Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia

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The mortality of chronic heart failure (CHF) doubles either when CHF patients are depressed or when their plasma norepinephrine (NE) level exceeds those of controls by ≈40%. We hypothesized that patients with major depression had centrally driven, sustained, stress-related, and treatment-reversible increases in plasma NE capable of increasing mortality in CHF patients with depression. We studied 23 controls and 22 medication-free patients with melancholic depression. In severely depressed patients before and after electroconvulsive therapy (ECT), we measured cerebrospinal fluid (CSF) NE, plasma NE, plasma epinephrine (EPI), and plasma cortisol hourly for 30 h. In mildly-to-moderately depressed melancholic patients, we assessed basal and stress-mediated arterial NE appearance. Severely depressed patients had significant increases in mean around-the-clock levels of CSF NE ($P < 0.02$), plasma NE ($P < 0.02$), plasma EPI ($P < 0.02$), and plasma cortisol ($P < 0.02$). CSF NE, plasma NE, and cortisol all rose together throughout the night and peaked in the morning. Each fell to control values after ECT. Mildly-to-moderately melancholic patients also had increased basal ($P < 0.05$) and stress-related ($P < 0.03$) arterial NE-appearance rates. Severely melancholic depressed, medication-free patients had around-the-clock increases in plasma NE levels capable of increasing mortality in CHF. Twenty-four-hour indices of central noradrenergic, adrenomedullary, and adrenocortical secretion were also elevated. Concurrent diurnal rhythms of these secretions could potentiate their cardiotoxicity. Even mildly-to-moderately depressed melancholic patients had clinically relevant increases in the arterial NE-appearance rate. These findings will not apply to all clinical subtypes of major depression.

cerebrospinal fluid | epinephrine | major depression | cardiovascular disease | chronic heart failure

The coexistence of major depression with chronic heart failure (CHF) doubles the mortality of CHF (1–3). CHF patients with asymptomatic left ventricular dysfunction coupled with high plasma norepinephrine (NE) levels also have a doubling in mortality (4). In one study, plasma NE levels equal to 40% or greater than those in their controls also doubled CHF mortality (5). Even a modest (25%) increase in plasma NE levels over 4 months more than doubled mortality in CHF patients (6). Prior studies have shown that elevated NE levels in patients with CHF can be further increased in an additive fashion by the superimposition of complications known to be associated with increased NE levels (7). Thus, substantially increased NE release in depression would result in significant increases in the burden of NE hypersecretion in patients with CHF who become depressed.

Evidence of increased NE secretion in major depression could help explain increased mortality in patients with CHF who are depressed. However, results from prior studies of NE secretion in depression have been contradictory (reviewed in ref. 8). This ambiguity is likely to reflect almost exclusive reliance on a single measurement of NE level, differences in severity, regimens of antidepressant treatments, and a failure to control for the diagnostic heterogeneity of depressive subgroups. Here, we studied only patients with melancholic depression, characterized by hyperarousal, insomnia, early morning awakening (a diurnal pattern in mood in which the depression is at its worst in the morning), and loss of appetite. We reasoned that patients with melancholic depression would be the group most likely to have NE hypersecretion. We excluded patients with other depressive subtypes, including atypical depression, associated with lethargy, fatigue, hypersomnia, and hyperphagia (9).

Methods

Subjects. ***Continuous-sampling study of severe depression.*** Studies of severely depressed patients were conducted under an Institutional Review Board (IRB)-approved protocol (90-M-199). We studied eight female and two male unmedicated patients with melancholic depression with a mean age of 40.9 ± 2.7 yr (mean ± SD, range 26–54) and six female and six male healthy volunteers with a mean of age 37.7 ± 2.2 yr (mean ± SD, range 27–53). Because of the unequal numbers of males and females in the patient and control groups, we separately reanalyzed the data for female patients and female controls. In addition, patients served as their own controls in the longitudinal study of the depressed phase followed by restudy after electroconvulsive therapy (ECT) (see below).

Study of arterial NE-appearance rate in mild/moderate depression. Under an IRB-approved protocol (88-M-162), we studied eight male

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Abbreviations: BP, blood pressure; CHF, chronic heart failure; CSF, cerebrospinal fluid; ECT, electroconvulsive therapy; EPI, epinephrine; NE, norepinephrine; SNS, sympathetic nervous system.

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and three female unmedicated patients with melancholic depression [mean age 39.8 ± 9.4 yr (mean ± SD), range 28–56 yr] and nine male and four female healthy volunteers (mean age 40.3 ± 9.1 yr, range 26–60 yr). Patients for the study of arterial NE-appearance rate had been medication-free for at least 3 weeks before the study.

Discontinuation of medication did not take place for the purpose of participation in either study. All subjects were on a low-monoamine diet for 3 days before the study, and premenopausal female patients were studied only during the early follicular phase of the menstrual cycle.

Clinical Evaluation of All Subjects. Patients underwent structured interviews using the Schedule for Affective Disorders and Schizophrenia–Lifetime (SADS–LA) and met DSM III-R (American Psychiatric Association) and ICD-10 [World Health Organization (10)] criteria for unipolar major depression. All patients had classic features of melancholic depression, including inappropriate guilt, early morning awakening, loss of appetite, depressive symptoms worse in the morning, and loss of pleasure in usual activities. The Hamilton rating scale for depression in the continuous-sampling study revealed a mean depression score of 33.1 ± 3.4. This score represents patients with a severe depression. The mean Hamilton depression score for patients in the study of arterial NE-appearance rate was 19.1 ± 2.1 (mild to moderate).

Procedures. ***Continuous-sampling study.*** After the insertion of venous and lumbar intrathecal catheters at 7:00 a.m., sampling for cerebrospinal fluid (CSF) NE, plasma NE, and epinephrine (EPI) began at 9:00 a.m. and continued hourly for 30 h. Cortisol was measured every 30 min. The pre-ECT CSF NE levels in these patients are published in ref. 11, which focused on the relationship between CSF NE and CSF corticotropin-releasing hormone (11).

We monitored sleep via 12-lead EEG in all patients before and after ECT and in all controls. Eight of the 11 patients volunteered for longitudinal study while depressed and after bilateral ECT. ECT treatments were administered every other day, three times per week. The mean number of ECT treatments was 9.2 ± 1.4 (mean ± SD). Patients were restudied at 28 ± 8.6 days after ECT was completed.

Statistical analysis. There were some variations across CSF-sampling studies in the exact starting and stopping times of sampling for which data were available for analysis. Data were cropped by eliminating some values at the beginning or end of some studies to achieve a uniform beginning and ending time for the time-series analysis across all subjects and studies.

We calculated the mean value of the 30-h series for each hormone and compared the log-transformed values by using an unpaired Student *t* test for control vs. patients before ECT. The mean values for each hormone in depressed patients before and after ECT were compared in a paired Student *t* test of untransformed difference scores.

In addition to these analyses, we also conducted repeated-measures ANOVA of four 6-h blocks to determine whether hormone elevations were as elevated at night as during the day (time by diagnosis interaction).

Analysis of 24-h rhythm. CSF NE, plasma NE, plasma EPI, and plasma cortisol levels were analyzed for circadian rhythmicity. The presence of sinusoidally varying diurnal trends was tested by cosinor analysis.

Cross-correlation analysis. Cross-correlation analyses were performed on series of measurements of the four substances, as described in ref. 11, to determine the interrelationships of their diurnal rhythms.

Cross-correlation with detrending. Cross-correlation with detrending was also used to assess relations among mediators independent of the circadian component but, rather, by independent patterns of fluctuations among all compounds (12).

Pearson correlations. To test the hypothesis that individuals with high levels of cortisol have high levels of CSF NE, plasma NE, EPI, and cortisol, Pearson correlations of the mean 30-h values of these hormones were computed.

Study of Arterial NE-Appearance Rate. An infusion of *l*-(2,5,6) ring-labeled ^{3}H-NE [specific activity = 40–60 Ci/mmol (1 Ci = 37 GBq)] was administered at a rate of 1.25 μCi/min, producing no measurable pressor response. At 15 and 20 min during the infusion, hemodynamic measures were obtained, and we withdrew arterial and venous blood samples for measurement of baseline arterial NE-appearance rate (or spillover). The subjects then played, for 20 min, a video game that they had practiced earlier. After a rest period of 10 min, hemodynamic measures and blood samples were again obtained, and yohimbine (0.125 mg/kg bolus, followed by a 0.001 mg/kg/min infusion) was administered i.v. for 20 min (13). Yohimbine is an alpha-2 noradrenergic blocker that increases the release of NE into plasma. Afterward, both ^{3}H-NE and yohimbine infusions ended.

Statistical analysis was conducted as follows. The arterial NE-appearance rate was calculated from the following formula:

$$\text{Arterial NE appearance rate } (NE_{sp}) = \text{arterial NE } (NE_a) \times \text{NE clearance } (NE_{cl}).$$

Arterial plasma NE-clearance and -appearance-rate measures were initially analyzed across study conditions by repeated-measures ANOVA, with diagnosis (depressed vs. control) as a grouping factor and study condition (baseline, video game, rest, and yohimbine time points) as the repeated-measure factors. In addition, to calculate changes in parameters across conditions for each subject, the peak responses to the video game and yohimbine were determined. From these calculations, the changes between baseline and peak video game, and pre- and post-yohimbine were computed. These measures were compared between groups by using *t* tests.

Assays. Plasma and CSF NE and other catecholamines were measured by HPLC, with electrochemical detection after batch alumina extraction, as described in ref. 14. The detection limit for NE was <10 pg/ml. Intraassay variability was 3.1%; interassay variability was 4.6%.

For the study of arterial NE-appearance rate, the amounts of ^{3}H-NE in each plasma sample and in a sample of the infusate administered to each subject were measured in fractions of the HPLC column eluate corresponding in retention time to that of NE applied to the column in a mixture of catecholamine standards.

Plasma cortisol was measured by direct RIA with a commercial kit (Diagnostic Products, Los Angeles). All samples from the same subject were analyzed together, and assay runs included both patients and control subjects. The interassay coefficient of variation was <15%.

Results

Continuous-Sampling Study of Severe Depression. ***Pulse rates and blood pressure (BP) measurements. Total patient group vs. controls.*** Patients with major depression studied during the depressed phase had significantly increased pulse rates (89.2 ± 10.6 vs. 70.7 ± 6.6, respectively; $P < 0.0001$); systolic BP (mean ± SD, 127.7 ± 14.4 vs. 116.6 ± 9.8, respectively; $P < 0.04$); and diastolic BP (79.6 ± 9.0 vs. 71.4 ± 6.9, respectively; $P < 0.03$) (see Table 1, which is published as supporting information on the PNAS web site).

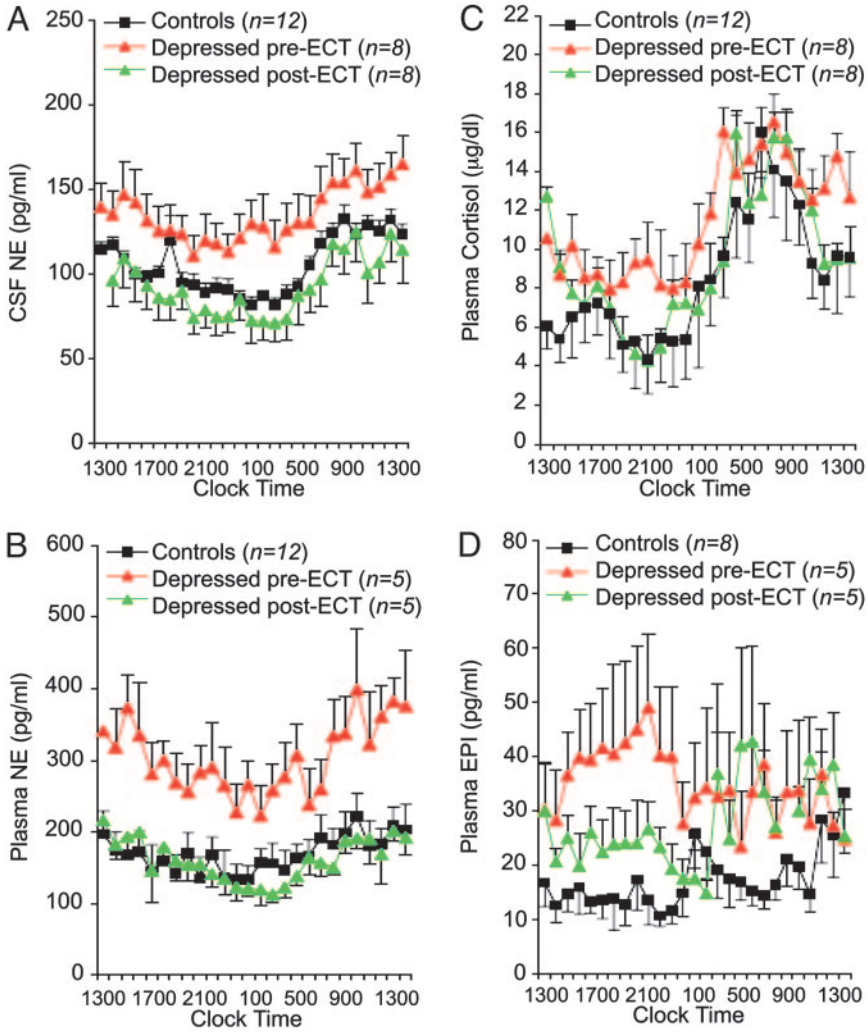

Fig. 1. Around-the-clock curves of CSF NE, plasma NE, plasma EPI, and plasma cortisol levels (mean ± SE) before and after ECT. (*A*) CSF NE levels in control subjects and in patients before and after ECT. (*B*) Plasma NE levels in control subjects and in patients before and after ECT. (*C*) Plasma cortisol levels in control subjects and in patients before and after ECT. (*D*) Plasma EPI levels in control subjects and in patients before and after ECT.

Patients studied before and after ECT. ECT induced significant decreases in pulse rates (88.6 ± 10.3 vs. 75.8 ± 7.7, respectively; $P < 0.006$); systolic BP (126.9 ± 14.7 vs. 112.1 ± 16.5, respectively; $P < 0.03$); and diastolic BP (80.9 ± 6.7 vs. 67.9 ± 9.7, respectively; $P < 0.003$) (see Table 2, which is published as supporting information on the PNAS web site).

Data in female subjects. Compared with female controls, female depressed patients had significantly higher pulse rates (89.9 ± 9.0 vs. 72.1 ± 6.0, respectively; $P < 0.01$); systolic BP (127.4 ± 12.2 vs. 114.6 ± 5.6, respectively; $P < 0.05$); and, at a trend level, diastolic BP (79.3 ± 7.7 vs. 71 ± 1.6, respectively; $P < 0.06$).

CSF NE. *Total patient group vs. controls.* Mean 30-h CSF NE levels were significantly higher in depressed patients than in controls (139.6 ± 36.5 vs. 102.9 ± 24.9, respectively; $P < 0.02$) (Fig. 1*A*). The CSF NE levels were consistently higher at all time points, including overnight while patients slept, as documented by a nonsignificant diagnosis by time interaction.

Patients studied before and after ECT (Fig. 1A). In eight patients studied before and after ECT, CSF NE fell significantly after ECT (133.9 ± 38.9 vs. 90.5 ± 36.0, respectively; $P = 0.05$).

Data in female subjects. Female depressed patients had significantly higher mean CSF NE levels than did female controls (141.5 ± 29.3 vs. 104.8 ± 25.4, respectively; $P < 0.05$).

Plasma NE. *Total patient group vs. controls.* The mean 30-h plasma NE levels, like the CSF NE levels, were significantly higher in depressed patients than in controls (287.6 ± 84.8 vs. 174.5 ± 85.4, respectively; $P < 0.01$) (Fig. 1*B*). The plasma NE levels were higher at all time points, including at night while patients slept (there was no significant diagnosis by time interaction). The NE levels in patients were 40% higher than in controls from 2 a.m. to 1 p.m. The peak plasma NE level occurred at 10 a.m.

Patients studied before and after ECT. Mean 30-h plasma NE levels fell significantly after ECT (304.6 ± 92.6 vs. 158.4 ± 34.9, respectively; $P < 0.05$) (Fig. 1*B*).

Data in female subjects. Female depressed patients had higher mean plasma NE than did female controls (291.3 ± 86.3 vs. 153.7 ± 32.7, respectively; $P < 0.01$).

Plasma cortisol. *Total patient group vs. controls.* Depressed patients had significantly higher mean 30-h plasma cortisol levels than did controls (11.6 ± 3.5 vs. 8.5 ± 2.2, respectively; $P < 0.02$) (Fig. 1*C*). Cortisol levels were similarly elevated throughout the 24-h period (there was no significant diagnosis by time interaction).

Patients studied before and after ECT. Plasma cortisol values fell in depressed patients after ECT (9.5 ± 2.2) so that they no longer differed significantly from those of controls, but the change itself was not significant ($P = 0.31$) (Fig. 1*C*).

Plasma EPI. *Total patient group vs. controls.* Depressed patients had significantly higher mean 30-h plasma EPI levels than did controls [35.2 ± 20.6 vs. 17.1 ± 7.5, respectively; Satterthwaite unequal variance $t(8.85) = 2.34$, $P < 0.05$] (Fig. 1*D*).

Patients studied before and after ECT. EPI levels fell after ECT so that they no longer differed significantly from controls (28.7 ± 16.0). The change between pre- and post-ECT levels was not significant ($P = 0.42$) (Fig. 1*D*).

Correlations among hormones. *Lag correlations.* Lag correlations showed that, around the clock, plasma and CSF NE are both significantly correlated with plasma cortisol at lag zero and for several hours thereafter, reflecting that the diurnal patterns of plasma and CSF NE are similar to that of cortisol but lag slightly behind cortisol. Similarly, CSF and plasma NE are correlated at lag zero.

Detrended analyses. Detrended lag correlations revealed that, around the clock, CSF NE was significantly correlated, independent of the diurnal rhythm, with both plasma NE and plasma cortisol in controls and depressed patients. Thus, the levels of plasma NE and plasma cortisol both rose and fell with CSF NE independent of the diurnal influence but, rather, with respect to moment-to-moment fluctuations around the clock.

Pearson correlations. Mean 30-h levels of EPI were correlated at a relatively high level with both mean daily cortisol ($r = 0.75$, $P < 0.001$) and plasma NE ($r = 0.71$, $P < 0.004$) but not with CSF NE ($r = 0.32$, $P = 0.24$). Plasma NE and CSF NE mean daily values were correlated to a lesser degree ($r = 0.48$, $P < 0.03$) and plasma NE with plasma cortisol ($r = 0.44$, $P < 0.05$).

12-lead EEG-monitored sleep. *Total sleep time.* Total sleep time was similar in depressed patients and controls (mean ± SD, 295.6 ± 188.2 vs. 310.9 ± 56.8 min, respectively, NS). Total sleep time was also similar in patients studied while depressed and after ECT (295.6 ± 188.2 vs. 313 ± 134.1 min, respectively, not significant).

Sleep latency. Sleep latency in patients fell significantly after ECT from 41.7 ± 77.2 to 13.8 ± 30.3 min ($P < 0.02$).

REM latency. REM latency was significantly shorter in depressed patients than in controls (47.1 ± 58.2 vs. 120.9 ± 46.4 min, respectively; $P < 0.01$). REM latency significantly increased in depressed patients studied after ECT (47.1 ± 58.2 vs. 82.2 ± 44.7 min, respectively; $P < 0.05$) but was still significantly shorter than in controls (82.2 ± 44.7 vs. 120.9 ± 46.4, respectively; $P < 0.05$).

Before ECT, there were no relationships between the levels of CSF NE, plasma NE, plasma cortisol, or plasma EPI and the severity of clinical depression, as assessed by the Hamilton rating scale. Moreover, there was no correlation between improvement after ECT and levels of CSF NE, plasma NE, plasma cortisol, or plasma EPI.

The time of the 24-h peak for plasma NE was 10 a.m. The peak cortisol levels occurred at 7 a.m.; cortisol levels at 10 a.m. were close to the values of their peak levels. EPI levels were quite high at 9 a.m. Interestingly, these are the times of maximal vulnerability to myocardial infarction and sudden death.

Study of Arterial NE-Appearance Rate in Mild/Moderate Depression.

Heart rate and blood pressure. *Baseline.* Heart rate was significantly higher in patients than in controls at baseline (mean ± SD, 73.9 ± 8.5 vs. 63.4 ± 11.4, respectively; $P < 0.02$).

Video game. Maximum heart rate during the video game was significantly greater than at baseline (95.8 ± 22.0 vs. 78.2 ± 24.6, respectively; $P < 0.03$).

Yohimbine. Heart rate during the infusion of yohimbine was significantly greater than in controls (78.1 ± 15.5 vs. 60.0 ± 16.6, respectively; $P < 0.05$). Systolic and diastolic blood pressures were similar in depressed patients and controls under all conditions.

Basal arterial NE and induced arterial NE-appearance rate. *Baseline.* The plasma NE concentration was nonsignificantly higher in depressed patients vs. controls (222 ± 108 vs. 155 ± 38 pg/ml, respectively; NS). The NE clearance in the depressed patients was also higher than in controls (2.89 ± 0.85 vs. 2.47 ± 0.76 liters/min, respectively; NS) (see Table 3, which is published as supporting information on the PNAS web site). The combination of a somewhat higher plasma NE and NE clearance led to significantly elevated arterial NE-appearance rate measured in arterial plasma (610 ± 316 vs. 371 ± 183 pg/min, respectively; $P < 0.05$) (Fig. 2).

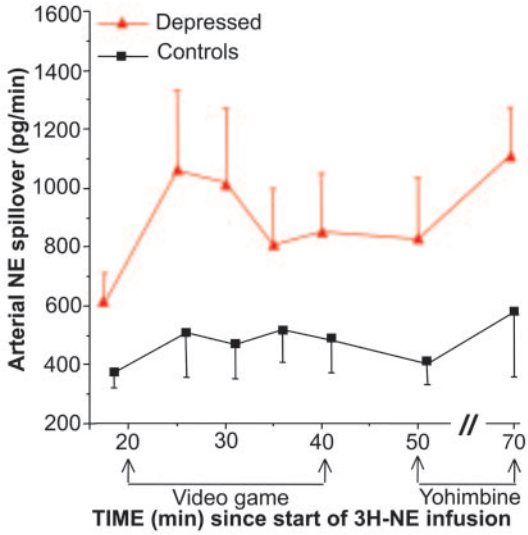

Fig. 2. Arterial NE appearance rate (or NE spillover) at baseline and in response to psychological stressor, video game, and yohimbine, an alpha 2 antagonist that increases the release of NE into plasma.

Response to video game. Maximal arterial NE during the video game was significantly increased in the depressed patients (376 ± 193 vs. 242 ± 66 pg/ml, respectively; $P < 0.05$). Maximal arterial entry rate of NE during the video game was significantly increased in the depressed patients compared with controls ($P < 0.01$). In addition, the depressed patients showed a significantly greater maximal increase in arterial NE-appearance rate during the video game (443 ± 234 vs. 254 ± 159 pg/min, respectively; $P < 0.05$) (Fig. 2).

Response to yohimbine. Arterial NE-appearance rate in response to yohimbine in depressed patients was also significantly increased (1,174 ± 389 vs. 778 ± 357 pg/min, respectively; $P < 0.03$), although the relative increase was similar to that in controls (492 ± 256 vs. 407 ± 329 pg/min, respectively; $P > 0.2$) (Fig. 2).

Discussion

Severely Depressed Patients. Severely depressed patients had significant increases in pulse rates and blood pressures and in around-the-clock levels of CSF NE, plasma NE, plasma EPI, and plasma cortisol. From 2 a.m. to 1 p.m., the patients' NE levels exceeded control levels by a magnitude similar to that associated with a doubling of mortality in patients with CHF. Plasma NE levels peaked at 10 a.m. CSF NE, plasma NE, and plasma cortisol had highly concordant diurnal rhythms. Their levels rose together progressively during the night and peaked together in the morning, a time of maximal vulnerability to myocardial infarction and sudden death (15).

As noted, CSF NE, plasma NE, and plasma cortisol reach their peaks in the morning. One of the cardinal manifestations of melancholic depression is a diurnal rhythm in the severity of depressed affect. In melancholic depression, the depressive symptoms are at their worst in the morning and may improve somewhat as the day progresses. In contrast, atypical depression,

another important clinical subgroup of major depression, is associated with the least severe depression symptoms in the morning and an increase in the evening.

These findings were not artifacts of sleep deprivation. Total sleep time and sleep latency were similar in patients and controls. Patients had the characteristic decreased REM latency reported in prior studies and tended to fall asleep earlier, awakening earlier as well. Although the gender ratio was different in patients and controls, the results were similar when we compared only female patients with female controls. For the ECT data, patients served as their own controls. In addition, these findings do not relate to the conscious distress of major depression. CSF NE, plasma NE, and plasma cortisol began to rise early in the night and rose progressively throughout the night to peak in the morning.

A voluminous literature has accumulated concerning the secretion of NE in major depression. A review of this topic is well beyond the scope of this article and has been recently published (8). Overall, compared with the <10 papers reporting increased NE secretion in depression, there are far more reporting decreased levels of NE secretion.

CSF NE. Available data indicate that CSF and plasma NE derive from different compartments and that the correlation we note between CSF and plasma NE reflects the capacity of noradrenergic neurons in the brain, apart from the sympathetic nervous system (SNS), appears to stimulate the SNS. Thus, a bidirectional blood–brain barrier exists for the passage of NE in and out of the CNS. In the dysautonomia of the Shy–Drager syndrome, although plasma NE levels are extremely low, CSF levels are normal or even increased (16).

CNS NE has effects distinct from those of plasma NE that are important to the mechanisms by which a superimposed depression increases mortality in patients with CHF. Brainstem noradrenergic neurons projecting to the hypothalamus may cause vascular vasoconstriction, independent of the SNS. Moreover, this pathway, although independent of the SNS, nevertheless contributes to SNS activation (17). Thus, an activation of the CNS noradrenergic system has implications for the burden of vasoconstriction and SNS activation imposed by the presence of a melancholic depression.

CNS noradrenergic neurons are also likely to contribute to the classic symptoms of major depression as well. Locus coeruleus activation leads to generalized alarm, activation of the amygdala fear system, and inhibition of areas of the prefrontal cortex that are essential to determining the likelihood of punishment or reward and that exert cortical inhibition on the hypothalamic–pituitary–adrenal axis and the SNS (18). We now know that there is a pronounced loss of glial cells in the subgenual prefrontal cortex, a defect that could contribute to the abnormalities noted here. Parenthetically, NE increases glucose metabolism in the brain and can do so to the extent that it can result in cerebral ischemia.

These findings potentially relate to the mode of action of the ECT-induced amelioration of depression, in which both CSF and plasma NE levels are dramatically reduced. That ECT can down-regulate both the central and peripheral noradrenergic systems in depressed patients is compatible with the observation that all antidepressants tested thus far decrease the firing rate of locus coeruleus neurons in conscious, freely moving rats (19).

CHF patients also have increased levels of NE in the CNS (20). The increased levels of centrally derived NE in CHF are likely to be a consequence of the hemodynamic changes in CHF patients. These changes could either underlie or exacerbate the adverse effects of increased plasma NE in patients with CHF. They could also predispose patients with CHF to depressive illness, which, in turn, could further exacerbate the CHF.

Plasma NE. Excessive NE released from peripheral terminals exerts many effects that increase morbidity and mortality in patients with CHF. NE not only raises blood pressure but also increases myocardial 0_2 consumption, activates platelets, accelerates ventricular remodeling, induces myocyte apoptosis, and is arrythmogenic. Although the plasma concentrations noted here appear to be below the threshold for any direct cardiovascular or vascular effects, it is the much higher intrasynaptic concentrations associated with such elevations in plasma NE that are cardiotoxic (21).

Plasma NE is not secreted in isolation but often with other cardiotoxic compounds whose levels were elevated in our patients. EPI increases cardiac 0_2 consumption and platelet aggregation and is arrythmogenic both directly and through lowered serum potassium levels. Cortisol excess can contribute to hypertension and insulin resistance, sensitizes adrenergic receptors, and increases the activity of phenylethanolamine-*N*-methyltransferase), the rate-limiting enzyme in EPI synthesis.

Working together, both NE and EPI contribute significantly in the development of *in vivo* pressure overload and cardiac hypertrophy (22). The highly concordant diurnal rhythms of CSF NE, plasma NE, and plasma cortisol add an extra measure of cardiotoxicity.

The concurrent peaks of CSF NE, plasma NE, and plasma cortisol as well as the high morning levels of plasma EPI could theoretically be related to the observation that the maximal time for myocardial infarction and sudden death occurs in the morning. The progressive rise of CSF NE, plasma NE, and plasma cortisol throughout the night, as patients slept, also suggests that it is especially important to be attentive to covering CHF patients with beta blockers throughout the night. Elevations in CSF NE, given the role of CNS NE in peripheral hemodynamics independent of the SNS, provides a theoretical rationale for considering beta blockers that are lipophilic for passage across the blood–brain barrier.

Mildly-to-Moderately Depressed Patients: Study of Arterial NE-Appearance Rate. The plasma level of NE reflects its entry into plasma and its clearance from this compartment. A high rate of entry and a low level of clearance will give very high NE levels. A low level of entry and a high rate of clearance will give very low plasma NE levels. Thus, plasma NE levels reflect entry and clearance from blood. Accordingly, the amount of NE released *per se* does not dictate plasma levels of NE on its own. Rather, arterial NE-appearance rate (or arterial spillover) requires the measurement of arterial plasma, which contains the sum of all NE exiting the venous system, as well as the rate of NE clearance from this compartment.

Two prior studies have reported increases in arterial NE-appearance rate in depression. Esler *et al.* (23) found increased NE turnover in 6 of 10 depressed patients. Veith *et al.* (24) reported an increased entry rate of NE into arterialized venous blood. To our knowledge, our study is unique in its assessment of arterial NE-appearance rates at rest and during a psychological challenge in depressed patients.

Neither the patients' baseline plasma NE nor clearance was significantly greater than in controls. However, the concurrence of somewhat higher plasma NE levels and reduced clearance, in the aggregate, led to higher arterial NE-appearance rates. Thus, the relatively greater NE arterial levels compared with plasma NE levels alone could underestimate total body appearance rate of NE, thus potentially accounting for some of the discrepancies in the literature.

Although our patients had significantly higher basal arterial NE-appearance rates, their net responses to the video game were, nevertheless, greater than those of controls. The patients also reached significantly higher maximal appearance rates during the psychological stressor. These findings are compatible

with the principle that superimposed pathogenic stimuli can further increase NE release in a subject who already has elevated plasma NE concentrations.

The NE responses to psychological stress are of a level comparable to those seen during a panic attack in patients with panic disorder (25). Such sympathetic stimulation induced by cognitive challenges preferentially and markedly involves the sympathetic outflow to the heart. Thus, patients with CHF who have even a mild-to-moderate depression could be at greater risk because of the superimposed depression.

Our findings further support the premise that major depression is a systemic disease and add to the urgency for diagnosing and treating major depression in patients with CHF complicated by depression. Because these findings have been documented only in patients with melancholic depression, they may not be relevant to all forms of depressive illness.

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