Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function

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Aims
We investigated the relationship between autonomic nervous system balance, systemic immune activation, endothelial dysfunction, and depression in patients free of coronary heart disease (CHD) with increased CHD risk.

Methods and results
Depression status (Beck Depression Inventory, BDI), selected CHD risk factors, inflammation markers, measures of heart rate variability (HRV), and indices of endothelial function (flow-mediated dilation, FMD) were evaluated in 415 subjects free of CHD, diabetes mellitus, and other life-threatening conditions, with at least two CHD risk factors among the following: older age, male gender, current smoking, hypertension, and dislipidaemia. Overall, 51.7% of the participants were males, aged 57.6 ± 8.8 years on average (minimum 30, maximum 70). Almost half were hypertensive, 43.9% were dyslipidemic, 30.4% current smokers, and 23.1% showed a depressive symptomatology (BDI ≥ 10). Logistic regression showed that, as compared with non-depressed individuals and after adjustment for age, gender, and hypertension, depressive subjects were significantly more likely to be smokers, to have higher total cholesterol, higher C-reactive protein, and Interleukin-6. In addition, depressed subjects were more likely to have altered HRV and their FMD was severely impaired (adjusted odds ratio of 1% increase = 0.72; 95% CI: 0.61–0.86).

Conclusion
Our data indicate an independent association between depression and impaired HRV, systemic inflammatory, and endothelial function. These mechanisms play a role not only in the complication of advanced forms of disease, but also promote and/or accelerate the early disease and connect depression and CHD.

Keywords
Depression disorders • Coronary heart disease • Autonomic nervous system • Endothelial function • Inflammation markers

Introduction
In the last decade, the association between depression and an increased risk of cardiovascular events has been repeatedly demonstrated in both the general population1 and patients with coronary heart disease (CHD).2,3 To account for this association, several potential explanations have been suggested including poor adherence to the therapy and a different lifestyle of depressed individuals,4 modifications in platelet function,5 abnormal autonomic tone,6 systemic immune activation,7 and endothelial dysfunction.8

Among the above, altered cardiac autonomic tone represents one of the most plausible explanations: a sympatho-vagal imbalance due to an excessive cardiac sympathetic modulation and/or inadequate cardiac parasympathetic tone has been reported in depressed6 and CHD patients.9 In addition, it has been advocated that one of the effects of sympatho-vagal imbalance leading to sympathetic predominance might be to trigger inflammation,10 whose marker levels are increased in subjects with clinical depression.11,12 Finally, it is known that endothelial function is impaired in patients with higher levels of inflammatory markers,13 and recent evidence suggests that depressive disorders are associated with vascular...
endothelial dysfunction in young adults without CHD and patients with CHD.

These factors were separately reported to be altered in depressed subjects free of CHD as well as in patients with both depression and CHD. To provide insights on the issue, a cross-sectional analysis was conducted simultaneously to investigate the association between depression and autonomic nervous system balance, systemic inflammatory response, and endothelial function in patients at risk for CHD but free from disease.

Methods

Study population

All CHD free individuals (negative exercise test results) entering our department (from primary care referral) between September 2003 and November 2005 were asked to participate in the study. A total of 590 subjects were asked to participate, 415 of them satisfied the selection criteria and made up the final sample. Patients signed the informed consent and underwent blood testing, depression evaluation, and clinical examinations. We measured the body mass index (BMI, kg/m²), and obesity was defined as BMI ≥ 30. Echo-doppler and blood sampling were carried out in the morning, after an overnight fast of at least 12 h; CHD medications (beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors) were tapered off and discontinued at least 48 h before the exams.

Subjects were included in the study, if they had at least two CHD risk factors among the following: age ≥ 60 years, male gender, current smoking (≥ 1 cigarette/day), hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or current treatment for hypertension), dislipidaemia (serum cholesterol > 240 mg/dL, or triglycerides > 150 mg/dL, or current treatment for dislipidaemia), and family history of CHD (if at least one of the parents or siblings aged ≤ 55 years had CHD).

Exclusion criteria were presence of neoplasm, kidney or liver failure, systemic inflammatory disease, and/or current antidepressant treatment, left bundle block, paced rhythm, Wolff–Parkinson–White syndrome or patho-physiological conditions that could alter the analysis of heart rate variability (HRV): diabetes mellitus, peripheral neuropathy, atrial fibrillation, and ejection fraction < 45%.

Reasons for the exclusion were cancer detection (n = 3), apparent CHD (n = 7), kidney or liver failure (n = 2), systemic inflammatory disease (n = 2), diabetes mellitus (n = 53), current antidepressant treatment (n = 21), one among left bundle block, paced rhythm, Wolff–Parkinson–White syndrome, atrial fibrillation, and ejection fraction < 45% (n = 8), missing data on some items of the depression score (n = 25), and refusal to provide informed consent was due to the high number of exams to which they had to submit (n = 56).

A total of 212 (51.1%) of the participants were males, aged 57.6 ± 8.8 years on average (minimum 30, maximum 70 years). Hypertensive patients were 49.4% of the total, 43.9% were dyslipidaemic, and 30.4% current smokers.

Assessment of depressive mood

Depression was evaluated at baseline using the Beck Depression Inventory (BDI), a 21-item self-reported measure of depressive symptomatology. Scores range from 0 to 63: a score ≥ 10 is considered a valid indication of clinically significant depression. Complete depression scoring was available for 96% of the cohort because the study personnel were trained to require completion of the questionnaire. Patients with missing data on some items were excluded by the study.

Assessment of heart rate variability

The 24-h Holter recordings were analysed by a Del Mar Avionics Holter System 563/A. The analysis was performed using confirmation, which permits manual labelling of each artefact, premature beat, and pause. Time-domain components of HRV were evaluated and the following parameters were considered in the analysis: standard deviation (SD) for the time between normal-to-normal complexes in the entire 24-h electrocardiographic recording (SDNN), SD of the average normal-to-normal intervals for each 5-min period (SDANN); root-mean square of differences of successive RR intervals (RMSSD); the percentage of adjacent RR intervals > 50 ms apart (pNN50). With these conditions, SDNN represents the SD of the circadian sinus node cycle length; SDANN represents the SD of the 5-min mean cycle lengths over the entire 24-h recording, providing an index of the variability of the average of 5-min intervals over 24 h; pNN50 integrates the previous measure as it stands for short-term HRV.

Assessment of vascular endothelial function

Flow-mediated dilation (FMD) of the brachial artery is considered a valid and reliable non-invasive index of endothelial function. After 15 min of supine relaxation, brachial artery diameter in the non-dominant arm was measured with high-resolution vascular ultrasound (Hewlett-Packard, SONOS 2000 with a 7.0-MHz linear-array transducer) and commercially available software (Brachial Analyzer version 3.2.3, Medical Imaging Applications). The vessel was scanned in longitudinal section, and the centre was identified when the clearest views of the anterior and posterior artery walls had been obtained. Arterial diameter over a 1–2 cm segment was determined for each image with a semiautomatic edge-detection algorithm. Blood flow velocity in the brachial artery was recorded continuously throughout the study with pulsed-wave Doppler. The artery diameter was measured continuously for 1 min at baseline; during 5 min of reduced blood flow (induced by inflation to 300 mmHg of a pneumatic cuff placed at a site distal to the segment of the artery being analysed); finally during 5 min of reactive hyperaemia after cuff release. After a second 15-min period of supine relaxation, vessel diameter was again measured continuously for 5 min after administration of 0.4 mg of sublingual nitroglycerine (NTG). FMD was defined as the maximum percentage increase in vessel diameter during reactive hyperaemia from 10 to 120 s post-deflation of the occlusion cuff. NTG-induced dilation was defined as the peak percentage change in arterial diameter 3–5 min after the administration of NTG.

Biological measurements

After 30 min of rest, venous blood was collected in ethylene diamine tetraacetic acid (EDTA) and stored at −80°C until the time of analysis. Total cholesterol and triglycerides were measured by means of enzymatic methods using commercial kits in an automatic analyzer (Boehringer). HDL-cholesterol was determined after precipitation of apolipoprotein B by enzymatic methods (Boehringer). LDL-cholesterol was calculated according to the Friedewald formula. Fibrinogen (Clauss method), C-reactive protein (Latex/BN II, Dade Behring), Interleukin-6 (IL-6, Quantikine human IL-6), and Tumour necrosis factor-α (TNF-α, Quantikine High Sensitivity human TNF-α, R&D Systems Minneapolis, Minnesota) were also measured.

Data analysis

Characteristics of depressed and non-depressed subjects were initially compared using Fisher’s exact and Kruskal–Wallis tests for categorical and continuous variables, respectively. Correlations between BDI
score and all continuous variables investigated were assessed using Spearman’s rho coefficient.

To evaluate independent associations between BDI score and other variables under investigation, we used both multivariable logistic and linear regression analysis. In the logistic analysis, the dependent variable was depression status as defined by a BDI score ≥ 10. In the linear regression analysis, the dependent variable was the logarithm of the BDI score, which was transformed on a logarithmic scale because of its skewed distribution (Shapiro–Wilk).

We defined regression models a priori including potential confounders (age, gender, smoking, and hypertension) and other variables of interest (obesity, total cholesterol, C-reactive protein, IL-6, FMD, SDANN). Each covariate was tested in its original form or categorized or log-transformed if needed. In addition, each included variable was tested for multicollinearity (using both Pearson correlation and Spearman coefficient) with all other variables already included, as well as for potential interaction terms and/or quadratic/cubic terms. We found very few variables that were collinear and chose to include the most relevant one from a clinical point of view (hypertension instead of systolic or diastolic blood pressure; total cholesterol instead of LDL-cholesterol).

Once a final logistic model was identified, its goodness of fit was assessed through Hosmer–Lemeshow test, and its predictive power computing the area under the Receiving Operator Curve. The outlier analysis was based upon the calculation of Pearson and standardized residuals, change in Pearson chi-square and deviance chi-square, Dbeta influence statistic and leverage (hat diagonal matrix). Specifically, we found 18 influential observations and repeated the analysis excluding these, with no substantial changes. However, given that the number of outliers approached 5% of the total number of patients in the model, the final model was conservatively based upon robust standard errors.

The validity of the final linear regression model was assessed as follows. The assumption of constant error variance was checked graphically, plotting Pearson residuals vs. fitted values, and formally, using Cook and Weisberg’s test for heteroscedasticity. High leverage observations were identified computing Pearson, standardized, and studentized residuals, Cook’s D influence, Welsch distance and hat diagonal matrix. We found 27 high leverage observations and repeated the analysis excluding these, with no substantial changes. However, given that the number of outliers approached 5% of the total number of observations in the model, the final model was conservatively based upon robust standard errors.

There were missing values only for total cholesterol (n = 7) and LDL-cholesterol (n = 8); all final models were repeated excluding total cholesterol and included covariates coefficients and P-values did not relevantly change.

Beyond those variables included in the regression models, all other variables investigated were tested for inclusion and were not significant.

The results of the logistic analysis are presented as OR and 95% confidence limits, whereas the results of the linear regression analysis are presented as beta-coefficients, their standard errors and standardized coefficients, in order to quantify the relative contribution of each covariate to the prediction of BDI score.

Statistical significance was defined as a two-sided P-value < 0.05 for all analyses, which were carried out using STATA software, version 8.2 (Stata Corp., College Station, TX, USA).

Results

A total of 96 (23.1%) subjects showed a depressive symptomatology. Of these, 51 were mildly, 29 moderately, and 16 severely depressed.

Clinical characteristics of the sample by depression status are reported in Table 1. At bivariate analysis, the mean levels of most lipidic indices (total cholesterol, LDL-cholesterol, and triglycerides) were significantly higher in depressed than in non-depressed individuals. Obese patients and the use of diuretics and sartans were more frequently observed in depressed subjects, whereas gender, age, BMI, blood pressure, and other CHD risk factors were comparable between the two groups.

As shown in Table 2, most inflammation markers (C-reactive protein, IL-6, and TNF-α), most indices of HRV (SDNN, SDANN, and RMSSD), and the FMD were all significantly associated with the depression at bivariate analysis.

When BDI score was considered in its original continuous scale, it was positively correlated with total cholesterol, LDL-cholesterol, C-reactive protein, TNF-α, and inversely associated with blood pressure, FMD, NTG-induced dilation, and levels of SDANN and RMSSD (all Spearman P-values < 0.05).

The results of the multivariable analyses investigating the association between depression and abnormalities in autonomic tone, systemic immune activation, and endothelial dysfunction are reported in Tables 3 and 4. We carried out both a linear regression analysis to investigate the potential association between all investigated variables and BDI score (Table 3), and a logistic regression to examine the relationship between the same variables and depression status (BDI score ≥ 10, Table 4).

The multiple regression model showed that, after adjustment for age, gender, smoking, and hypertension, there was an independent and positive association between BDI score (on a logarithmic scale) and total cholesterol, C-reactive protein, and IL-6 levels (with a cut-off value of 2 pg/mL). In contrast, FMD and SDANN were negatively correlated with BDI score. Standardized coefficients indicated that the most important domains in predicting BDI scores were C-reactive protein levels (standardized coefficient = 0.494), SDANN (−0.178) and total cholesterol (0.167).

With the exceptions of current smoking and obesity, the results of the logistic regression analysis were similar: in the logistic model, a depressive mood was significantly associated with higher total cholesterol [odds ratio (OR) = 1.27 each 10 mg/dL increase]; C-reactive protein levels ≥ 1.0 mg/dL (OR = 5.83); IL-6 levels ≥ 2.0 pg/mL (OR = 1.89, although with borderline significance); impaired FMD (OR = 3.57 for those with <5% FMD); and low levels of SDANN (OR = 2.27 for those with <100 points of SDANN).

Obesity and current smoking were significant predictors of depression status (although the latter was borderline), however they were not related to BDI score in the linear regression analysis.

Further adjustments for the other covariates investigated and the inclusion of interaction terms did not relevantly change the results either in terms of magnitude of the associations or their significance (data not shown).

Discussion

In this sample of depressed subjects at risk for CHD, we found a significant and independent association between depression mood and indices of autonomic nervous system alteration, inflammatory system deregulation, and endothelial dysfunction. After controlling for potential confounders, such as age, gender, clinical
characteristics, and medical management, depressed patients were significantly more likely to show a reduced HRV, increased inflammation markers, and endothelial dysfunction.

The originality of our approach stems from the integration of all these measures in one setting, with a panoramic view of the different biochemical, neurophysiological, and vascular functional parameters. In addition, we studied a population of asymptomatic patients, without clinically overt forms of CHD. The three mechanisms of endothelial dysfunction, autonomic dysregulation, and inflammation—which are potentially inter-related—all play a role in depression. What is even more important, this role is observed in patients who were asymptomatic for ischaemic heart disease. It is tempting to hypothesize that these mechanisms may come into play not only in the amplification and in complication of advanced forms of disease, but also in the initiation and progression of the early disease in bridging depression and CHD.

**Heart rate variability and depression disorder**

Among time-domain measures of HRV, SDNN, and SDANN are indices of both parasympathetic and sympathetic tone as mediated by baroreflex activity. RMSSD and pNN50 are measures of the modulation of parasympathetic tone.16

At bivariate analysis, patients with coronary risk factors and depression disorders showed decreased SDNN, SDANN, and RMSSD compared with those without depression, while pNN50 was not significantly reduced. At the multivariable analysis, the only variable of HRV that remained significant was SDANN. This might indicate that the reduction of HRV observed in subjects with coronary risk factors and depression disorders is mainly due to increased sympathetic tone rather than to reduced vagal activity. SDANN estimates long-term components of HRV. The long-term measures have been regard as reflecting the response of cardiac regulation of slower fluctuations due to baroreflexes, neurohormonal rhythms and circadian patterns to challenges of daily life (differences between day and night, and both physical and mental activity).16

We found that, compared with non-depressed patient HRV was significantly reduced in depressed patients, indicating greater autonomic dysfunction. It is known that sympathetic predominance with high catecholamine concentrations has pro-atherogenetic properties. In fact, various studies have documented a relationship between autonomic dysfunction and the severity or progression of CHD.20 suggesting that depression disorders associated with HRV.

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### Table 1 Characteristics of study participants by depression status

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beck Depression Inventory (BDI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Non-depressed (BDI &lt; 10) n = 319</td>
<td>Depressed (BDI ≥ 10) n = 96</td>
<td>P&lt;</td>
<td>Correlation with BDI score (Spearman P)</td>
</tr>
<tr>
<td>Age, year</td>
<td>57.7 ± 9</td>
<td>57.1 ± 9</td>
<td>0.50</td>
<td>0.9</td>
</tr>
<tr>
<td>Male gender, % (n)</td>
<td>51.7 (156)</td>
<td>49.0 (47)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.1 ± 3</td>
<td>26.6 ± 4</td>
<td>0.89</td>
<td>0.9</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30), % (n)</td>
<td>8.2 (26)</td>
<td>33.3 (32)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Current smoking, % (n)</td>
<td>29.1 (93)</td>
<td>34.4 (33)</td>
<td>0.38</td>
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</table>

**Clinical characteristics**

- Family history of coronary heart disease, % (n): 34.8 (111) vs 40.6 (39) (P = 0.33)
- Dislipidaemia, % (n): 42.9 (137) vs 46.9 (45) (P = 0.56)
- Hypertension, % (n): 47.6 (152) vs 55.2 (53) (P = 0.20)
- Systolic blood pressure, mmHg: 142 ± 21 vs 145 ± 18 (P = 0.08)
- Diastolic blood pressure, mmHg: 81.1 ± 7 vs 82.4 ± 8 (P = 0.18)
- Total cholesterol, mg/dL: 208 ± 23 vs 217 ± 25 (P = 0.002)
- Low-density lipoprotein, mg/dL: 125 ± 24 vs 135 ± 20 (P = 0.001)
- High-density lipoprotein, mg/dL: 52.9 ± 12 vs 52.6 ± 18 (P = 0.67)
- Triglycerides, mg/dL: 138 ± 30 vs 145 ± 34 (P = 0.002)
- Blood glucose, mg/dL: 92.2 ± 11 vs 93.6 ± 11 (P = 0.21)

**Drug treatments**

- Beta-blockers, % (n): 34.5 (110) vs 34.4 (33) (P = 0.99)
- Angiotensin-converting enzyme-inhibitors, % (n): 31.0 (99) vs 38.5 (37) (P = 0.17)
- Calcium-antagonists, % (n): 20.7 (66) vs 26.0 (25) (P = 0.26)
- Diuretics, % (n): 36.0 (115) vs 47.9 (46) (P = 0.042)
- Sartans, % (n): 29.1 (93) vs 45.8 (44) (P = 0.003)
- Statins, % (n): 25.1 (80) vs 26.0 (25) (P = 0.89)
- Platelet aggregation inhibitors, % (n): 37.0 (118) vs 38.5 (37) (P = 0.81)

Continuous variables are reported as means ± SD.
*Kruskal–Wallis test for continuous variables; Fisher’s exact test for categorical ones.*
abnormalities could promote early atherosclerosis and/or accelerate the progression of atherosclerosis through platelet aggregation, the stimulation of inflammation, and the alteration of lipoprotein metabolism. In addition, HRV imbalance might increase the risk of mortality in depressed CHD patients through myocardial ischaemia, ventricular arrhythmias and sudden cardiac death, and promote and/or accelerate coronary atherosclerosis.

Markers of inflammation, endothelial dysfunction, and depression disorder

Concerning inflammation status, the present analysis confirms the relationship between depression disorders and high levels of inflammation markers. Specifically, increased levels of C-reactive protein and IL-6 were independently associated with depression.
after correction for potential confounders. Despite the different design of the study, and the fact that we included women also, our results are similar to those of PRIME\textsuperscript{12} and MONIKA-KORA case–control study.\textsuperscript{11}

With respect to endothelial dysfunction, recent evidence demonstrated a strong and independent association between endothelial dysfunction and cardiovascular events in patients with and without CHD.\textsuperscript{23,24} The present study found similar impairment in depressed subjects, who showed significantly lower FMD compared with healthy individuals.

Inflammation has the possibility of impairing FMD through the reduction of the bioavailability of endothelium-derived vasodilators, thereby decreasing the expression of endothelial nitric oxide synthase (eNOS) and nitric oxide synthesis, in part by reducing the half-life of messenger eNOS.\textsuperscript{25} Another potential explanation is the influence mediated by IL-6 on the autonomic nervous system balance, as it affects the hypothalamic–pituitary–adrenal axis at the level of the pituitary and adrenal glands.\textsuperscript{26} Indeed, as the effects of inflammation are seen in the endothelium, heart and the brain, its activation may increase the deregulation of the autonomic system and endothelium-dependent blood flow responses in depressed subjects, as it has already been demonstrated in other populations.\textsuperscript{27}

### Table 4

Results from logistic regression model predicting depression (Beck Depression Inventory score ≥10), with forced entry of age, gender, current smoking and hypertension

<table>
<thead>
<tr>
<th>Variables</th>
<th>Depression OR (Robust 95% CI)</th>
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<tbody>
<tr>
<td>Age (1 year increase)</td>
<td>0.99 (0.95–1.02)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.94 (0.53–1.69)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.88 (1.01–3.53)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.41 (0.80–2.47)</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30)</td>
<td>2.66 (1.30–5.44)</td>
</tr>
<tr>
<td>Total cholesterol (10 mg/dL increase)</td>
<td>1.27 (1.11–1.46)</td>
</tr>
<tr>
<td>C-reactive protein (≥1 vs. &lt;1 mg/dL)</td>
<td>5.83 (3.24–10.55)</td>
</tr>
<tr>
<td>Interleukin-6 (≥2 vs. &lt;2 pg/mL)</td>
<td>1.89 (1.01–3.69)</td>
</tr>
<tr>
<td>Flow-mediated dilation (≥5 vs. ≤5%)</td>
<td>0.28 (0.15–0.53)</td>
</tr>
<tr>
<td>SDANN (≥100 vs. &lt;100 U\textsuperscript{b})</td>
<td>0.44 (0.25–0.76)</td>
</tr>
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</table>

\textsuperscript{a}Standard deviation of the average of NN intervals for each 5-min period.

Logistic model parameters: number of obs. = 408; Wald chi-squared = 79.6; Hosmer–Lemeshow goodness of fit \( P = 0.12 \); area under the Receiving Operator Curve (ROC) = 0.84. Each OR is adjusted for all factors included in the table.

as potential confounders of the relationship between depression and HRV, inflammation, and endothelial dysfunction markers. Indeed, although both obesity and smoking may interact strongly with inflammation and depression, they did not act as confounders of the association between C-reactive protein and IL-6 levels with depression, and all significant predictors of depression remained such after controlling for both. As regards obesity, this finding may be surprising and is in disagreement with what was reported by Ladwig et al.\textsuperscript{10} Such difference may be explained, at least in part, by the diverse sample and methodology used to assess depression: Ladwig et al. enrolled males only and adopted a subscale from the Von Zerssen method rather than BDI.

With regard to the role of obesity and smoking as a predictor of depression, the discrepancy between the results of the logistic and linear regression analysis (in which neither BMI nor obesity were significant) may be surprising. However, it may just reflect the existence of clinically relevant cut-offs for depression (BDI ≥10) and obesity (BMI > 30). Indeed, when both depression (assessed through BDI, CES-D, DSM-III or others) and BMI(261,735),(325,750) and HRV are treated as continuous variables, results from literature do not suggest a simple linear relationship between the two variables.\textsuperscript{28,31} In contrast, an increasing prevalence of smoking was observed as CES-D score increased in the National Health and Nutrition Examination Survey.\textsuperscript{32} However, besides the use of a different instrument to evaluate depression, much more evidence exists, which suggests an association of smoking with depression when treated dichotomously.\textsuperscript{33}

### Limitations

From this sample, however, it is not possible to clarify whether endothelial dysfunction has a direct relationship with depression disorders or simply represents a marker of other coronary risk factors related to endothelial dysfunction. In fact, by nature of its cross-sectional design, the study does not establish causality between depressive mood and CHD. Anyway, some aspects of this relationship have been already demonstrated in healthy men\textsuperscript{17} and the present study was intended to investigate further associations still to be assessed in CHD free population, assessing for the first time three indices of CHD (inflammation, HRV, and endothelial function) simultaneously in depressed patients.

Other relevant limitations of the study include the relatively small sample size, coming from a single centre, and the fact that other mechanisms and patho-physiological contexts other than those investigated might modulate (or confound) the association between cardiovascular disease and depression; i.e. platelet aggregation, lifestyle changes, alcohol assumption, etc. As a critical point, it also has to be considered that HRV was monitored for 24 h without considering the possible interference of physical and mental activity, and with the interruption of drugs active on cardiovascular system for at least 48 h before and during the HRV tests that could have influenced the response of the autonomic system. In addition, we do not determine the circadian variations of HRV.

### Conclusions

In patients without heart disease, a depression symptomatology was associated with HRV imbalance, elevated inflammatory, markers, and endothelial dysfunction. Our findings are relevant to...
from the patho-physiological viewpoint, but also possibly as a therapeutic target, since there are today several pharmacological, dietary, and lifestyle options to treat endothelial dysfunction and inflammation very early and effectively in the course of the disease.

**Conflict of interest:** none declared.

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**References**


CLINICAL VIGNETTE

Paradoxical embolism with an intact interatrial septum

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A 71-year-old woman with a recent onset of recurrent transient ischaemic attacks was referred for further diagnostic assessment. Stroke occurred each time shortly after performing a Valsalva manoeuvre. The patient mentioned a stable dyspnoea NYHA II, a mildly reduced exercise capacity, and no history of palpitations.

Transoesophageal echocardiography could not detect an intracardiac right-to-left shunt, but showed a delayed appearance of a massive amount of contrast bubbles in the left atrium. By evaluating each pulmonary vein, the contrast flow originated only from the right superior pulmonary vein (Panel A). These findings suggested the presence of a pulmonary arterio-venous malformation in the right superior pulmonary lobe, causing recurrent paradoxical embolisms. The diagnosis was confirmed by a CT-scan of the chest. The fistula was located anteriorly in the right upper pulmonary lobe, with a hypertrophied supplying artery and draining vein (Panel B, arrow).

The patient was re-admitted for (selective) pulmonary angiography and fistula occlusion. The arterio-venous fistula was selectively cannulated and injected with contrast (Panel C). The fistula was successfully coiled with a COOK MWCE-8-PDAS coil (William Cook, Europe). No residual shunt nor damage to the native, non-fistulous parenchyma, was present (Panel D). However, to prevent embolization of thrombus distal of the coil, a vitamin K-antagonist was initiated for a period of 6 months.