences			
Mean BMI (SD)	23.29 (4.51)	23.02 (4.15)	t(125)= 0.36, p=0.72
Mean typical coffee use (SD) (scale 0 – 9)	3.39 (2.90)	2.88 (2.92)	t(125)= 0.98, p=0.33
Mean typical nicotine use (SD) (scale 0 – 9)	0.07 (0.33)	0.01 (0.12)	t(125)= 1.45, p=0.15
Mean typical tea use (SD) (scale 0 – 9)	2.50 (2.48)	2.23 (2.57)	t(125)= 0.59, p=0.56
Mean typical caffeine soda use (SD) (scale 0 – 9)	6.15 (1.97)	5.55 (2.48)	t(125)= 1.47, p=0.15

Table 3

Physiological differences

	Depressed (N=54)	Healthy (N=73)	Test statistic
Mean Heart Rate (beats/min) (SD)	75.14 (10.38)	70.75 (9.93)	t(125)= 2.41, p= 0.02
Mean log10(RSA) (SD)	−1.05 (0.26)	−1.01 (0.23)	t(125)= −0.82, p= 0.40
Mean Skin Conductance Level (micromhos) (SD)	10.05 (3.59)	11.17 (4.87)	t(125)= −1.43, p= 0.16
Mean Systolic Blood Pressure (SD)	112.62 (29.89)	116.24 (22.60)	t(125)= −0.78, p= 0.44
Mean Diastolic Blood Pressure (SD)	62.23 (17.52)	61.63 (14.69)	t(125)= 0.21, p= 0.83
Mean Pre-ejection period (sec) (SD)	0.13 (0.02)	0.13 (0.02)	t(125)= 0.82, p= 0.41