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Abstract

Background: Recent studies have shown that depressive disorder is associated with impaired baroreceptor or baroreflex sensitivity, which is proposed to be a predisposing factor for sudden death in patients with manifest cardiac disease. These studies have not evaluated the afferent and efferent components of the cardiac baroreflex loop or other baroreflex mechanisms that regulate target processes (cardiac metabolism and blood pressure variability) related to the impairment. The objective of this study was to gain more insight into autonomic functioning in depressive disorder to more fully examine the potential basis for increased cardiac mortality. *Methods:* The subjects were 28 women and men with unipolar major depression who were taking antidepressant medications and who were in partial remission and free of cardiovascular or other serious disease, and 28 healthy control subjects matched for sex, age, and ethnicity. The two samples were compared for negative affective dispositions (anger expression, hostility, defensiveness, anxiety), spontaneous (closed-loop) baroreflex activity, heart rate, heart rate variability, systolic blood pressure, and heart rate-systolic blood pressure double product under resting conditions. *Results:* Depressed patients showed a general disposition to anger suppression coupled with higher hostility and anxiety, and lower defensiveness. The patients showed higher general sympathetic activity (high levels of blood pressure, low frequency heart rate variability) and lower parasympathetic-related activity (high heart rate and reduced high frequency heart rate variability) with affected cardiac metabolism estimated by the double product. Depressed patients had lower baroreflex sensitivity related to a higher gain of the afferent component of the baroreflex without respective gain adjustment of its efferent component (reflex gain 'de-afferentation'). It was coupled with a compensatory higher number of effective baroreflex reactions (reflex gating 're-afferentation'). Antidepressant agents and depressed mood had additional independent effects on baroreflex sensitivity through the efferent component of the cardiac baroreflex loop. *Conclusions:* The data indicate that different baroreflex components and mechanisms may be impaired in patients with depression and may contribute to their increased cardiac risk.

Key words: baroreflex sensitivity, baroreflex effectiveness, cardiac risk, depression, heart rate variability.

Abbreviations: HRV – heart rate variability; HF-HRV –high frequency component of HRV; BRS - baroreflex sensitivity; BP - blood pressure; SBP – systolic BP; BEI - baroreflex effectiveness index; RRI – R-wave to R-wave interval; HR-BP – heart rate and blood pressure product; MDD – major depressive disorder; HAM-D17 - the 17-item Hamilton Depression Scale; SNRI - norepinephrine and serotonin reuptake inhibitors; SSRI - selective serotonin reuptake inhibitors; BMI - body mass index; CM - Cook-Medley Hostility Inventory; ANGIN, ANGOUT, ANGTOT - Anger In, Anger Out, total Anger Expression of the Spielberger Anger Expression Scale; STAI - Spielberger Trait Anxiety Inventory; MC - Marlowe-Crowne Scale of Social Desirability; ECG – electrocardiography; FIR - finite impulse response; for other physiological abbreviations, see Table 1.

Introduction

There is emerging evidence that depressed patients have a significant loss of cells in the prefrontal cortex (Rajkowska, 2000), a brain area important in mood regulation and in cortical control of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. The evidence supports the concept of depression as a systemic disease with primary medical manifestations. Depression is associated with cardiovascular disease, diabetes, and osteoporosis (Carney et al., 2005; Grippo and Johnson, 2002). Prospective treatment of depressed patients with comorbid cardiovascular pathology may increase the chances of good medical outcome and survival (Gold and Charney, 2002; Carney et al., 2005).

The prefrontal cortex is part of the limbic system and assumed to be involved in the modulation of autonomic responses to stress and emotional stimuli, thus considered a visceral-motor cortical region. Ineffective coping strategies may lead to mood disturbance (e.g., depression) coupled with disorganized prefrontal cortex activity, which affects cortisol and norepinephrine secretion and, in turn, produces a highly adverse biochemical environment with negative metabolic outcomes (McEwen, 2004). Moreover, the prefrontal cortex directly modulates cardiovascular control (Resstel et al., 2004), and cardiac autonomic activity (e.g., related to baroreflex) is sensitive to the early stage of dysregulation of emotions and cognition.

There is considerable evidence of autonomic cardiovascular dysregulation in depressed patients, including elevated resting and 24-hour heart rate, increased heart rate responses to physical stressors, reduced respiration-related high-frequency component of heart rate variability (HF-HRV), and high variability in ventricular repolarization (see, e.g., Carney et al., 2005). These dysregulations have been associated with increased mortality and cardiac morbidity, especially in vulnerable populations such as depressed patients (see Grippo and Johnson, 2002). HF-HRV is one of the most widely used measures of cardiac autonomic activity in humans (Task Force Report, 1996). Beat-to-beat variability in the heart's rhythm

is determined primarily by autonomic modulation of the intrinsic cardiac pacemakers. Low HF-HRV suggests insufficient cardiac parasympathetic modulation (Task Force Report, 1996). Many studies, although not all (Yeragani et al., 1992), have found HF-HRV to be lower in depressed psychiatric patients than in controls (Dallack and Roose, 1990; Imaoka et al., 1985; Rechlin, 1994a). HRV is lower in depressed than in nondepressed patients with stable coronary disease (Carney et al., 1995; Krittayaphong et al., 1997) and is reduced in patients with a recent history of acute myocardial infarction (Carney et al., 2001).

The arterial baroreflex contributes substantially to parasympathetic regulation of the heart (La Rovere et al., 1995). Although HF-HRV and baroreflex sensitivity (BRS) are correlated, BRS has been shown to be a better predictor of parasympathetic tone during parasympathetic blockade (Reyes del Paso et al., 1996). BRS is a measure of the functioning of a reflex loop involving pressure-sensitive nerves (i.e., baroreceptors) mainly in the carotid arteries and the aorta. Reduced baroreflex sensitivity (BRS) may be a marker of increased cardiac risk associated with depression or comorbid anxiety (Broadley et al., 2005; Carney et al., 2005; Grippo and Johnson, 2002; Hughes et al., 2006; Watkins et al., 1998; Watkins et al., 1999; Watkins and Grossman, 1999; Pitzalis et al., 2001). This association may be secondary to metabolic changes, mainly related to age (Hunt et al., 2001; Sposito and Barreto-Filho, 2004). The reduction in BRS may not be a pathological process, but rather a physiological adaptation (i.e., the baroreflex gain 'de-afferentation' mechanism between afferent and efferent components of the baroreflex) to reduced blood pressure (BP) variation, changed BP steady state, or to other baroreflex and non-baroreflex processes to achieve BP and cardiac work stabilization (see Burattini et al., 2004).

Thus, the activity of different (afferent, efferent, peripheral, and central) components of the baroreflex loop in their impact on BRS and HRV measures should be assessed to distinguish primary and secondary factors in baroreflex impairment related to cardiovascular function in affective states. As BRS is derived from the central integration of two separate gains in the afferent and efferent phases of a loop, an independent impact of the afferent and

efferent components of the spontaneous baroreflex on its integrated gain may help uncover the basis of altered BRS in its relation to affective condition.

Moreover, the effectiveness of baroreflex mechanisms of BP stabilization should be evaluated to distinguish pathological and normal physiological processes in the cardiovascular system during affective states. The effectiveness of the buffering action of the baroreflex in BP stabilization has not been evaluated in most studies of patients with depressive symptoms (see, e.g., Broadley et al., 2005; Carney et al., 2005; Pitzalis et al., 2001; Watkins & Grossman, 1999). Watkins and Grossman (1999) suggested that low BRS may be a marker of increased risk of cardiac events associated with depression, but in their comparison of patients with many or few depressive symptoms, the decline of BRS was not associated with significant changes in BP variability. That fact questions whether decreased BRS is a pathological process in all cases. The reduced effectiveness of the arterial baroreflex in humans leads to an increase in BP variability, and mean BP levels remain largely unchanged in chronic conditions (Cowley et al., 1973; Ramirez et al., 1985). Thus, the role of baroreflex activity in regulating BP may be important for the prognosis of cardiac morbidity in patients with depression. The impairment of BP stability, but not a change of BRS itself, may introduce an additional strain on myocardial energy balance, which can cause transient subendocardial ischemia, tissue hypoxia, and myocardial dysfunction (Feigl, 1983; Gamble et al., 1974, Walston et al., 1978).

Blood pressure variability within a steady state (e.g., standard deviation of BP) may reflect the effectiveness of baroreflex mechanisms in BP regulation (Mancia et al., 1986). Because the baroreflex is known to impose an inverse relationship between HR and BP, this implies that it should attenuate variations in their product. The extent to which such variations will be reduced depends on the size of the reflex adjustment of HR for a given change in BP. Thus, the baroreflex may help isolate the heart from the metabolic impact of sudden hemodynamic disturbances not only by attenuating perturbations of BP but also by stabilizing the double product (Van Vliet and Montani, 1999; Van Vliet et al., 2002).

However, the baroreflex mechanism is a more complex physiological process and is not restricted to the baroreflex sensitivity function. Recent physiological studies (Carr et al., 2001; Harper, 1991; Paton and Kasparov, 2000; Resstel et al., 2004; Snitsarev et al., 2002) revealed a critical role for other mechanisms in baroreflex control. With a primary effect on central functional unbalance, these mechanisms suggest an additional etiological factor for cardiac risk in mood disorders. For example, high basal sympathetic activation (e.g., high circulating norepinephrine and angiotensin II levels), a condition frequently found in depressed patients (see, e.g., Grippo and Johnson, 2002), leads to a decline in the effective baroreflex sequences by a partial (gain) or total (gating) central 'de-afferentation' mechanism to allow for the maturational rise in arterial pressure (Airaksinen et al., 2001; Paton and Kasparov, 2000).

The sequence technique of BRS evaluation offers a means of quantifying the central gating process using the so-called baroreflex effectiveness index (BEI), which measures the number of times the baroreflex is effective in overcoming the non-baroreflex influences that regulate the sinus node (Di Rienzo et al., 2001b). A reduction of the BEI may occur in conjunction with an increase in BRS (Di Rienzo et al., 2001b). Thus, the number of times the baroreflex inhibits the sinus node (the baroreflex 'gating' mechanism) may be taken as another measure of its effectiveness in controlling the circulation (Di Rienzo et al., 2001b; Parati et al., 2000; Rüdiger and Bald, 2001).

Recent findings (see, e.g., Di Rienzo et al., 2001a; Halamek et al., 2003) raise questions about the phase relationship between BP and the cardiac inter-beat interval (R-wave to R-wave interval, RRI). In the case of baroreflex, gain (i.e., sensitivity) might correspond to the magnitude of change in RR-interval for a given change in blood pressure, but the phase relation is described by quantifying the phase shift (delay) between systolic blood pressure (SBP) and RR-interval coupling. If the phase of transfer function is not steady from the point of view of hemodynamic stability, then it is conceivable that any benefits of increased gain of the baroreflex control of heart rate might be less apparent.

Both baroreflex gain and variability of phase may provide important and independent information about circulatory control and stability (Di Rienzo et al., 2001a) and provide important additional information regarding the risk of sudden cardiac death (Halamek et al., 2003). Indeed, in some conditions, the RR-interval is in phase with or slightly leads arterial pressure changes, but in others it follows pressure changes (Cohen and Taylor, 2002; De Boer et al., 1987). These baroreflex heart reaction delays were found unrelated to fast versus slow heart rates (Di Rienzo et al., 2001a). Thus, baroreflex buffering measured by the gain in cardiac feedback may be redistributed among different phase shifts (lags with 0, 1, or 2 beats, Di Rienzo et al., 2001b) related to BP changes by the baroreflex 'phase' mechanism.

All these baroreflex mechanisms serve to control the arterial pressure, i.e. to steer the pressure toward some "normal" steady state (e.g., mean SBP), to diminish BP fluctuation around it (e.g., BP variability) or to keep BP fluctuation within a range between the "up" and "down" SBP set points. The term "set point" denotes the operating point of the cardiovascular system related to a BP level within a SBP range, which is determined by physiological parameters and mechanisms (e.g., baroreflex regulatory up or down reactions). To keep BP within the set point range the baroreflex mechanisms should control the balance of number, gain, and phase of SBP-RRI sequences during hemodynamic load and unload on baroreceptors.

We evaluated baroreflex mechanisms by retrieving and calculating baroreflex variables from sequences of spontaneous baroreflex reactions. Up to now, the method of spontaneous baroreflex evaluation has been used to derive baroreflex sensitivity (gain) in the same way that pharmacological (phenylephrine hydrochloride and sodium nitroprusside) manipulation techniques have been used. However, the method of spontaneous baroreflex evaluation makes it possible to assess additional components of cardiac baroreflex regulation. A major objective of the present study was to introduce and examine these additional physiological components as a means of exploring mechanisms in the relationship between depression and cardiac functioning.

We hypothesized that impaired baroreflex is related to compensated and de-compensated interactions between more central (e.g., gain of the efferent component of the baroreflex loop) and more peripheral (e.g., gain of the afferent component of the baroreflex loop) processes underlying the autonomic abnormalities observed in depressed patients, a condition which may contribute to increased risk of cardiac pathology. This study was conducted to examine the coupling of different baroreflex components (e.g., afferent and efferent) and mechanisms (e.g., 'gain', 'phase', and 'gating') with biomarkers of increased cardiac risk (e.g., instability in BP and HR-BP 'double' product) in patients with major depressive disorder (MDD) and to determine if a similar coupling occurs in healthy subjects.

We predicted that patients with the negative affect structure related to major depression (a general disposition to higher hostility, anger, and anxiety) would have reduced HRV and BRS (baroreflex gain) compared to healthy people. We also predicted that impairment in other baroreflex mechanisms (e.g., an increase in BEI or a phase delay in baroreflex cardiac feedback) and instability in target (SBP) processes would differentiate patients with depression from healthy subjects. The blood pressure instability would be reflected in the effectiveness of different baroreflex mechanisms and might be evaluated by BP variability, stability in "up" and "down" SBP set points for cardiac baroreflex regulatory reactions, and the HR-BP 'double' product. Thus, the main focus of the study was the effectiveness of mechanisms of baroreflex functioning associated with depressive mood disorder.

Methods

Subjects

Data for the depressed subject sample were collected in a study of yoga as a complementary treatment of depression. The subjects were recruited by advertisements and letters to clinical faculty. The data were obtained at the initial screening and assessment. This sample included 17 female and 11 male subjects, aged 20 to 52 (mean = 36.2) years. There were 23 Caucasian- and 5 Asian-Americans, with a diagnosis of

Major Depressive Disorder of mild to moderate severity, confirmed with the Mini-International Neuropsychiatric Interview ("MINI") (Sheehan et al., 1998). Morbidity time, number of episodes, and duration of medication treatment were assessed. Subjects were excluded for Axis I diagnoses of bipolar disorders, delirium or dementia, schizophrenia, other psychotic disorders, or current substance-related or eating disorders. All were taking antidepressant medication and were in partial remission at the time of the study, partial remission defined by scores between 7 and 18 on the 17-item Hamilton Depression Scale (HAM-D17; Hamilton, 1967). Antidepressant medication was categorized into three groups according to the main treatment agent: 1 - serotonergic agents (12 patients); 2 – combined serotonergic and noradrenergic agents (6 patients); 3 - dopaminergic agents (10 patients). In some cases anxiolytic (2 patients), sedative (3 patients), or/and anticonvulsant (4 patients) agents were used as adjunctive medication (8 patients). Previous studies (Broadley et al., 2005; Grippo et al., 2006; Hughes et al., 2006; Rechlin, 1994b) showed that some cardiovascular measures (baroreflex sensitivity and HRV) were not significantly different between those receiving no treatment and those taking serotonergic agents. Treatment with dual-acting norepinephrine and serotonin reuptake inhibitors (SNRI) versus selective serotonin reuptake inhibitors (SSRI) did not demonstrate differences in parasympathetic activity (Bar et al., 2004). However, other classes of antidepressants (e.g., dopaminergic agents) were not evaluated for their effects on BRS in depressed patients, but were thought to affect heart rate regulation via central or peripheral mechanisms (Grippo and Johnson, 2002). In this study, patients treated by serotonergic agents were used as a reference group for evaluation of the possible influence of dopaminergic agents on cardiovascular activity. Although we analyzed effects of the main treatment agents on the cardiovascular variables, some effects might be biased in patients with more complex medication. As additional analyses showed that exclusion of patients with an adjunctive medication of any of three agent groups (anxiolytic, sedative, and anticonvulsant) separately or all together did not affect the main findings, only main treatment effects were considered.

The data for the depressed subjects were matched with data obtained from a sample of 220 healthy subjects in a study of psychosocial factors and blood pressure. Each depressed subject was closely matched with a healthy subject of the same gender, age, and ethnicity. The healthy subjects had been screened to exclude individuals with any psychiatric disorder. Exclusion criteria for both samples included a history of heart disease or diabetes, body mass index (BMI) > 32, or drug use likely to affect cardiovascular functions.

Questionnaires and Personality tests

In both samples, during the intake process, information was collected on health history and demographic characteristics, and subjects completed personality scales. The following scales were used for both samples: 1) The Cook-Medley Hostility Inventory (CM) reflects a cynical and mistrusting attitude toward others (Cook and Medley, 1954); 2) The Spielberger Anger Expression Scale (Spielberger, 1988) provides scores on two dimensions of anger expression, Anger In (ANGIN) and Anger Out (ANGOUT), plus total Anger Expression (ANGTOT); 3) The Spielberger Trait Anxiety Inventory (STAI) measures the general disposition to experience anxiety frequently (Spielberger, 1979); 4) The Marlowe-Crowne Scale of Social Desirability (MC) indicates a tendency not to report negative emotional states or traits (Crowne and Marlowe, 1960), which we label as "defensiveness" (Jorgensen et al., 1995).

Physiological Data

Biopac System (Goleta, CA) hardware was used to acquire the physiological data under resting conditions in a sound-proof laboratory. Continuous surface electrocardiography (ECG) was recorded to confirm the sinus origin of the beats. ECG electrodes were placed in the Lead II axis--above right and below left of the heart with a ground on the right side of chest below the rib cage, permitting measurement of the RR-interval. With the appropriate size cuff applied to the middle finger of one hand, beat-to-beat arterial blood pressure (BP) was estimated using the Finapres (Ohmeda, CO, USA).

Respiration was recorded with the Biopac Respiratory Effort Transducer, a belt placed around the lower rib cage measuring changes in chest circumference. After attachment and calibration of the transducers, the data were recorded for 20 min. The signals were sampled at 2000 Hz for ECG and BP and 62.5 Hz for respiration, at 12-bit resolution, and stored in a computer. All recordings were automatically and visually examined to verify ECG beat and BP wave classification.

RR-interval series were first derived from the raw ECG, using a QRS-complex template detection algorithm to obtain R-peak localization as the apex of the interpolating parabolas. The accuracy of R-peak detection was checked by automatic and visual screening with automatic correction for artifacts (missed or erroneous beats).

Systolic BP levels were first derived from the raw BP recording, using a BP-wave template detection algorithm. Each detected BP-wave was transformed to the slope of the data in the search range, and then a point with 15% of the maximum slope was searched to localize a BP-peak. This method helps reduce the jitter effect on BP-peak detection induced by local vascular influences on BP-wave shape. The accuracy in BP-peak detection was checked by automatic and visual screening with correction for artifacts (missed or erroneous waves).

Irregular beats related to extra beats and blocks (atrial or ventricular ectopic beats or atrioventricular nodal rhythms) and outliers in RRI and BP were excluded for the sequence method analysis (see below). Irregular intervals (artifacts, extra beats, and blocks) were automatically examined against the correct time series and deleted or substituted if abnormal for the RR-interval variability analysis. After linear interpolation, the RR-intervals were resampled at 4 Hz.

RR-interval and BP variability analysis

Multistage band-pass linear filtering was adopted to suppress any other sources of variation in cardiac signal. The RRI variances of residual time series (the filtered waveform) after a band-pass optimal FIR (finite impulse response) filtering for alien frequencies and baseline trend were used to calculate heart rate variability or RRI variability (ms^2) in three

frequency bands: very low frequency (VLF) power (0.0075-0.075 Hz), low frequency (LF) power (0.075-0.125 Hz), and high frequency (HF) power (0.125-0.50 Hz). The fractional very low, low, and high frequency powers were calculated by dividing the individual values by the total power after log-transformations (normalized units, prefix –n–); LF/HF ratio after log-transformations and the natural logarithms (prefix –ln–) of the very low, low, and high frequency powers were also calculated. Mean RRI (ms) was also calculated.

BP variability measures were calculated: means of successive differences (+MSDp for increased SBP, -MSDp for decreased SBP), mean, standard deviation, and range of SBP levels (mmHg).

Sequence method analysis

BRS and other baroreflex indexes were measured by the "sequence" method (see Di Rienzo et al., 2001a). RR-interval and systolic pressure time series were scanned by software to identify sequences during which both RR-interval and preceding systolic pressure (with lag 0, 1, and 2 beats, separately) increased ('up' sequences) or both decreased ('down' sequences) successively in parallel over three or more beats (RRI and SBP ramps). We required a minimum change of 3 ms for RR-interval and 1 mmHg for systolic pressure per beat and a minimum correlation of .80 between the parallel values. The software calculated means of least squares linear regression slopes (BRS, ms/mmHg) and their variation (standard deviation, SDBRS) for up (+) and down (-) sequences with lags 0, 1, and 2, separately.

We also calculated the ratio between the number of up (+RRI/+SBP) or down (-RRI/-SBP) sequences and the total number of up or down SBP ramp-like changes (SBP ramps with and without RR-interval changes), in order to derive the Baroreflex Effectiveness Index (BEI, Di Rienzo et al., 2001b) separately for up (+BEI) and for down (-BEI) sequences for each lag. The total number of effective baroreflex changes for up (+BEIt) and down (-BEIt) sequences for the 3 lags was: BEIt = BEI0 + BEI1 + BEI2.

Since latency in heart rate controlled by the baroreflex can also fluctuate over time (see, e.g., Di Rienzo et al., 2001a; Halamek et al., 2003) modulation of baroreflex latency estimated by a mean lag (+/-LAG) between SBP and RRI ramps during the recording time was measured for all up and down baroreflex sequences over a lag window ranging from zero to two beats: LAG = ((BEI0*1 + BEI1*2 + BEI2*3)/(BEI0 + BEI1 + BEI2))-1. Thus, the mean baroreflex latency was expressed by the number of heart beats (Di Rienzo et al., 2001a). We also calculated the linear regression slope (gain) separately for SBP (mmHg/sec) and RRI (ms/sec) ramps of the detected SBP and RRI sequences in relation to time (+BPS, -BPS, +RRIS, and -RRIS, respectively) to distinguish the separate impact of the afferent and efferent components of the baroreflex on its integrated gain.

To evaluate blood pressure stability, means of SBP set points (mmHg) for baroreflex effects (+SP and -SP) and ranges between those SBP set points for up and down sequences were also calculated for different lags. To evaluate the metabolic constraint of the heart (Van Vliet and Montani, 1999; Van Vliet et al., 2002), we computed the HR-BP 'double' product as the product of mean heart rate and mean SBP ($mmHg \cdot beat \cdot min^{-1}$).

Data processing for R-peaks and BP-peaks detection, artifact search and replacement, RR-interval and SBP variability, and baroreflex sequences was performed off-line with customized interactive computer programs written in the Spike2 programming environment (Cambridge Electronic Design, Cambridge, England; programs written by DMD). The abbreviations and definitions of all physiological variables are presented in Table 1.

Data Analysis

The two samples (patients and healthy subjects) were compared by paired *t* test for the matched pairs of subjects. In addition, models of repeated-measures multivariate analyses of variance (MANOVA) or covariance (MANCOVA) treated Diagnosis as a repeated factor, considering Drug (antidepressant medication), morbidity time, number of episodes or duration of medication treatment (months) as a separate fixed factor or covariate

to analyze the relative contribution of disorder complication or drug treatment to differences obtained between patients and matched control subjects.

A one-way ANOVA model using Levene's Test of equality of error variances of dependent variables treated Drug (antidepressant medication) as a fixed factor, and univariate or multivariate ANCOVA model treated HAM-D17 scores, morbidity time, number of episodes or duration of medication treatment as covariates to evaluate their separate effects on physiological activity in the depressed sample. Post-hoc (pairwise and correlation) analyses were conducted for significant ANOVA and ANCOVA effects. The Bonferroni test was used when the variances were equal, and the Tamhane's T2 test was used when the variances were unequal. The power of each effect was calculated to estimate strength of the effect.

As each pair of subjects was matched for Age, Ethnicity, and Sex, these variables were controlled for. A P value of $< .05$ was considered significant. All statistical analyses were performed with SPSS for Windows, Release 12.0 (SPSS Science, Chicago, IL).

Results

MDD diagnosis effects on demographic, personality and physiological variables.

There was no difference in age and BMI between the patients and controls (Table 2). Tables 2-4 summarize the findings for the personality trait differences, RR-interval, SBP, baroreflex, and the heart rate variability indexes. Depressed patients had higher scores on STAI, ANGIN, and CM and lower scores on MC compared to the controls, and they had higher values for mean SBP, MSD of pressure, nVLF and nLF of RRI variability, the LF/HF ratio, and HR-BP product, and lower values for mean RRI, lnHF, and nHF of RRI variability. Patients had lower baroreflex sensitivity (BRS) and more gain stability (lower SDBRS) for lags 0 to 2, coupled with significantly higher gain of the afferent component of the baroreflex loop (BP ramps), but not with changes in the efferent component (RRI ramps).

In depressed patients, the lnHF component of RRI variability, the LF/HF ratio, all up and down BRS variables and their efferent (RRISs) components, but not their afferent (BPSs) components, were significantly related (r= -.39, p = .043, r= .39, p = .042, rs= -.53-.60, ps < .005 and rs= -.55-.58, ps < .005, respectively) to HR-BP (double product), as one of the proposed end-points of baroreflex regulation. Moreover, in both groups, the double product was negatively correlated with the nVLF component of RRI variability (r= .53, p < .005 in the depressed sample and r= .48, p = .01 in the controls).

The patients had significantly higher SBP set points (SP) for up and down baroreflex sequences, but similar SP ranges between them compared to controls for the same lags. However, for both depressed and healthy subjects, the SP ranges significantly increased for baroreflex reactions from 0 lag to 1 and 2 lags. This suggests that despite the differences between the two samples in mean SBP and various SBP set points (i.e., different BP steady states), the baroreflex in the depressed sample continued to react to SBP changes within unaffected SBP set point ranges for the appropriate lag between SBP and RRI ramps. Fast baroreflex (i.e., with 0 lag) reacted within a narrow SP range, but delayed baroreflex (i.e., with 1 and 2 lags) related to BP rises and falls within wider SP ranges in both groups of subjects. However, the cardiac metabolism measure (HR-BP) was coupled significantly with the SP0 range related to fast (i.e., with 0 lag) baroreflex only in depressed subjects (r = -.38, p = .047).

Depressed patients showed significantly higher total baroreflex up reactions (+BEIt) compared to controls. This effect was related to an increase in the number of delayed baroreflex reactions (+BEI2) in patients compared to controls. In control subjects, correlational analyses showed that the number of delayed baroreflex down reactions (-BEI1, -BEI2 and -LAG) and the number of delayed baroreflex up reactions (+BEI2) were positively correlated with SBP range (rs = .49-.54, ps < .01 and r = .36, p = .058, respectively). The number of delayed baroreflex down reactions (-BEI1 and -BEI2) was positively correlated with -MSDp (r = .51, -.52, p < .01) in depressed patients.

Drug (antidepressant medication), number of episodes, duration of medication treatment, and morbidity time effects for CV variables.

The multivariate analyses showed that Drug as an independent factor, Duration of medication treatment, Number of episodes, or Morbidity time as covariates had little effect on the between-group (Diagnosis) differences in the physiological variables. However, one-way ANOVAs and post-hoc comparisons showed significant main Drug effects on the baroreflex activity in the depressed subjects (Table 5). Patients treated by dopaminergic agents had lower values of gain of full baroreflex loop and its efferent component compared to the subjects treated with serotonergic and noradrenergic agents.

Results of one-way ANOVAs and post-hoc comparisons suggest that Drug effects could be related to other factors. For example, patients treated by dopaminergic agents had higher age, higher scores for STAI, longer duration of medication treatment, and more morbidity time compared to groups treated with serotonergic and noradrenergic agents (Table 5). ANCOVA results indicated that only morbidity time had an effect on BRS measures ($F(1, 26) = 4.54 – 9.17$, $p = .043 - .006$, power = .54 - .83, $r = -.40 - .53$), but not on the efferent or afferent component of the baroreflex loop: a longer history of depression was associated with a greater decrease in BRS scores in the patients. Duration of medication treatment was positively related to STAI and psychic anxiety component of HAM-D17 ($r = .50$, $p = .007$ and $r = .48$, $p = .011$, respectively), but not to cardiovascular variables. Age did not affect these drug relationships to baroreflex gain (see below). Depression severity, as defined by the depressive mood component of the HAM-D17 (dHAM-D17), had an impact on both BRS and the efferent component of fast baroreflex (Wilk's $\lambda = .60$ and .65, $F(4, 23) = 3.77$ and 3.11, $p = .017$ and .035, power = .81 and .72, $r = -.47$ and -.40, respectively) that was independent of Drug treatment: higher depressive mood was associated with lower up and down BRS and RRIS at the 0 and 1 phase shifts.

Interrelationships between demographic and physiological variables.

Additional analyses found that in controls age was negatively correlated with gain variables of the fast baroreflex: –BRS0 and –BRS1 (r=-.48, p = .01 and r=-.44, p = .02, respectively), and with activity of its efferent (-RRIS0) component (r=-.40, p = .036). However, in patients, age correlated with gating variables of the delayed baroreflex reactions: +BEI2 and –BEI2 (rs= .40, ps < .05 for both), and the mean of baroreflex phase shift: +LAG and –LAG (r= .55, p = .003 and r= .59, p = .001, respectively). Moreover, in patients, age correlated positively with BMI (r= .61, p = .001) and with LF/HF ratio (r= .43, p < .05). In both groups, significant correlations were found between gain, gating, phase components of baroreflex, and heart rate variability measures (Table 6). No significant correlations were found in either group for the afferent component of the baroreflex loop.

In the control group, BRS was significantly correlated with the gain of both components of the baroreflex loop: negatively with BPS (rs = -.41 -.50; ps = .032 - .007) and positively with RRIS (rs = .79 - .89; ps = .0001) in the respective baroreflex phase and ramp. However, in the controls, gain fluctuations of the afferent and efferent components did not relate to each other. In contrast, in the depressed patients, BRS significantly correlated only with gain of the efferent components (RRIS) of the baroreflex loop (rs = .83 - .92; ps = .0001) in the respective baroreflex phase and ramp. Moreover, for patients, gain fluctuations of the afferent and efferent components were significantly and positively related to each other (rs = .45 - .50; ps = .016 - .006).

Discussion

Analysis of the negative affect structure of patients with major depressive disorder showed that they differed from healthy subjects in a general disposition to anger suppression coupled with higher hostility or an attitude of cynical mistrustfulness, resentment, and interpersonal antagonism, and anxiety with lower levels of defensiveness. This dispositional structure is thought to be related to general sympathetic arousal and reduced parasympathetic activity, presumed risk factors for cardiovascular disease (Suls and Bunde, 2005). This autonomic nervous system pattern is related to the loss of general inhibitory

down regulation from the prefrontal cortex to subcortical neural structures due to mood and emotional disturbances (Thayer and Siegle, 2002).

The cardiovascular effects in the patients were shown in higher levels of sympathetic activity (e.g., high level of systolic blood pressure, high absolute and relative levels of low frequency heart rate variability) and lower parasympathetic-related activity (high heart rate and reduced high frequency heart rate variability). Moreover, depressed patients had lower baroreflex sensitivity coupled with a higher gain of the afferent component of the baroreflex, which suggests a peripheral origin of the decline in baroreflex sensitivity: the threshold for baroreflex reactions was shifted to a higher gain in systolic blood pressure ramps without concurrent gain adjustment of the efferent component of the loop. This increase in baroreflex threshold was coupled with higher steady state of systolic blood pressure (the mean of systolic blood pressure), but not its instability. The finding supports the hypothesis of a partial, central gain 'de-afferentation' or inhibition mechanism in the baroreflex regulation of blood pressure, determined by general sympathetic arousal, allowing for the maturational rise in arterial pressure (Airaksinen et al., 2001; Paton and Kasparov, 2000). However, this regimen of baroreflex control seems related to greater stability or rigidity of the baroreflex threshold, i.e., restricted gain (sensitivity) variation among baroreflex reactions to blood pressure changes as estimated by the standard deviation of baroreflex sensitivity.

The higher gain of the afferent component of the baroreflex is a result of strain in cardiac work and metabolism, as estimated by the affected heart rate and blood pressure double product, via a tonic increase in ventricular contractility (inotropic activity) caused by an increase in sympathetic outflow to the ventricular myocardium (Paton et al., 2005). Thus, peripheral norepinephrine hyperactivity in depressed patients may lead to increased sympathetic cardiac tone. In turn, this may further cause an increase of low frequency heart rate variability and reduced baroreflex sensitivity due to augmented gain in the afferent component of the baroreflex loop that is not compensated for by efferent parasympathetic flow to the heart.

The observed reduction of the high frequency component of heart rate variability in the patients may not be related parasympathetic tone withdrawal, but to the centrally restricted range of baroreflex gain by sympathetic arousal or cardiac sympathetic nerve tonic hyperactivity (a part of general sympathetic hyperarousal), which restrains vagally mediated heart period oscillations (Cohen and Taylor, 2002; Taylor et al., 2001). This is supported by the finding that the efferent 'parasympathetic' component of the baroreflex loop was not affected in the depressed patients compared to controls.

Complications of the depressive disorder related to morbidity time, number of episodes, duration of medication treatment, and specific drug use did not affect these main differences in sympathetic activation. However, depressed mood level and specific drug treatment had significant additional and independent effects on baroreflex sensitivity, which were coupled with gain alteration of the efferent component of the baroreflex loop. The gain of the efferent component of the cardiac baroreflex is proposed to be related primarily to parasympathetic activity. Indeed, correlational analyses showed that the efferent component, mainly for down reactions, was related to parasympathetic dominance (higher relative level of high frequency heart rate variability), which affected the gain of the full baroreflex loop. Moreover, decrease of the gain of this component related to fast baroreflex down reactions determined the decline of baroreflex sensitivity with age (as a proxy of metabolic and hormonal constraints) in healthy subjects. In the depressed patients, activity of the efferent component of baroreflex determined level of cardiac metabolism (heart rate and blood pressure 'double' product).

Given the extensive comorbidity of mood and cardiovascular disorders, and the increased likelihood of cardiovascular problems in patients with depression, it is important to consider therapeutic treatments that do not have adverse cardiovascular side effects for mood disorders. Tricyclic antidepressants are considered safe for depressed patients, but the cardiotoxic and anticholinergic effects of these drugs sometimes preclude their use in depressed patients with cardiovascular disease (Glassman and Shapiro, 1998; Rechlin, 1994b). Serotonin-specific reuptake inhibitors showed fewer cardiovascular side effects

than tricyclic antidepressants (Grippo et al., 2006; Roose et al 1998; Roose and Spatz 1999; Sheline et al 1997). In the current study considerable difference in the baroreflex indices between patients treated by serotonergic and dopaminergic agents indicates an anticholinergic effect of dopaminergic agents on cardiovascular regulation. Among various drug treatments differences in baroreflex sensitivity coupled with the efferent component of the baroreflex loop suggest that oral administration of dopaminergic agents modulates the baroreflex via its effects on heart period (chronotropic activity of the heart) by peripheral parasympathetic activity or central cholinergic activity. However, recent pharmacological data suggest that central serotonergic mechanisms may affect regulation of chronotropic activity of the heart in psychiatric patients. Treatment with serotonin reuptake inhibitors was shown to increase the high frequency component of heart rate variability in depressed subjects and in patients with anxiety or post-traumatic stress disorder (Grippo et al., 2006). Thus, in contrast to depressed patients treated with dopaminergic agents, for those treated with serotonergic and complex serotonin and norepinephrinergic agents, it is likely that the differences between drugs may be due to a relative augmentation of baroreflex sensitivity coupled with higher gain of the efferent component of the baroreflex loop.

However, this apparent gain improvement in the baroreflex sensitivity due to adjustment of chronotropic activity of the heart in some treated depressed patients should be evaluated for its beneficial and harmful effects on cardiac function. Indeed, although activation of the vagus is assumed to be responsible for the cardioprotection (Billman, 2002), to be an effective antiarrhythmic action, increased baseline vagal activity should also demonstrate an effective outcome in cardiac metabolic condition (e.g., in our case the heart rate and blood pressure 'double' product) when the heart is stressed (Billman, 2002). However, this change in baroreflex sensitivity was not coupled with improvement in the 'double' product. Since depressed patients compared to controls had general sympathoexcitation with a gain increase of the afferent component of the baroreflex, greater benefits for heart metabolism might be expected from a decline of augmented inotropic activity. In contrast, the adjustment of chronotropic activity to enlarged inotropic activity

may consolidate the new steady state of a tonic increase of cardiac contractility and higher strain in cardiac work in these patients without improvement in cardiac metabolism.

In a physiologically normal condition, increase in baroreflex sensitivity is coupled with a reduction in stroke volume (Casadei, 2001) due to vagally mediated baroreflex control of left ventricular myocardial contractility (Casadei et al., 1992; Karlocai et al., 1998; Lewis et al., 2001). The current study supports the literature in showing that in healthy subjects the higher baroreflex sensitivity was determined by both a low gain of its afferent 'sympathetic' component restricted by stroke volume and a high gain of its efferent component, related to parasympathetic regulation of heart period (i.e., parasympathetic-sympathetic reciprocity). It was not the result of gain adjustment or compensation of the efferent to the afferent baroreflex component (i.e., parasympathetic-sympathetic co-activation). In contrast, in the depressed patients, the high baroreflex sensitivity was determined only by a high gain of the efferent 'parasympathetic' component by compensation of the augmented gain of the afferent component (the parasympathetic-sympathetic co-activation or gain 'compensation' mechanism). This contrast of baroreflex sensitivity regulation was coupled with a difference in gain variation of baroreflex responses to blood pressure changes with more stable or restricted in range baroreflex sensitivity for the latter condition. Thus, the current study suggests that targeting the precise mechanisms that underlie the association between depression and heart disease with pharmacological agents might improve the prognosis for depressed cardiac patients. The benefits and harmful effects of baroreflex sensitivity changes on cardiac function should be evaluated for underlying mechanisms: the more open in gain and range efferent-afferent components gain 'decoupling' (i.e., sympathetic-parasympathetic 'decoupling' or reciprocity) mechanism or the gain and range restricted efferent-afferent components gain 'compensation' (i.e., sympathetic-parasympathetic 'compensation' or co-activation) mechanism. The former condition involves more energy economic metabolism which contrasts with the more energy costly cardiac metabolism of the latter.

Besides the large inotropic (i.e., cardiac contractility) effect of depressive disorder and chronotropic (i.e., heart period) effects of specific antidepressant drugs, another mechanism related to depressed mood was found to influence heart period regulation. The direct influence of prefrontal cortex on baroreflex control (Resstel et al., 2004) can explain the impairment of baroreflex sensitivity associated with depressed mood. This appears to occur via the prefrontal cortex down regulation of gain of the efferent component of the baroreflex loop. A cumulative effect of all three processes influencing baroreflex sensitivity may explain the detected negative relation of morbidity time to baroreflex sensitivity in the development of depression.

Beside the baroreflex gain, other mechanisms such as baroreflex phase, as estimated by the lag or latency between systolic blood pressure and RR-interval changes, and the baroreflex gating process, as estimated by a number of effective baroreflex reactions to systolic blood pressure ramps, are affected by major depressive disorder. So far the nature of these mechanisms has not been well defined. In order to address this unexplored feature of baroreflex regulation, additional correlational analyses were conducted. These analyses showed that in both groups latency of the baroreflex was related to relative sympathetic dominance, mainly affected by parasympathetic suppression (lower relative level of high frequency heart rate variability). The baroreflex gating process was related to relative sympathetic dominance, mainly affected by sympathetic activation (wider blood pressure range, higher relative level of low frequency heart rate variability) for the total and delayed baroreflex reactions. For the fast baroreflex reactions, the baroreflex gating process was related to relative parasympathetic dominance, mainly affected by parasympathetic activation (higher relative level of high frequency heart rate variability). This contrast may be coupled with the relationship of fast baroreflex reactions to systolic blood pressure fluctuations (blood pressure set point range) closer to a steady state of systolic blood pressure (the mean of blood pressure) and the delayed baroreflex reactions to systolic blood pressure fluctuations further from the mean of systolic blood pressure. For instance, sympathetic hyperactivation in the depressed patients may have caused elevated systolic

blood pressure and shifted set points of systolic blood pressure for baroreflex reactions due to a baroreflex gain 'de-afferentation' (inhibition) mechanism, which was accompanied or followed by a compensatory increase in number of delayed baroreflex up reactions (gate-related 're-afferentation' for baroreceptor loading) as estimated by baroreflex effectiveness scores. In the depressed patients at rest, it augmented the total number of baroreflex reactions close to 100 per cent in relation to up ramps of systolic blood pressure. However, this kind of compensation, as estimated by heart rate and blood pressure 'double' product, seemed to be insufficient to improve cardiac metabolism in depressed subjects. Thus, the number of delayed baroreflex up reactions is another marker of a stressful condition, which is also affected by age in patients with depressive disorder. It is possible that some baroreceptors, which have a different location and different neuronal pathways (β-adrenergic and cholinergic) for cardiac regulation (Bianchi-da-Silva et al., 2000; O'Leary et al., 2003) and a different speed in their response to blood pressure change (approximately 50 ms for the aortic arch and 200 ms for carotid sinus after the R-wave, Eckberg and Sleight, 1992) are more sensitive to unloading (aortic arch region) than to loading (carotid sinus) of baroreceptors (Bianchi-da-Silva et al., 2000). In healthy subjects, the baroreceptors of the aortic arch region (fast baroreflex down reactions) were gain sensitive to age (as a proxy of metabolic and hormonal constraints). In depressed patients, however, the upward shift of the steady state of blood pressure loads the gaiting mechanism for signals from the baroreceptors of the carotid sinus (delayed baroreflex reactions). That makes this circuitry more vulnerable to age-related metabolic dysfunctions (e.g., dyslipidemia).

In contrast to healthy subjects, the depressed patients showed relationships of the intensity of cardiac metabolism ('double' product) to activity of the efferent component of baroreflex and the operating (i.e., set point) range of systolic blood pressure for baroreflex responses. This may reflect the general transfer from the energy economic mode (sympathetic-parasympathetic reciprocity) of autonomic regulation of cardiac metabolism in healthy subjects to the energy costly autonomic mode (sympathetic-parasympathetic co-

activation) of homeostatically biased physiological conditions in patients. The importance of the operating ranges and autonomic modes in relation to gain, gating, and phase mechanisms of baroreflex regulation needs to be evaluated more intensively in future studies. Paton et al. (2005) stated that simultaneous co-activation of cardiac sympathetic and parasympathetic branches of the autonomic nervous system (sympathetic-parasympathetic 'compensation' or co-activation mode in baroreflex mechanism in our case) allows precise control of response direction, but restricts the dynamic range and gain of the response. In depressed patients, this condition appears to restrict the ability to cope with physical and cognitive challenges (Davydov, 2000; Shapiro et al., unpublished). In terms of reflex control of the heart, this is important in critical physiological situations (e.g., fight/flight, defense/attack, orienting reflex, during diving and wrestling; Berezantsev et al., 2000; Gianaros and Quigley, 2001). In these critical conditions the operating range needs to be confined (in our case, relation of the 'double' product regulation to a narrow baroreflex set point range [SP0], lower baroreflex sensitivity and its variability) but precisely controlled (in our case, regulation of baroreflex by the singular parasympathetic efferent component). In our data, depressed subjects showed such critical physiological regulation during resting conditions.

In contrast, during reciprocal control of both autonomic limbs, both the range and gain are massively increased in either direction (Paton et al., 2005). In the present study, this mode of autonomic control was related to decoupling of the 'double' product from a narrow baroreflex operating range and to baroreflex sensitivity regulation by reciprocal control from both afferent and efferent components of the loop. This pattern is advantageous in that it guarantees flexibility in the choice of future response direction (e.g., fight or flight, defense or attack) as well as high speed and large magnitude of a response (e.g., orienting, startle or defensive response). This permits less restricted capabilities in response to physical and cognitive challenges, but may be less efficient for precise adjustments in response. In terms of reflex control of the heart, this condition may be found under rest conditions in healthy

subjects showing this physiological readiness, capacity, or reserve for emergency and critical physiological situations (e.g., Berezantsev et al., 2000) and for various physical and cognitive challenges (Davydov, 1998; Davydov and Shapiro, 1998a, 1998b).

Our data are therefore consistent with the hypothesis that change of baroreflex sensitivity may be adaptively different as estimated by the various baroreflex components and the regulated target processes. Indeed, depressed patients with concurrent sympathetic and parasympathetic co-activation may be in physiologically 'critical' (hyperarousal) condition or chronic stress, but patients with reciprocal sympathetic activation and parasympathetic suppression seem to be sensitized to recurrent acute stressful events (i.e., for fight or flight responses). In both cases, if the increased heart work due to sympathoexcitation coupled with parasympathetic activation in sustained stress or coupled with parasympathetic suppression with sensitization to acute stress is not energetically supported by metabolic protectors of cardiac performance, it may lead to malignant ventricular arrhythmias and sudden cardiac death. This hypothesis should be tested in future studies. It should be noted that baroreflex sensitivity is largely a measure of cardiac vagal control of heart period, and although its vagal and sympathetic control are usually reciprocal in a healthy subject at rest, this is not always the case in physiologically critical situations (e.g., diving) and 'critical' conditions like depressive disorder. The transfer from the reciprocal to co-activated autonomic mode of the two branches relationships is determined by a general sympathetic arousal, which causes a blood pressure increase via the central mechanism of elevation of baroreflex threshold coupled with a compensatory higher number of baroreflex up reactions with restricted range (i.e., higher rigidity for adaptive changes) of baroreflex sensitivity to increased cardiac contractility. This transfer between autonomic modes may explain the stress-related changes in power ratio for low and high frequency components of heart rate variability. It may be related to the change from reciprocity of parasympathetic-sympathetic relationships with the vagus dominant in unexcitable conditions of a subject (estimated by power of the high frequency component, see Taylor et

al., 2001) to co-activated mode of their relationships during stressful and affective conditions (estimated by power of the low frequency component, see Task Force Report, 1996). Thus, this study helps distinguish between sympathoexcitation and parasympathetic suppression as a primary pathological mechanism of the cardiac baroreflex impairment in patients with major depressive disorder and emphasizes an important role of the physiological mechanism of transfer between coactivation and reciprocal modes of autonomic functioning in heart rate regulation.

Some limitations need to be considered when interpreting the results of this study. First, since, major depressive disorder is an episodic phenomenon, more standardized guidelines for measuring physiological activity in patients with major depressive disorder (e.g. timepoint of measurement during a treatment and morbidity course) need to be considered for the comparison of results of different studies. Moreover, there is no consensus on the criteria for severity of depression. In our study we used a practical, although arbitrary, evaluation of patients according to their HAM-D scores. Second, the current patient group had a specific negative affective structure, which may have complicated the disorder configuration. Depressed patients with other negative affective dispositions (e.g., anger out expression), mood, and behavioral disturbances, or other morbidity histories and treatment regimens may show different patterns of cardiovascular regulation (Davydov and Lavrova, 2004; Lavrova and Davydov, 2000, 2001). For instance, in our study, antidepressants differed in their effects on various components of baroreflex functioning. The specific drugs used by patients did not affect the main findings. However, there were no patients in the study who were drug free. Some of the effects reported for depression may be due to common physiological effects of the antidepressants and their partial remission effects. Thirdly, the cardiovascular system is sensitive to sex hormonal conditions (e.g., menstrual cycle), sex, ethnicity, and age differences. In the current study, each depressed patient and paired healthy control were matched in sex, ethnicity, and age. However, we can not be sure that the sympathetic and vagal dysregulation found in our patients with major depressive disorder will be the same in other depressed patients with

differing demographics, neuropsychiatric syndromes, morbidity, treatment course, and affective dispositions. The findings from the depressed patients in our current sample lead us to conclude that the studied baroreflex mechanisms represent a central autonomic dysregulation underlying one of the pathways by which depressive disorder has an impact on cardiac functioning.

Conclusions

The study supports the view that depression is a disorder with complex effects on physiological functions. The data indicate that baroreflex sensitivity is impaired in depressed patients even when they are in partial remission. This impairment may contribute to their increased ischemic heart disease risk. The study used varying paradigms in order to gain more insight into autonomic functioning in depressive disorder to more fully examine the potential role of these mechanisms in increased cardiac mortality. The findings indicate that the sequence technique of spontaneous baroreflex evaluation has advantages compared to techniques of the open-loop (e.g., pharmacological) baroreflex gain measure in distinguishing the separate impact of afferent and efferent components of the baroreflex loop on integrated baroreflex gain. As compared to other methods (e.g., the frequency domain and mathematical models), which also evaluate baroreflex activity in closed-loop conditions, the sequence technique allowed us to distinguish the separate impact of gain and gating components of baroreflex on regulation of blood pressure. Moreover, a unique feature of the sequence technique compared to other approaches used to estimate spontaneous baroreflex is a separate evaluation of baroreflex mechanisms for baroreceptor loading (mainly carotid sinus) and unloading (mainly aortic arch region), which reveals a different susceptibility to pathological processes. The study demonstrated the importance of the interaction between different baroreflex mechanisms (e.g., gain, phase, and gating) and components (e.g., afferent and efferent or inotropic and chronotropic) for regulation of target system activity (e.g., cardiac metabolism). The findings suggest the need for refining our understanding of complex relationships between baroreflex mechanisms and affective states as they affect cardiac functioning.

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TABLE 1. Glossary of abbreviated terminology related to physiological measures.

Variables	Descriptions
SBP (mmHg)	Mean of systolic blood pressure
SDSBP (mmHg)	Standard deviation of SBP
SBP range (mmHg)	Difference between maximum and minimum SBP
-/+MSDp (mmHg)	Mean of successive differences for down (-) and up (+) SBP changes
HR-BP ($mmHg \cdot min^{-1}$)	Product of mean heart rate and mean SBP
RRI (ms)	Mean of R-R intervals
VLF, LF, HF (ms^2)	Variance or variability of RRI (synonym: heart rate variability, HRV) at very low, low, and high frequency bands
lnVLF, lnLF, lnHF	Natural logarithm of RRI variance or variability at the VLF, LF, and HF bands.
nVLF, nLF, nHF (nu)	Ratio of lnVLF, lnLF, lnHF to a natural logarithm of the total RRI variance or variability
LF/HF	Ratio of lnLF and lnHF
-/+BRS0(1, 2) (ms/mmHg)	Mean regression slopes (gains) for down (-RRI/-SBP) and up (+RRI/+SBP) sequences of RRI and SBP changes with different phase shifts (lags with 0, 1, or 2 beats). A measure of a gain of the full baroreflex loop at different phases and for different directions.
SDBRS0(1, 2)	Regression slope variability (standard deviation of BRS) for all up and down sequences with different phase shifts (lags with 0, 1, or 2 beats). A measure of a gain fluctuation of the full baroreflex loop at different phases. It represents a level of co-activation (positive correlation of gains) between the afferent and efferent components in the baroreflex loop: more fluctuation – less positive correlation.
-/+BPS0(1, 2) (mmHg/s)	Mean regression slopes (gains) for down (-SBP/t) and up (+SBP/t) SBP ramps of detected SBP and RRI sequences with different phase shifts (lags with 0, 1, or 2 beats) in relation to time (t, one beat per sec). A measure of gain of the afferent component of the baroreflex loop at different phases and for different directions.
-/+RRIS0(1, 2) (ms/s)	Mean regression slopes (gains) for down (-RRI/t) and up (+RRI/t) RRI ramps of the detected SBP and RRI sequences with different phase shifts (lags with 0, 1, or 2 beats) in relation to time (t, one beat per sec). A measure of gain of the efferent component of the baroreflex loop at different phases and for different directions.
-/+BEI0(1, 2) (%/100)	The ratio between the number of down (-RRI/-SBP) or up (+RRI/+SBP) sequences and the total number of up or down SBP ramp-like changes (SBP ramps with and without RR-interval changes). The so-called Baroreflex Effectiveness Index (BEI) or the number of effective baroreflex reactions. A measure of gating effect on baroreflex reactions at different phases and for different directions.
-/+BEIt (%/100)	The total number of down (-) or up (+) effective baroreflex reactions for all phases (BEIt=BEI0+BEI1+BEI2). A measure of total gating effect on baroreflex reactions for different directions.
-/+LAG (beats)	Baroreflex latency estimated by a mean lag between SBP and RRI ramps for all down (-) or up (+) baroreflex sequences over a lag window ranging from zero to two beats: LAG = ((BEI0*1 + BEI1*2 + BEI2*3)/(BEI0 + BEI1 + BEI2))-1. A measure of phase effect of baroreflex reactions for different directions.
-/+SP0(1, 2) (mmHg)	Means of SBP set points for initiation of down (-) and up (+) baroreflex reactions. The SBP start point or the first SBP reading of SBP ramp in the baroreflex sequences: the highest point for down sequences and the lowest point for up sequences.
SP0(1, 2) range (mmHg)	Range between the SBP set points for down and up sequences at different lags (difference between -SP and +SP).

TABLE 2. Age, personality, blood pressure, and heart rate mean and variability measures in depressed and control subjects. Mean (SD)

Variables	Depressed Subjects	Controls	Paired *t* test (*p*)	Power
Age (years)	36.2 (10.9)	36.5 (10.2)	.234	.22
BMI	23.7 (3.4)	24.2 (3.4)	.541	.09
STAI	53.0 (10.8)	35.3 (7.0)	<.001	1.00
ANGOUT	14.0 (13.3)	13.3 (2.5)	.412	.13
ANGIN	18.6 (4.5)	15.2 (3.8)	.007	.80
ANGTOT	43.4 (6.1)	45.6 (6.4)	.209	.24
MC	12.9 (5.1)	18.4 (4.6)	<.001	1.00
CM	21.0 (7.9)	16.1 (6.3)	.020	.67
SBP (mmHg)	129.2 (21.9)	114.7 (20.6)	.008	.80
SDSBP (mmHg)	8.8 (3.1)	8.3 (2.9)	.547	.09
SBP range (mmHg)	55.9 (20.8)	47.8 (12.9)	.061	.47
-MSDp (mmHg)	2.28 (.70)	1.75 (.49)	.002	.93
+MSDp (mmHg)	2.39 (.78)	1.82 (.55)	.002	.92
HR-BP ($mmHg \cdot min^{-1}$)	9072.3 (1947.2)	7246.0 (1510.8)	.001	.94
RRI (ms)	871.6 (126.0)	965.1 (141.9)	.021	.66
VLF (ms^2)	1202.0 (819.3)	797.0 (463.9)	.044	.53
lnVLF	6.80 (.86)	6.50 (.65)	.196	.25
nVLF (nu)	.883 (.085)	.822 (.072)	.020	.67
LF (ms^2)	2536.5 (3544.7)	1010.3 (951.4)	.046	.52
lnLF	7.20 (1.22)	6.60 (.81)	.067	.45
nLF (nu)	.929 (.091)	.834 (.079)	.001	.93
HF (ms^2)	621.0 (604.3)	1284.2 (1170.3)	.018	.68
lnHF	5.97 (1.10)	6.79 (.93)	.010	.77
nHF (nu)	.768 (.079)	.857 (.093)	.001	.95
LF/HF	1.215 (.105)	.980 (.113)	<.001	1.00

TABLE 3. Measures of baroreflex gain, gating, and phase activity in depressed and control subjects. Mean (SD)

Variables	Depressed Subjects	Controls	Paired *t* test (*p*)	Power
+BRS0 (ms/mmHg)	9.03 (4.84)	13.34 (6.23)	.007	.81
-BRS0 (ms/mmHg)	10.06 (5.46)	15.40 (6.78)	.001	.96
+BPS0 (mmHg/s)	3.30 (.87)	2.83 (.65)	.015	.71
-BPS0 (mmHg/s)	3.25 (1.05)	2.64 (.54)	.002	.90
+RRIS0 (ms/s)	30.40 (18.79)	36.15 (16.3)	.252	.20
-RRIS0 (ms/s)	33.00 (21.01)	39.01 (16.0)	.244	.21
+BRS1 (ms/mmHg)	9.16 (5.59)	13.20 (7.25)	.027	.62
-BRS1 (ms/mmHg)	10.67 (5.94)	15.93 (8.43)	.003	.88
+BPS1 (mmHg/s)	3.54 (1.01)	2.99 (.75)	.022	.65
-BPS1 (mmHg/s)	3.28 (1.11)	2.61 (.63)	.003	.88
+RRIS1 (ms/s)	32.37 (19.77)	36.93 (17.29)	.395	.13
-RRIS1 (ms/s)	34.78 (21.52)	39.06 (17.24)	.414	.13
+BRS2 (ms/mmHg)	9.73 (7.16)	13.07 (7.03)	.092	.39
-BRS2 (ms/mmHg)	9.94 (5.39)	14.57 (8.51)	.012	.74
+BPS2 (mmHg/s)	3.65 (1.08)	3.12 (.91)	.043	.54
-BPS2 (mmHg/s)	3.27 (1.19)	2.88 (.74)	.066	.45
+RRIS2 (ms/s)	34.61 (22.02)	38.60 (20.45)	.487	.11
-RRIS2 (ms/s)	32.41 (20.09)	40.00 (19.67)	.180	.26
SDBRS0	5.35 (3.59)	7.52 (3.34)	.025	.63
SDBRS1	5.71 (3.79)	8.10 (4.34)	.025	.63
SDBRS2	5.84 (4.11)	8.50 (4.03)	.016	.70
+LAG (beats)	.809 (.241)	.717 (.255)	.206	.24
–LAG (beats)	.767 (.247)	.662 (.252)	.092	.39
+BEIt (%/100)	1.01 (.45)	.77 (.29)	.047	.52
-BEIt (%/100)	.77 (.39)	.67 (.32)	.367	.14
+BEI0 (%/100)	.41 (.19)	.36 (.15)	.323	.16
-BEI0 (%/100)	.33 (.16)	.33 (.11)	.896	.05
+BEI1 (%/100)	.35 (.20)	.26 (.14)	.088	.40
-BEI1 (%/100)	.25 (.16)	.20 (.13)	.223	.27
+BEI2 (%/100)	.25 (.18)	.15 (.10)	.030	.60
-BEI2 (%/100)	.18 (.15)	.14 (.15)	.325	.16

TABLE 4. SBP set points for baroreflex reactions in depressed and control subjects. Mean (SD)

Variables		Depressed Subjects	Controls	Paired *t* test (*p*)	Power
+SP0 (mmHg)		126.5 (22.2)	112.1 (20.9)	.008	.79
-SP0 (mmHg)		131.9 (22.2)	118.0 (20.9)	.010	.77
+SP1 (mmHg)		125.9 (22.2)	112.1 (21.1)	.013	.73
-SP1 (mmHg)		133.1 (22.3)	119.3 (20.4)	.010	.77
+SP2 (mmHg)		125.3 (22.8)	111.2 (21.6)	.011	.75
-SP2 (mmHg)		133.1 (22.5)	120.7 (20.7)	.021	.66
SP0 range (mmHg)		5.5 (3.2)	6.0 (3.1)	.516	.10
SP1 range (mmHg)		7.3 (3.3)	7.2 (4.5)	.937	.05
SP2 range (mmHg)		8.4 (4.0)	9.8 (6.7)	.263	.20
Paired *t* test (*p*)	SP0 vs. SP1 range	<.001	.041		
	SP0 vs. SP2 range	<.001	.003		
	SP1 vs. SP2 range	.035	.009		
Power	SP0 vs. SP1 range	1.00	.54		
	SP0 vs. SP2 range	.98	.88		
	SP1 vs. SP2 range	.57	.77		

TABLE 5. Age, personality, and physiological variables in depressed subjects among the treatment groups. Treatment (a main treatment agent): 1 - Serotonergic agents (+others** in some cases); 2 - Serotonergic & noradrenergic agents (+others** in some cases); 3 - Dopaminergic agents (+others** in some cases). ** - Anxiolytic, sedative or anticonvulsants agents.

	Treatment groups (Mean and SD)			
Variables	1 (n = 12)	2 (n = 6)	3 (n = 10)	*p*, F(2,25), power
Age	30.1 (10.0)*	36.7 (9.9)	43.3 (8.5)	.012, 5.32, .79
STAI	50.2 (8.4)	46.5 (11.0)*	60.3 (10.0)	.017, 4.84, .75
Medication treatment (months)	43.7 (50.1)	23.6 (24.0)*	140.7 (109.4)	.008, 5.94, .83
Number of episodes	2.6 (1.1)	2.6 (1.7)	3.1 (1.5)	.702, .36, .10
Morbidity time (months)	130.0 (91.2)*	132.0 (168.0)*	334.80 (180.8)	.006, 6.32, .86
+BRS0 (ms/mmHg)	10.51 (3.47)*	12.48 (6.57)*	5.18 (2.08)	.002, 7.93, .93
-BRS0 (ms/mmHg)	11.10 (3.45)*	14.06 (8.55)	6.42 (2.75)	.012, 5.35, .79
+BRS1 (ms/mmHg)	10.77 (3.66)*	13.07 (8.49)*	4.90 (1.87)	.004, 7.06, .90
-BRS1 (ms/mmHg)	12.24 (4.46)*	13.95 (9.15)	6.83 (2.85)	.026, 4.24, .69
+BRS2 (ms/mmHg)	11.54 (4.67)*	14.06 (12.17)	4.97 (1.74)	.019, 4.69, .74
-BRS2 (ms/mmHg)	10.82 (4.46)*	13.90 (7.45)	6.58 (2.64)	.018, 4.79, .74
+RRIS0 (ms/s)	36.27 (15.82)*	39.62 (25.85)	17.83 (10.20)	.022, 4.45, .71
-RRIS0 (ms/s)	38.25 (15.68)*	44.88 (32.84)	19.59 (9.68)	.028, 4.16, .68
+RRIS1 (ms/s)	39.70 (15.50)*	41.46 (27.42)*	18.14 (10.54)	.012, 5.36, .79
-RRIS1 (ms/s)	42.48 (17.71)*	44.36 (31.15)	19.78 (8.78)	.016, 4.88, .75
+RRIS2 (ms/s)	44.13 (18.98)*	41.98 (29.15)	18.76 (10.28)	.012, 5.36, .79
-RRIS2 (ms/s)	39.10 (18.22)*	42.36 (26.98)	19.07 (8.60)	.022, 4.51, .72

* - significant post-hoc differences compared to the treatment group 3.

Table 6. Pearson correlations between baroreflex-related and normalized heart rate variability measures in depressed and control subjects. No significant correlations were found for the afferent component of the baroreflex loop for either of the groups.

	Heart rate variability measures							
	Controls				**Depressed subjects**			
Baroreflex measures	nVLF	nLF	nHF	LF/HF	nVLF	nLF	nHF	LF/HF
+BRS0	-.44*	-.13	.24	-.37	-.39*	-.01	.41*	-.51**
-BRS0	-.43*	-.26	.31	-.55**	-.35	.03	.43*	-.50**
+BRS1	-.39*	-.05	.23	-.28	-.35	.04	.38*	-.43*
-BRS1	-.50**	-.25	.35	-.56**	-.34	.00	.43*	-.53**
+BRS2	-.39*	-.07	.29	-.34	-.35	-.04	.27	-.37*
-BRS2	-.52**	-.27	.31	-.53**	-.34	.04	.36	-.43*
+RRIS0	-.48*	-.03	.17	-.21	-.46*	.06	.29	-.30
-RRIS0	-.51**	-.15	.34	-.47*	-.45*	-.06	.24	-.38*
+RRIS1	-.42*	.04	.22	-.19	-.43*	.13	.33	-.28
-RRIS1	-.49**	-.06	.43*	-.49**	-.44*	-.04	.27	-.39*
+RRIS2	-.43*	-.06	.26	-.31	-.43*	.06	.28	-.29
-RRIS2	-.44*	-.08	.40*	-.46*	-.44*	.01	.24	-.32
+BEI0	.05	.10	.31	-.20	-.15	.22	.42*	-.29
-BEI0	-.04	.37	.41*	-.07	-.08	.52**	.52**	-.05
+BEI1	.46*	.45*	.12	.30	.05	.61**	.23	.37*
-BEI1	.36	.74**	-.08	.70**	-.13	.63**	.14	.51**
+BEI2	.39*	.48*	-.39*	.81**	.05	.63**	.09	.55**
-BEI2	.32	.64**	-.30	.83**	-.22	.56**	.03	.56**
+BEIt	.39*	.44*	.08	.32	-.02	.61**	.31	.26
-BEIt	.28	.72**	-.03	.65**	-.17	.68**	.27	.40*
+LAG	.32	.26	-.42*	.63**	.17	.32	-.27	.65**
-LAG	.25	.38*	-.50**	.80**	-.12	.23	-.24	.51**

* Correlation is significant at the 0.05 level.
** Correlation is significant at the 0.01 level.