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Metyrapone Improves Endothelial Dysfunction in Patients With Treated Depression

Andrew J. M. Broadley, MRCP,* Ania Korszun, MRCPsych,† Eltigani Abdelaal, MRCP,* Valentina Moskvina, PhD,‡ John Deanfield, FRCP,§ Christopher J. H. Jones, FRCP,† Michael P. Frenneaux, FRCP, FACC*

Birmingham and London, England; and Cardiff, Wales

OBJECTIVES This study sought to examine the effect of metyrapone on endothelial dysfunction in patients with treated recurrent major depression.

BACKGROUND Depression is an independent risk factor for the development of coronary heart disease, and patients with depression have endothelial dysfunction, an atherogenic abnormality. This abnormality may be attributable to abnormal hypothalamic-pituitary-adrenal (HPA) axis function, a feature of depression, resulting in increased exposure to cortisol. Cortisol administration produces endothelial dysfunction in healthy subjects.

METHODS We measured endothelial function using flow-mediated dilation (FMD) of the brachial artery in 30 patients with depression and in 36 matched control subjects. Patients were randomized (double blind) to metyrapone (an inhibitor of cortisol synthesis) or placebo, and FMD was remeasured 6 h later.

RESULTS At baseline, FMD was impaired in patients versus control subjects (mean [standard error]), −1.27% [0.91%] vs. 4.37% [0.59%] ($p < 0.001$). The FMD was similar in the placebo and the metyrapone patient groups at baseline (0.17% [1.04%] vs. −2.72% [1.30%], $p = 0.11$). Metyrapone significantly reduced plasma cortisol levels. There was a significant improvement in FMD in the metyrapone group from −2.72% [1.30%] to 3.82% [0.99%] ($p < 0.001$), whereas the change in the placebo group, from 0.17% [1.04%] to 1.15% [1.14%], was not significant. Analysis of covariation showed that the effect of metyrapone was significant ($p = 0.034$).

CONCLUSIONS Inhibition of cortisol production by metyrapone ameliorates the endothelial dysfunction seen in depression, suggesting that the mechanism of the endothelial dysfunction may involve cortisol. (J Am Coll Cardiol 2006;48:170–5) © 2006 by the American College of Cardiology Foundation

Epidemiologic evidence has shown depression to be an independent risk factor for the subsequent development of coronary heart disease (CHD), even after controlling for other risk factors such as smoking, although the biological mechanisms underlying this apparently causal association are not yet known (1,2). It has recently been reported that patients with newly diagnosed, untreated depression have endothelial dysfunction (3), and we showed similar dysfunction in young patients with treated depression whose mood was normal at the time of the study and who had no other conventional cardiovascular risk factors (4).

Endothelial dysfunction is a key factor in the atherosclerotic process, and is seen in association with all of the traditional risk factors for atherosclerotic vascular disease, including smoking (5), diabetes (6), hypercholesterolemia (7), and hypertension (8), well before the development of clinically apparent disease. It therefore seems likely that endothelial dysfunction may play a role in the increased CHD risk associated with depression.

The pathophysiological basis for endothelial dysfunction in depression is not yet known but may be related to abnormal function of the hypothalamic-pituitary-adrenal (HPA) axis, which is a characteristic feature of depression. Such abnormalities include cortisol hypersecretion (9), failure of normal suppression of cortisol production after oral dexamethasone (10), and loss of the normal circadian rhythm of cortisol secretion (11). The overall picture is of impaired feedback and consequent HPA axis hyperactivity. However, the extent of these abnormalities is variable within a population with depression, and HPA axis function may perhaps best be described as dysregulated (12). As a consequence of this abnormal HPA axis function, it seems probable that patients with depression are exposed to generally increased levels of cortisol, without necessarily exhibiting frank hypercortisolemia, and in particular do not enjoy a normal circadian nocturnal nadir. Short-term oral cortisol produces endothelial dysfunction in healthy subjects (13), and chronic elevation of cortisol is associated with early atherosclerosis (14). We therefore hypothesized that endothelial dysfunction in depression may be mediated, at

From the *Department of Cardiovascular Medicine, University of Birmingham, Birmingham, England; †Department of Psychological Medicine, St. Bartholomew's and Royal London Hospital School of Medicine, London, England; ‡Department of Psychological Medicine, University of Wales College of Medicine, Cardiff, Wales; and the §Department of Cardiology, Great Ormond Street Hospital for Children, London, England. This work was supported by the British Heart Foundation. The first two authors contributed equally to this work.

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Abbreviations and Acronyms

ANCOVA = analysis of covariance
CHD = coronary heart disease
ECG = electrocardiogram
FMD = flow-mediated dilation
GTN = glyceryl trinitrate
GTNMD = glyceryl trinitrate-mediated dilation
HPA = hypothalamic-pituitary-adrenal
NO = nitric oxide

least in part, by cortisol. To test this hypothesis we examined the acute effect of oral metyrapone, an inhibitor of adrenal 11-hydroxylase and therefore also of cortisol synthesis, on endothelial dysfunction in treated patients with a rigorously defined diagnosis of recurrent major depression.

METHODS

Subjects. We conducted a randomized, double-blind, placebo-controlled trial. Ethical permission was obtained from our local research ethics committee. We recruited patients with a history of recurrent major depression comprising two or more episodes of unipolar depression of at least moderate severity, separated by at least two months of remission, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and the International Classification of Diseases and Related Health Problems (ICD)-10 (15,16). Exclusion criteria included a history of psychotic symptoms that were mood incongruent or present when there was no evidence of a mood disturbance, intravenous drug use with a previous diagnosis of dependency, depression occurring solely in relation to alcohol or substance abuse, or depression occurring secondary to medical illness or medication. All patients were treated and in remission at the time of the study.

Patients were interviewed using the Schedule for Clinical Assessments in Neuropsychiatry (SCAN), a set of instruments validated in assessing, measuring, and classifying the psychopathology and behavior associated with the major adult psychiatric disorders. The ratings from the SCAN interview were entered into CATEG5 (World Health Organization, Division of Mental Health, Geneva, Switzerland), a computerized scoring program that provides diagnoses according to DSM-IV and ICD-10 operational definitions. We also recruited healthy control subjects to provide an age- and gender-matched reference range for brachial artery flow-mediated dilation (FMD). Exclusion criteria for both groups included a history of heart disease or any acquired risk factors for CHD (smoking within the last 10 years, hypertension, diabetes mellitus, plasma cholesterol >6.3 mmol/l), age <18 years or >55 years, body mass index >30 kg/m^2, current pregnancy or menopause or any other condition, drug treatment, or dietary supplements known or likely to affect the measured variables.

Subjects were initially studied in the morning beginning at 8:30 AM, having fasted and avoided alcohol for at least 24 h and caffeine for at least 12 h. On arrival their height and weight were measured, their cardiovascular system was examined, and a 12-lead electrocardiogram (ECG) was performed. After attachment to an ECG monitor and fitting of a Portapres noninvasive continuous blood pressure monitor (TNO Biomedical Instrumentation, Affligem, Belgium), subjects rested supine in a quiet, temperature-controlled environment for 20 min.

Assessment of endothelial function. Brachial artery FMD was then measured using a previously validated technique (17). Briefly, high-resolution ultrasound (7.5 MHz) was used to visualize the brachial artery above its bifurcation at the elbow. An M-mode ultrasound image was fed to a wall tracking system (Vadirec 101, Medical Systems Arnhem, Oosterbrek, the Netherlands), which was able to determine the diastolic diameter of the artery with a resolution of <10 μm. All measurements were performed by a single observer. For measurement of brachial artery diameter at baseline, intraobserver variability was 0.73% for subjects with depression and 0.53% for control subjects. A wrist cuff was inflated to and maintained at between 250 and 300 mm Hg for five min and then released, causing reactive hyperemia in the hand, which in turn led to increased flow through the observed segment of brachial artery. Increased flow through an artery increases the shear stress at the blood-endothelium interface and stimulates healthy endothelial cells to produce the vasodilator nitric oxide (NO). Some of the NO produced diffuses into the vascular smooth muscle layer adjacent to the endothelium, inducing relaxation and vessel dilation. The dilation of the brachial artery in response to increased flow—the FMD—was measured at one-min intervals for the next eight min. The greatest change from baseline within the first three min was taken to be FMD, and was expressed as a percent of baseline diameter. Once the artery had returned to baseline diameter, 1 ml of glyceryl trinitrate (GTN) solution containing 50 μg of GTN was administered sublingually and brachial artery dilation was measured 3 min later, as a measure of glyceryl trinitrate-mediated endothelium-independent dilation (GTNMD).

Blood sampling. With the subjects still supine, blood was taken for measurement of plasma urea and electrolytes, glucose, triglyceride, cholesterol (total, high-density, and low-density), cortisol, and full blood count, all of which were analyzed in our hospital's main laboratory. After venesection the subjects were allowed to sit up and were given a standard low-fat snack and a drink. The purpose of the control group was to provide normal baseline FMD measurements for comparison with the depression group, and they were not studied further after the morning visit.

Metyrapone/placebo. Subjects with depression were randomized in a double-blind fashion to one of two groups: the intervention group was given metyrapone 750 mg with their snack, and a further 750-mg dose to be taken with their midday meal 3.5 h later. The placebo group was given matching placebos. We chose this dosing schedule because earlier work has shown that this regimen produces a

Table 1. Baseline Characteristics of Depression and Control Groups

Characteristic	Depression	Control	p
Anthropomorphic			
Age (yrs)	40.1 [1.88]	39.5 [1.7]	NS
Male (n)	8/30 (27%)	17/36 (47%)	NS
Body mass index	24.4 [0.58]	24.5 [0.53]	NS
Brachial artery diameter (mm)	2.90 [0.13]	2.99 [0.09]	NS
Hematologic			
Total cholesterol (mmol/l)	4.60 [0.16]	4.52 [0.16]	NS
HDL cholesterol (mmol/l)	1.56 [0.09]	1.46 [0.06]	NS
LDL cholesterol (mmol/l)	2.58 [0.15]	2.59 [0.15]	NS
Triglycerides (mmol/l)	1.01 [0.13]	0.99 [0.10]	NS
Fasting glucose (mmol/l)	4.78 [0.09]	4.86 [0.09]	NS
Hemodynamic			
Systolic BP (mm Hg)	114.6 [2.7]	112.7 [2.3]	NS
Diastolic BP (mm Hg)	74.2 [1.8]	70.0 [1.4]	0.066
Flow-mediated dilation (%)	−1.27 [0.91]	4.37 [0.59]	<0.001
GTN mediated dilation (%)	13.5 [1.12]	11.9 [1.23]	NS

NS = $p > 0.25$. Values in brackets are SEM.
BP = blood pressure; GTN = glyceryl trinitrate; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

significant reduction in plasma cortisol at 6 h and is well tolerated (18). Subjects then left the laboratory, and were asked to return 5 h later. They were asked to avoid heavy physical work or exercise in the interval between their visits. They were also asked to continue abstaining from alcohol and caffeinated drinks and to avoid fatty foods. In the interval between tests, they completed the Beck Depression Inventory as a measure of their current symptoms.

Return visit. On their return, subjects were placed in a supine position and were connected to the ECG and Portapres as before. The FMD was measured, and a blood sample was obtained for measurement of plasma cortisol. The FMD was thus measured approximately 6 h after the first dose of metyrapone/placebo. Finally, subjects underwent a brief structured interview so that they might be scored on the Brief Anxiety Scale questionnaire.

Statistical analysis. Group results are expressed as mean [standard error of mean]. Comparison of means was performed within groups using the Student paired *t* test and between groups using Student unpaired *t* test. The effect of placebo/metyrapone on change in cortisol level and on change in FMD was assessed by analysis of covariance (ANCOVA). A p value of <0.05 was considered significant.

RESULTS

Baseline. Thirty-two patients with depression were enrolled and randomized, but two were subsequently excluded because of technically inadequate initial FMD studies. Thirty completed the study (metyrapone = 15). We also measured brachial artery FMD in 36 healthy control subjects at baseline.

Depression and control groups were well matched for anthropomorphic and hematological characteristics. There was no difference in systolic blood pressure between groups, but diastolic blood pressure tended to be higher in the depression group (Table 1). The FMD was significantly impaired in the depression group, of whom 14 showed a paradoxical vasoconstriction in response to hyperemia, giving a negative overall value for FMD (−1.27% [0.91%] vs. 4.37% [0.59%], $p < 0.001$). Paradoxical vasoconstriction is an indicator of endothelial dysfunction and has previously been reported in disease-related and experimentally induced endothelial dysfunction in epicardial coronary arteries (19,20) and in brachial arteries (21–25) using the wrist cuff technique (17). The profile of brachial artery diameter change over time for the depression and control groups is shown in Figure 1. Within the depression group, the placebo and metyrapone groups were well matched for all characteristics (Table 2). They were taking a variety of

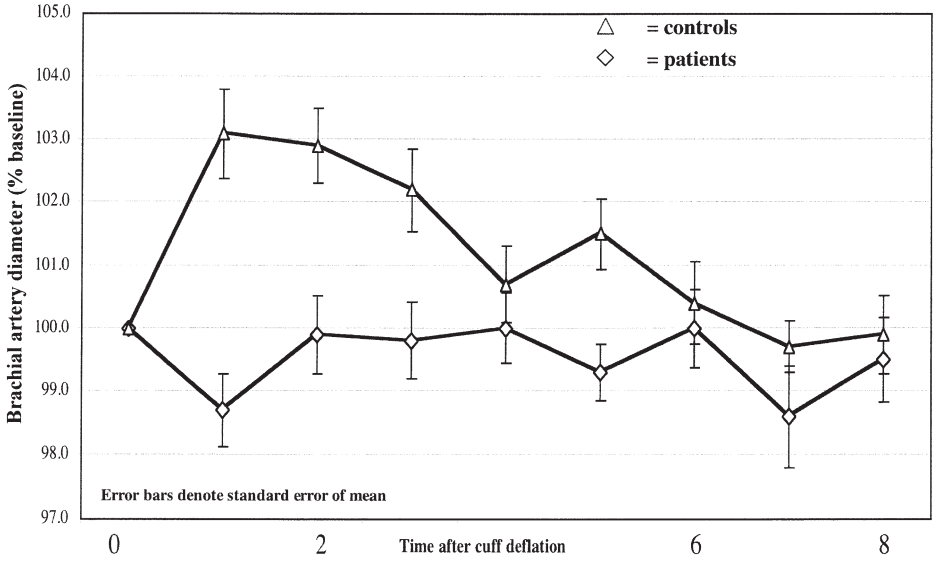

Figure 1. Brachial artery diameter change over time profiles: patients and control subjects (morning flow-mediated dilation).

Table 2. Baseline Characteristics of Placebo and Metyrapone Groups

Characteristic	Placebo	Metyrapone	p
Anthropomorphic			
Age (yrs)	39.4 [2.93]	40.7 [2.42]	NS
Male (n)	4/15 (27%)	4/15 (27%)	NS
Body mass index	25.3 [0.76]	23.5 [0.82]	NS
Brachial artery diameter (mm)	2.90 [0.17]	2.91 [0.20]	NS
Hematologic			
Total cholesterol (mmol/l)	4.65 [0.23]	4.54 [0.24]	NS
HDL cholesterol (mmol/l)	1.54 [0.14]	1.58 [0.11]	NS
LDL cholesterol (mmol/l)	2.63 [0.22]	2.52 [0.21]	NS
Triglycerides (mmol/l)	1.05 [0.13]	0.96 [0.13]	NS
Glucose (mmol/l)	4.91 [0.12]	4.64 [0.13]	NS
Cortisol (nmol/l)	359.4 [25.9]	342.4 [29.6]	NS
Hemodynamic			
Systolic BP (mm Hg)	116.7 [3.0]	112.5 [4.4]	NS
Diastolic BP (mm Hg)	75.5 [2.4]	72.9 [2.7]	NS
Questionnaire scores			
Beck Depression Inventory	16.0 [2.6]	18.2 [2.4]	NS
Basic Anxiety Scale	14.0 [1.8]	13.5 [1.9]	NS

NS = $p > 0.25$. Values in brackets are SEM.
Abbreviations as in Table 1.

prescribed antidepressants (Table 3). The number taking each type of agent was broadly similar between groups.

There was no significant difference at baseline between the placebo and metyrapone groups for FMD (0.17% [1.04%] vs. −2.72% [1.30%], $p = 0.11$) or GTNMD (13.7% [1.73%] vs. 13.2% [1.67%], $p = 0.84$). Paradoxical vasoconstriction occurred in six subjects in the placebo group and eight in the metyrapone group. Cortisol did not differ significantly at baseline between placebo and metyrapone groups (359.4 nmol/l [26.0 nmol/l] vs. 342.3 nmol/l [29.6 nmol/l]; $p = 0.67$).

Return visit. On the return visit, FMD was lower in the placebo than in the metyrapone group (1.15% [1.14%] vs. 3.82% [0.99%]) and was not significantly different from baseline. Paradoxical vasoconstriction occurred in five of the placebo group patients and two of the metyrapone group patients. In the metyrapone group, there was a significant increase in FMD (from −2.72% [1.30%] to 3.82% [0.99%], $p < 0.001$). The ANCOVA including baseline FMD as a covariate showed that the effect of metyrapone on FMD was significant ($p = 0.034$) (Fig. 2). The GTNMD did not change significantly in either group between visits. On the return visit, it was 13.8% [1.8%] and 15.2% [1.4%] in the placebo and metyrapone groups, respectively.

As expected on the basis of its diurnal pattern, which is not completely lost in depression, and habituation to the laboratory environment, plasma cortisol decreased in the placebo group from 359.4 nmol/l [26.0 nmol/l] in the morning to 278.3 nmol/l [34.8 nmol/l] in the afternoon ($p = 0.039$). However, in the metyrapone group, the decrease was much more marked, from 342.3 nmol/l [29.6 nmol/l] to 83.7 nmol/l [6.0 nmol/l] ($p < 0.001$), as anticipated. By ANCOVA, using baseline values as covariate, the effect of metyrapone on cortisol was significant ($p < 0.001$).

There was no significant correlation between cortisol levels and FMD at baseline or after metyrapone. There was no significant correlation between Beck Depression Inventory or Brief Anxiety Scale scores and FMD.

DISCUSSION

In this study, we confirm our report of severe endothelial dysfunction in patients with prior depression but no other established cardiovascular risk factors. We also show that metyrapone, an inhibitor of cortisol biosynthesis, markedly augments brachial artery FMD in these patients.

The degree of impairment of brachial artery FMD in these patients was marked; indeed, many of the patients had a mild transient reduction of brachial artery diameter after release of the wrist cuff. The magnitude of FMD varies substantially with the technique used. The widely used upper arm occlusion technique results in substantially higher FMD than the forearm or wrist cuff techniques (17,26). Mild constrictor responses are observed in many patients with severe endothelial dysfunction (by ourselves and by others) using the wrist cuff technique (4,17) but are not reported with the upper arm cuff technique. Indeed, the FMD observed in the present cohort of patients with treated depression is very similar to what we previously reported in a separate cohort of such patients (4,17). Whereas the inhibitor of NO synthesis N^G-monomethyl L-arginine blocked <40% of brachial artery FMD after release of the upper arm cuff, it completely blocked FMD after release of the wrist cuff; indeed, as in our study, there was a small brachial artery constrictor response (of approximately 2.5%) (17). Our observations (which were obtained using the wrist cuff technique) therefore imply a marked impairment of NO-mediated endothelium-dependent vasodilation of the brachial artery in patients with a prior history of depression. Brachial artery dilation in response to the NO donor GTN was normal. This may provide at least part of the explanation for the increased risk of cardiovascular events associated with depressive illness (1,2). Endothelial dysfunction manifested as impaired brachial artery FMD is associated with all of the known cardiovascular risk factors and is present before clinical manifestations of atheroscle-

Table 3. Antidepressant Therapy

Antidepressants	Placebo*	Metyrapone†
Tricyclic or tricyclic-like	2	4
SSRI	5	3
NARI	2	0
MAOI	0	1
SNRI	4	2
Lithium	1	1
None or noncompliant	3	6
Total	17	17

*One patient was taking an NARI and TCA-like drug, and one was taking an SNRI and lithium. †One patient was taking an SNRI and TCA-like drug, and one was taking an SNRI and lithium.
NARI = norepinephrine reuptake inhibitor; MAOI = monoamine oxidase inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

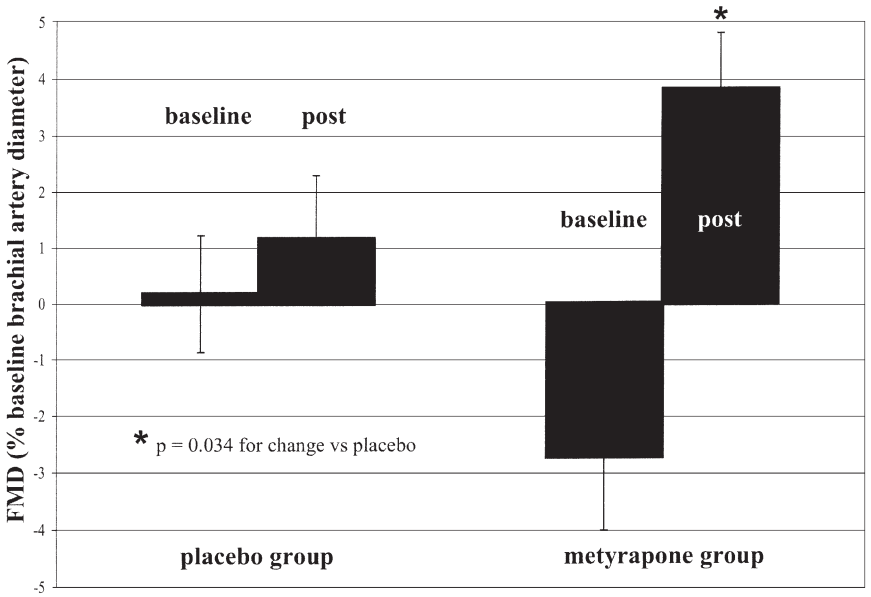

Figure 2. Change in flow-mediated dilation (FMD) after placebo/metyrapone.

rosis (5–8), and has been shown to predict the presence of preclinical coronary artery disease (27).

Our observation that metyrapone substantially augmented brachial artery FMD in patients with a prior history of depression suggests that cortisol may play an important role in mediating endothelial dysfunction in these patients. Metyrapone reduces adrenal cortisol synthesis by inhibiting the adrenal enzyme 11 hydroxylase. Consistent with this, metyrapone therapy reduced plasma cortisol levels. We recently showed that metyrapone also prevented the impairment of brachial artery FMD provoked by acute mental stress in healthy young subjects (28), suggesting that this may also be mediated by cortisol. In that study we also showed that metyrapone had no direct effect on NO release from human umbilical vein endothelial cells, therefore a direct effect of metyrapone on endothelial function, independent of its effect on cortisol, is very unlikely. A previous study has reported that five days of treatment with oral cortisol impaired the forearm vasodilator response to the endothelium-dependent agonist acetylcholine (29). The plasma cortisol levels achieved in these patients were, however, substantially higher than the modest elevation seen typically in acute episodes of depression (30). In treated patients who are in remission, morning plasma cortisol levels are typically within the normal range (as in this study). Nevertheless, there is often evidence of HPA axis dysregulation, with loss of normal circulation variation of cortisol secretions (31). This may explain in part the lack of a correlation between morning plasma cortisol levels and impairment of brachial artery FMD in this study. Furthermore, local vascular concentrations of cortisol are likely to be much more important than plasma concentrations. Local tissue levels of cortisol are influenced by activity of the two isoenzymes of II-beta hydroxysteroid dehydrogenase (HSD). The type I enzyme catalyses the conversion of inactive cortisone to active cortisol, and the type II enzyme catalyses the opposite reaction (31). Expression of these enzymes has been reported in the human vessels (32). Interestingly, in addition to inhibiting adrenal cortisol biosynthesis, metyrapone inhibits type I beta-HSD and may therefore have greater effects on tissue cortisol concentrations than on plasma concentrations (33).

Several possible mechanisms may mediate the adverse effect of cortisol on endothelial function. Glucocorticoids seem to inhibit NO synthesis by both endothelial nitric oxide synthase and inducible nitric oxide synthase in cell and tissue models via both a direct mechanism (34) and reduced production of the essential cofactor tetrahydrobiopterin (35). Glucocorticoids also have recently been shown to enhance vascular superoxide production (36).

Study limitations. For technical reasons, we were unable to quantify reactive hyperemia after cuff deflation. We cannot therefore exclude the theoretical possibility that metyrapone produced a significant increase in the reactive hyperemic response via an unknown mechanism, and that a greater flow stimulus rather than improved endothelial function was responsible for the enhanced FMD observed. This is unlikely.

Significance of the findings. Our findings strongly support a role for cortisol in mediating endothelial dysfunction in depression. Cortisol is also thought to play a role in the pathophysiology of the depression (37). Although metyrapone is not itself suitable as a therapeutic agent (although it has been tried in the past), our findings indicate a possible future direction in pharmacotherapy aimed at reducing CHD risk.

Reprint requests and correspondence: Dr. Michael P. Frenneaux, Department of Cardiovascular Medicine, The Medical School, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom. E-mail: m.p.frenneaux@bham.ac.uk.

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