Original Article

Specific Serotonin Reuptake Inhibition in Major Depressive Disorder Adversely Affects Novel Markers of Cardiac Risk

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There exists a growing body of evidence linking depression with cardiovascular events, although the mechanisms responsible remain unknown. We investigated the role of the autonomic nervous system and inflammation in the link between coronary heart disease and major depressive disorder (MDD), and examined the cardiac risk modification following pharmacological treatment of depression. We measured cardiac baroreflex function, heart rate variability, pulse pressure and high sensitivity C-reactive protein (hsCRP), all of which have an impact on cardiac risk, pre- and post-treatment in 25 patients with MDD, with no history of coronary heart disease, and in 15 healthy subjects. Treatment consisted of selective serotonin reuptake inhibitors for approximately 12 weeks. No significant differences were observed between untreated MDD patients and healthy subjects in blood pressure, heart rate, baroreflex sensitivity or heart rate variability. Pulse pressure and hsCRP, however, were significantly elevated in patients with MDD prior to treatment ($p=0.023$ and $p=0.025$, respectively). Moreover, while pharmacotherapy was effective in alleviating depression, surprisingly, each of cardiac baroreflex function, heart rate variability, pulse pressure and hsCRP was modified ($p<0.05$) in a manner likely to increase cardiac risk. In conclusion, this study demonstrated higher pulse pressure and hsCRP plasma levels in patients with MDD, which might contribute to increased cardiac risk. Following treatment vagal activity was reduced, as indicated by reductions in baroreflex sensitivity and heart rate variability, accompanied by increases in pulse pressure and plasma hsCRP levels. Mechanisms potentially responsible for generating cardiac risk in patients treated with selective serotonin reuptake inhibitors may need to be therapeutically targeted to reduce the incidence of coronary heart disease in this population. (*Hypertens Res* 2007; 30: 285–293)

***Key Words*: depressive disorder, antidepressants, inflammation, autonomic nervous system, risk factors**

Introduction

There is strong evidence that patients with major depressive disorder (MDD) are at increased risk of developing coronary heart disease (*1–4*). While the mechanism of increased cardiac risk attributable to MDD is not known, a number of reports indicate that the autonomic nervous system and

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inflammatory-mediated atherogenesis may play a role. Over recent years in the cardiology arena, much attention has focused on measures of heart rate variability and baroreflex sensitivity as markers of vagal function and indicators of future cardiac events (*5*). Indeed, reduced sensitivity of the arterial baroreflex, which is predominantly under vagal control, predicts poor outcome in patients following myocardial infarction (*6*). Diminished heart rate variability, which is also attributable to reduced modulation of heart rate by the cardiac vagus, has been described in patients with MDD (*7*).

The importance of inflammatory-mediated atherogenesis in the development of cardiac pathology is widely acknowledged. The observation of elevated plasma inflammatory cytokine concentrations in patients with MDD (*8–10*) raises the possibility that enhanced inflammatory-mediated atherogenesis may also be of importance in generating cardiac risk in MDD. A large prospective study investigating depression and inflammatory markers showed that participants with no history of coronary heart disease but with depression exhibited higher levels of high sensitivity C-reactive protein (hsCRP) than non-depressed participants (*11*). C-reactive protein (CRP) is an acute phase inflammatory marker and is an independent predictor of death from myocardial infarction (*12*). Lowering of CRP levels following statin therapy in patients with acute coronary syndromes results in better clinical outcomes and a reduction in the progression of atherosclerosis (*13*).

In patients with MDD with no underlying heart disease there is little definitive evidence that treating depression reduces the frequency or severity of cardiac events. However, a recent population-based case control analysis by Schlienger *et al*. indicated that current use of selective serotonin reuptake inhibitors (SSRIs) may be associated with a slight reduction in risk of an acute cardiac event (*14*).

Reduced heart rate variability, diminished baroreflex sensitivity, increased pulse pressure, and elevated plasma levels of hsCRP have been associated with an increased risk of future cardiac events in healthy subjects and in patients with existing coronary heart disease (*15–17*). However, whether these markers of cardiac risk are of relevance in the setting of MDD is currently uncertain. Moreover, whether antidepressant medications modify cardiac risk factors in a manner likely to reduce cardiac risk in those with no underlying cardiac pathology remains unknown. Accordingly, in this study we examined, in the setting of SSRI therapy of MDD, cardiac baroreflex function, heart rate variability, pulse pressure and hsCRP levels, which may have an impact on cardiac risk through their relation to cardiac vagal activity, arterial compliance and atherogenesis.

Methods

Participants

Twenty-five patients (11 male/14 female, aged 45±11 years) fulfilling the DSM-IV diagnostic criteria for MDD and 15 healthy subjects with no history of mental or physical illness (9 male/6 female, aged 39±11 years) were recruited from the general community by means of a newspaper advertisement. None of the patients or controls were on any form of medication. Patients were either newly diagnosed ($n=4$), or currently untreated after a recent relapse ($n=21$). All patients were screened for inclusion using two diagnostic instruments: the Mini International Neuropsychiatric Interview (MINI) and the Composite International Diagnostic Interview (CIDI [anxiety and mood disorders sections only]). The Hamilton Depression Scale (17 item) and Hamilton Anxiety Rating Scale (Ham D & A, respectively), the Clinical Global Impressions scale (CGI), and the Beck Depression Inventory (BDI-1) were used to monitor progress. Subjects who met all of the following criteria were eligible for entry: Ham D>18; BDI>18; positivity for major depression on MINI and CIDI; and assessment as having a significant major depression as the primary illness on interview by a psychiatrist. Exclusion criteria included coexistence of any of the following: heart disease, diabetes, medicated hypertension, alcohol/drug abuse, infectious diseases, co-morbid psychotic disorders, eating disorders, mental retardation, high suicide risk, personality disorders and epilepsy. Initial research studies were performed within 10 days of a confirmed diagnosis of MDD. Patients then commenced treatment with an SSRI according to standard dosing ranges for antidepressants ($n=16$ citalopram [40 mg/day], $n=5$ sertraline [200 mg/day], $n=3$ fluvoxamine [200 mg/day], $n=1$ fluoxetine [40 mg/day]). The choice of SSRI was based on clinical grounds and was made by the participating psychiatrist in consultation with the participant. Repeat research studies were performed after approximately 12 weeks of therapy (mean, 94±29 days). Patients were reviewed weekly for the purposes of the study, or more frequently if required on clinical grounds. Improvement in symptoms was defined by a decrease of >50% in Ham D scores and remission was defined as a Ham D<8. One patient, in whom treatment was voluntarily discontinued, did not return for follow-up study and was subsequently removed from the analyses. Healthy subjects were studied on only one occasion. Two subjects in both the control and MDD groups had elevated blood pressure (BP), and two participants in each group were smokers. The research protocol conformed to the relevant guidelines of the National Health and Medical Research Council of Australia and was approved by the Alfred Hospital Ethics Review Committee. Written informed consent was obtained from each subject prior to the study.

All investigations were performed with subjects in the supine position. Studies were conducted in the morning and caffeinated beverages and tobacco smoking were prohibited for 12 h prior to the study. Blood samples were obtained from a percutaneously inserted catheter placed in either the brachial or radial artery under strict sterile conditions as previously described (*18*). Data was obtained after at least 20 min of supine rest. Beat-to-beat BP was measured following arte-

Table 1. Demographic Data of Patients and Healthy Subjects

	Patients with depression (n=24)	Healthy controls (n=15)	p value
Male/Female	10/14	9/6	0.33
Age (years)	45±11	40±11	0.15
BMI (kg/m^2)	26±4	24±5	0.16
Trait anxiety score	64±7	35±9	<0.001***
State anxiety score	59±10	32±9	<0.001***
BDI	29±7	NA	NA
Ham D	26±3	NA	NA

BDI, Beck Depression Inventory; Ham D, Hamilton Depression Scale; NA, not available. Mean±SD.

Table 2. Blood Pressure, Heart Rate, Spectral Analysis, Cross Spectral Analysis and Spontaneous Sequences in Patients with MDD and Healthy Subjects

	Patients with depression	Healthy controls	p value
Blood pressure (SBP/DBP) (mmHg/mmHg)	131±14/69±9	132±18/69±10	0.76/0.69
Heart rate (bpm)	66±12	66±8	0.42
Pulse pressure (mmHg)	61±11	61±13	0.99
SBP and heart rate variability			
LF power (mmHg^2) of SBP	5.7±6.0	6.6±5.8	0.77
HF power (mmHg^2) of SBP	2.35±2.0	1.61±1.3	0.16
LF power (ms^2) of RR	1,122±1,244 (605)	1,015±137 (596)	0.53
HF power (ms^2) of RR	795±1,248 (204)	644±1,462 (217)	0.75
Cross spectral analysis			
LF gain (ms/mmHg)	11±8	12±9	0.93
HF gain (ms/mmHg)	16±21	18±20	0.78
Spontaneous sequences			
% of beats	36±15	38±20	0.98
Slope (ms/mmHg)	20±14	27±23	0.57
Inflammatory markers			
hsCRP (mg/l; median [25–75 percentile])	0.9 [0.5–1.7]	0.4 [0.2–1.0]	0.02

Data in parentheses represent the median value. MDD, major depressive disorder; SBP, systolic blood pressure; DBP, diastolic blood pressure; LF, low frequency; HF, high frequency; hsCRP, high sensitivity C-reactive protein.

rial catheterization. Heart rate and cardiac interval were determined from the lead III ECG recording. Measures of heart rate variability, baroreflex function, pulse pressure and hsCRP plasma concentration were determined by investigators blinded both to the group assignment and treatment phase.

Determination of BP and Heart Rate Variability

Hemodynamic data (*i.e.*, BP and lead III ECG) were acquired at 1,000 Hz using a PowerLab recording system (model ML785/8SP; ADInstruments, Castle Hill, Australia). For calculation of BP and heart rate variability, BP and ECG recordings were resampled at 10 Hz. Heart rate and systolic blood pressure (SBP) variability were quantified by use of a Fast Fourier Transform on a 1,024-point stationary time series (*19*). To perform spectral analysis, a resampling rate of 10 Hz was chosen without interpolation; that is, SBP and RR interval values were replicated every 0.1 s until a new BP cycle or R wave occurred within a 0.1 s window. The power of the SBP or RR interval spectrum was given in units of mmHg^2 or ms^2, respectively. The low frequency (LF) component was obtained by integrating the values of the consecutive bands from 0.04 to 0.15 Hz of the SBP or RR interval spectrum in order to include the 10-s (0.1 Hz) rhythm, and the high frequency (HF) component of the SBP or RR interval was fixed as 0.15–0.4 Hz according to the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (*20*). The pulse pressure was calculated by subtracting the diastolic blood pressure (DBP) from the SBP.

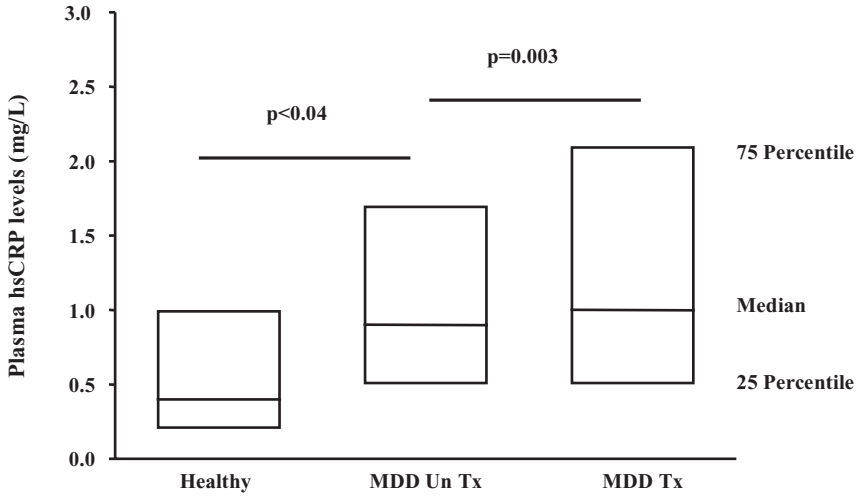

Fig. 1. *High sensitivity plasma C-reactive protein levels in healthy subjects and patients with depressive illness pre- and post-treatment. Results are presented as the median (25–75 percentile). Un Tx, untreated; Tx, treated.*

Cardiac Baroreflex Analysis

Cardiac baroreflex function was assessed using both cross spectral analysis (*21*, *22*) and the sequence method (*23*). In the sequence method of estimating baroreflex sensitivity, computer scanning is used to identify "spontaneous" sequences of three or more consecutive beats in which the SBP progressively rises and the cardiac interval progressively lengthens (type 1 sequences), or in which the SBP progressively falls and cardiac interval progressively shortens (type 2 sequences), with a lag of one beat. For each sequence, the linear correlation coefficient between the cardiac interval and SBP was computed and the sequence was validated when $r>0.85$. The slope between the cardiac interval and SBP was calculated for each validated sequence. The percentage of beats involved in such baroreflex sequences (%) and the average slope were calculated for each recording.

C-Reactive Protein

High sensitivity CRP plasma levels were determined using a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). The principle of the assay is that anti-CRP antibodies, coupled to latex micro-particles, react with CRP antigens in the samples to form a complex which is measured turbidimetrically. The lower detection limit of the assay was 0.03 mg/l and coefficient of variance was 0.62% within runs and 3.6% between runs ($n=21$).

Statistical Analyses

For comparing data between patients and healthy subjects, Student's *t*-test or the Mann-Whitney test were used as appropriate. A paired *t*-test or sign-ranked test was used to assess the effect of SSRI therapy. Normally distributed data are expressed as the mean±standard deviation, non-Gaussian distributed data are presented as the median with 25–75 percentile, and values of $p<0.05$ were considered to indicate statistical significance. Correlations between variables were determined using Pearson product-moment correlation, or Spearman rank order correlation if data were not normally distributed.

Results

Baseline Results

Demographic data for healthy subjects and patients are presented in Table 1. On average, patients had experienced 2.6 previous episodes of depression, with 72% having had 2 or more previous episodes. In 16% of patients the current episode was the first episode. In 16% of the population, the duration of the current episode was less than 3 months, while in 56% the duration of the current episode was greater than 12 months. Twenty-four percent described being depressed for over 5 years, and 67% of these patients had not been on an adequate previous treatment with an antidepressant. Thirty-two percent of patients had never been treated with antidepressants prior to this trial.

BP, heart rate, measures of baroreflex function and heart rate variability were similar in patients with untreated MDD and healthy subjects (Table 2). However, pulse pressure was significantly higher in the unmedicated depressed group compared with the healthy group ($t=-2.387$, df=33, $p=0.023$). Furthermore, hsCRP plasma concentrations were significantly elevated in the unmedicated depressed group (median 0.900 mg/l [25–75 percentile 0.500–1.700] *vs*. 0.400 mg/l [0.200–0.975], $T=233$, n(small)=15,

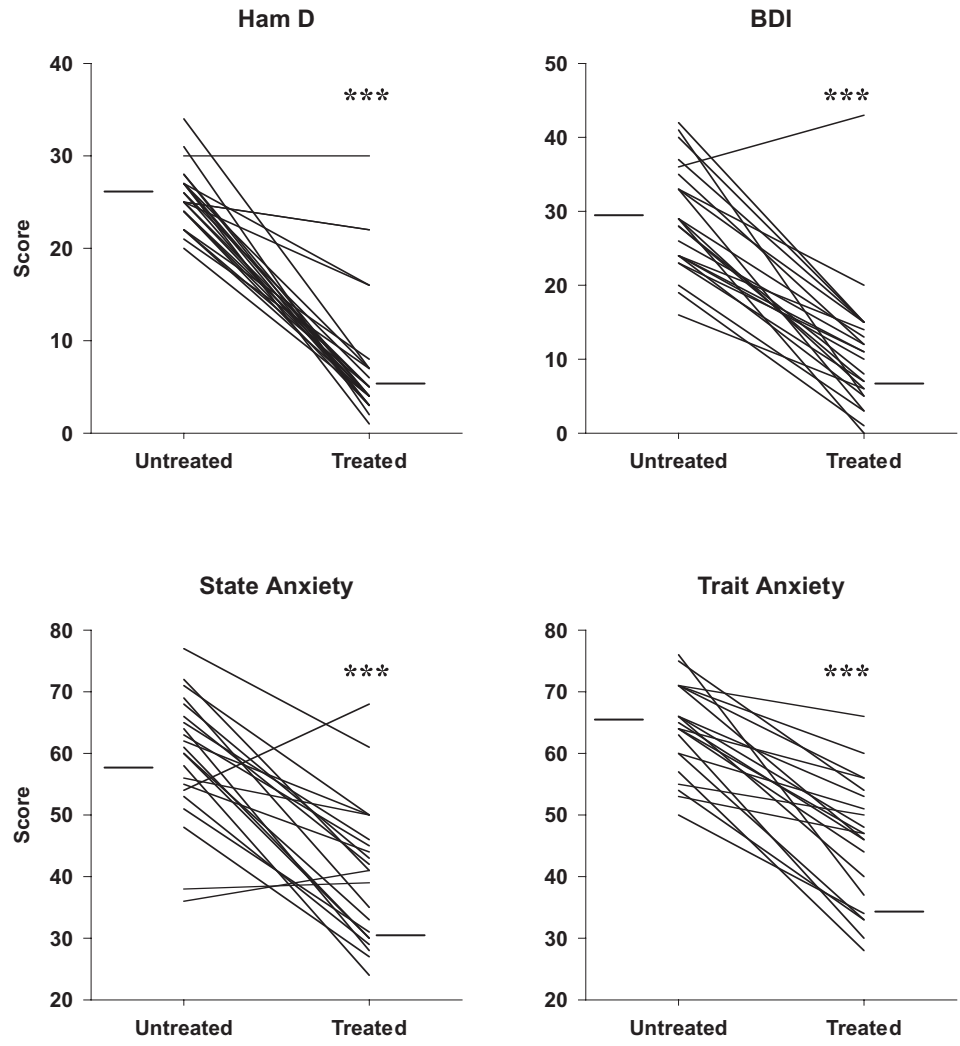

Fig. 2. *Measures of depression and anxiety pre- and post-SSRI treatment in patients with major depressive disorder (Beck Depression Inventory [BDI], Hamilton Depression Scale [Ham D], Spielberger's State-Trait Anxiety Inventory, selective serotonin reuptake inhibitor [SSRI]). Horizontal lines indicate mean values.* ***p $<$ *0.001, treated* vs. *untreated.*

n(big)=25, p=0.04) (Fig. 1).

The number of previous depressive episodes experienced by patients was significantly associated with the decrease in cardiac baroreflex sensitivity (r=−0.475, p=0.02). Moreover, and consistent with the view that increased incidence of episodes of depression is associated with increased cardiac risk, a significant positive relationship was observed between the number of previous episodes and the plasma concentration of hsCRP (r=0.428, p=0.05). No other significant correlations were observed between the psychometric and biological variables, or between hsCRP and the slope of the cardiac baroreflex, heart rate variability or pulse pressure.

Post-Treatment Results

In patients with MDD, treatment with an SSRI resulted in a marked improvement in both clinician-rated (Ham D scores reduced from 26 [24–28] to 10 [6–13], W=−213, T+=9, T−=−222, p<0.001) and patient-rated (BDI scores reduced from 29±7 to 7±7, t=13.209, df=20, p<0.001, Fig. 2) symptoms. Among the 24 patients, 3 did not respond to treatment based on their Ham D and BDI scores. Illustrative of a marked reduction in heart rate variability, treatment was associated with significant diminution in spectral power in the LF band of the RR interval (t=2.327, df=18, p=0.032, Table 3). In addition, baroreflex sensitivity, as indicated by the attenuation in both the gain of the transfer function in the LF band (t=2.134, df=18, p=0.048) and the slope of the cardiac baroreflex (t=3.302, df=22, p=0.003), was reduced (Fig. 3). While there were no significant alterations in SBP or DBP, pulse pressure was significantly increased in patients on an SSRI (61±11 *vs.* 68±23 mmHg, t=−2.205, df=16,

Table 3. Blood Pressure, Heart Rate, Spectral Analysis, Cross Spectral Analysis and Spontaneous Sequences in Patients with MDD before and after SSRI Treatment

	Untreated MDD	Treated MDD	*p* value
Blood pressure (SBP/DBP) (mmHg/mmHg)	131±14/69±9	134±15/64±17	0.40/0.18
Heart rate (bpm)	66±12	64±9	0.32
Pulse pressure (mmHg)	61±11	68±10	0.04
SBP and heart rate variability			
LF power ($mmHg^2$) of SBP	5.7±6.0	4.9±3.8	0.22
HF power ($mmHg^2$) of SBP	2.35±2.0	1.84±1.1	0.18
LF power (ms^2) of RR	1,122±1,244 (605)	655±583 (609)	0.03
HF power (ms^2) of RR	795±1,248 (204)	343±447 (213)	0.11
Cross spectral analysis			
LF gain (ms/mmHg)	11±8	8±4	0.05
HF gain (ms/mmHg)	16±21	11±11	0.10
Spontaneous sequences			
% of beats	36±15	35±20	0.92
Slope (ms/mmHg)	20±14	13±9	0.003

Data in parentheses represent the median value. MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; LF, low frequency; HF, high frequency.

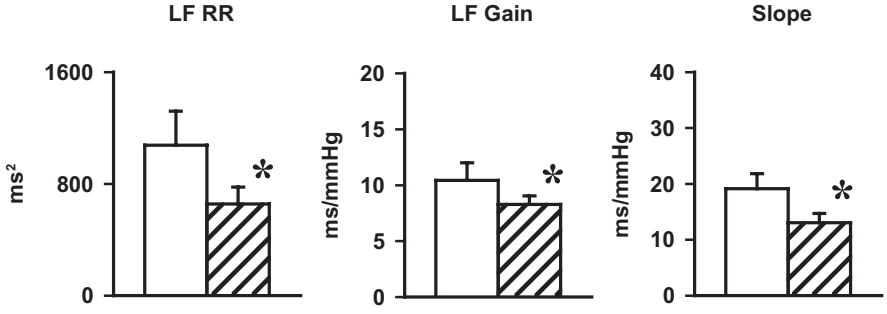

Fig. 3. *Low frequency RR intervals (LF RR), gain of the transfer function analysis between systolic blood pressure (SBP) and RR intervals in the low frequency band (LF gain), and slope of the cardiac baroreflex function estimated using the sequence method in patients with depression before (open bars) and after SSRI treatment (hatched bars) were determined, and all were found to be reduced by SSRI administration. Values are shown as the mean±SD. *Significantly different at* $p < 0.05$. *SSRI, selective serotonin reuptake inhibitor.*

$p=0.042$). In parallel, there occurred a significant elevation in hsCRP plasma levels following SSRI treatment, corresponding to a change from lower to moderate risk of coronary heart disease as expressed by hsCRP levels ($W=153$, $T+=182$, $T-=-29$, $p=0.003$ [Fig. 1]). A decrease in hsCRP concentrations was observed in only 5 patients with MDD. The subjects with higher hsCRP levels following SSRI administration had significantly higher trait anxiety levels on their second visit compared with subjects with lower hsCRP levels (47±11 mg/l and 35±10 mg/l, respectively, $t=-2.105$, df=25, $p=0.05$). Although the majority of patients in the current study were administered citalopram, the most specific of the SSRIs, the modifications in cardiac parameters observed following treatment occurred with all SSRIs used (data not shown).

Discussion

Reduced heart rate variability, diminished baroreflex sensitivity, increased pulse pressure and elevated plasma levels of hsCRP have been associated with an increased risk of future cardiac events in healthy subjects and in patients with existing coronary heart disease. Recent reports provide evidence of a link between vagal activity and inflammation. Dubbed the "cholinergic anti-inflammatory pathway," efferent vagal activity results in acetylcholine release which, in turn, suppresses the inflammatory response (*24*). Conversely, and consistent with our data in patients following SSRI therapy, reduced vagal activity, as indicated by parallel reductions in heart rate variability and the slope of the cardiac baroreflex, is

accompanied by increased release of proinflammatory cytokines. Overall, our results indicate that while SSRIs are highly effective in improving affect and reducing anxiety in patients with MDD, this class of drug may be associated with the promotion of a number of negative biological effects that have previously been demonstrated to be associated with increased cardiac risk.

Our combined analysis of heart rate variability and cardiac baroreflex function indicated that in unmedicated patients with MDD vagal function is not significantly impaired. Interestingly, the presence of comorbid depression in patients presenting with coronary artery disease has been demonstrated to be associated with a reduction in heart rate variability (*25–27*). Using cross spectral analysis, although no comparison was made with non-depressed subjects, Watkins *et al*. have previously demonstrated that anxiety, rather than depression severity, is associated with reduced baroreflex sensitivity (*28*). In the present study, however, we found no significant correlation between state or trait anxiety and measures of baroreflex sensitivity or heart rate variability. The potential importance of baroreflex sensitivity as a measure of cardiac risk emerged following experiments in dogs (*29*), where reduced baroreflex sensitivity was associated with a greater susceptibility to ventricular fibrillation during subsequent ischemic episodes. Subsequently, a large prospective study provided evidence that low values of baroreflex sensitivity and heart rate variability following myocardial infarction were associated with an increased risk of developing ventricular arrhythmia (*6*). Reduced baroreflex sensitivity has also been associated with elevated death rates due to other conditions, such as hypertension (*15*), obesity (*16*) and diabetes (*17*).

The clinical improvement observed in our patients following SSRI administration was accompanied by a substantial reduction both in heart rate variability and the slope of the cardiac baroreflex. The mechanisms that render SSRIs clinically effective have not been fully identified; moreover, the underlying mechanism of the effect of this class of drug on the cardiac baroreflex remains unknown. An action at the level of either the nucleus tractus solitarius (NTS) or ventrolateral medulla seems likely. Long-term administration of citalopram, the most selective serotonin reuptake inhibitor, has been associated with a downregulation of 5-HT_{1A} (serotonin) autoreceptors (*30*). Long-term administration may increase the availability of serotonin at serotonergic receptors in the central nervous system (*31*). Citalopram may reduce baroreflex sensitivity *via* stimulation of the 5-HT_2 or 5-HT_3 receptors. Indeed, baroreflex modulation in the NTS involves both catecholaminergic facilitation and serotonergic inhibition (*32*). Previous studies have shown that 5-HT_3 receptor activation in the NTS was associated with an inhibition of the cardiac component of the baroreceptor reflex in rats (*33*).

In the present study, the plasma hsCRP concentration was elevated in untreated patients with MDD, and increased with SSRI treatment. CRP is an acute phase inflammatory marker produced mainly in the liver (*34*) as a result of stimulation by interleukin-6 (*35*). Several studies have demonstrated that CRP is an independent predictor of death from cardiovascular incidents and myocardial infarction in both males and females, in people of different ages and from different ethnic backgrounds (*34*). Lower, moderate, and higher risk of coronary heart disease are expressed by hsCRP levels in the order of <1, 1–3, and >3 mg/l, respectively (*34*). A statement published in 2003 by the American Heart Association and the Centers for Disease Control and Prevention maintained that there is sufficient evidence that (hs)CRP consistently predicted coronary events in patients suffering from unstable angina or myocardial infarction (*35*). The predictive value of hsCRP persisted following adjustments for other prognostic indicators. The present findings illustrate that unmedicated patients with MDD have higher hsCRP levels than healthy subjects, with many falling into the range of moderate risk. Furthermore, following SSRI treatment the hsCRP plasma concentrations were further elevated, in some MDD patients into the CRP range associated with high cardiac risk. Recent studies have documented that the lowering of hsCRP levels following statin therapy in patients with acute coronary syndromes results in better clinical outcomes and a reduction in the progression of atherosclerosis, independent of lipid lowering (*13*, *36*).

Recently, pulse pressure has gained importance as a strong predictor of cardiovascular risk in both hypertensive and normotensive subjects (*37*, *38*). This risk is present independent of the mean SBP and DBP. In the present study, pulse pressure in patients with depression increased following SSRI treatment in the absence of modification of mean BP. The determinants of pulse pressure include the left ventricular ejection rate, the distensibility of large arteries, heart rate and total peripheral vascular resistance (*39*). In our patient group the heart rate was unchanged. The mechanisms responsible for the increased pulse pressure following therapy remain unknown at the present time.

Despite the proven efficacy of SSRI drugs in treating depression, our data indicate that in patients with MDD without demonstrable coronary heart disease there occur drug effects which are potentially adverse. Given the severity of the depressive illness of the participants, on ethical grounds the trial was of sequential rather than crossover design, and although the observed effects most likely represent specific drug actions, an artifact arising from the trial design cannot be totally excluded.

There is a dearth of information regarding the effects of SSRI treatment on cardiac risk markers in otherwise healthy patients with MDD. Mild bradychardia, dysrhythmia and syncope have been described in patients on chronic SSRI treatment (*40*). In addition, in a previous report SSRIs were not found to significantly reduce the risk of developing first-time myocardial infarction in patients free of factors predisposing to ischemic heart disease (*41*). However, a more recent study reported that subjects administered an SSRI had a reduced

chance of developing myocardial infarction (*42*). Also of note in the present context, our data indicate that SSRIs have an effect on CRP concentrations and, by inference, the development of inflammatory-mediated atherogenesis. In the Physicians' Health Study, which demonstrated a highly significant association between CRP and sudden cardiac death (*43*), the mean time between measurement of CRP and cardiac incident was 9.2 years. In our study, only 24% of patients had suffered from depressive illness for over 5 years, which is far less than the 9 years between CRP measurement and cardiac incident reported in the Physicians' Health Study. The most obvious chronic process whereby inflammation may be involved in the pathogenesis of sudden cardiac death is in the development of coronary atherosclerosis, which underlies the majority of cases of sudden cardiac death (*44*).

Our results suggest that while SSRIs are highly effective in improving affect in patients with MDD, this class of drug may be associated with the promotion of a number of negative biological effects that have been demonstrated to be associated with increased cardiac risk. In this study we examined cardiac baroreflex function, heart rate variability, pulse pressure and hsCRP levels, which may bear on cardiac risk through their relation to cardiac vagal activity, arterial compliance and atherogenesis, both before and after treatment with an SSRI in patients with MDD. While our study was limited by both size and a lack of extended follow up, our findings of reduced heart rate variability, diminished baroreflex sensitivity, increased pulse pressure and elevated plasma levels of hsCRP have, in other clinical contexts, been associated with an increased risk of future cardiac events in healthy subjects and in patients with existing heart disease. These results must be interpreted cautiously. However, there is no clear evidence that treatment of depression decreases future cardiovascular risk in those without existing heart disease. The possible importance of these cardiac risk factors in treated MDD clearly warrants further attention. Future randomized, double-blinded prospective studies are warranted to elucidate the possible importance of these cardiac risk factors in treated MDD.

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