Negative Feelings (Discontent) Predict Progress of Intima-Media Thickness of the Common Carotid Artery in Treated Hypertensive Men at High Cardiovascular Risk

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A number of psychosocial factors have been identified as cardiovascular risk factors. The purpose of the present study was to examine, in a prospective study, whether quality of life, as measured by the minor symptoms evaluation profile, was associated with progression of the intima-media thickness in the common carotid artery in a group of treated hypertensive men at high risk of cardiovascular disease (n = 97). Patients with any cardiovascular disease (myocardial infarction, angina pectoris, intermittent claudication, or stroke) at entry felt significantly more discontent, compared with patients without signs or symptoms of cardiovascular disease.

The change in maximum intima-media thickness during the follow-up period was associated with discontent at entry (r = 0.23, P = .03). The relationship between the change in maximum intima-media thickness and discontent at entry remained significant (P = .02) after adjusting for serum-cholesterol and concomitant cardiovascular disease.

In conclusion, discontent in treated hypertensive men at high cardiovascular risk was significantly and independently associated with an increase in maximum intima-media thickness in the common carotid artery. This finding suggests that the experience of well-being may influence the atherosclerotic process. Am J Hypertens 1996;9:545-550

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are not known. Tentatively, the sympathetic nervous system plays an important role as a link between cardiovascular disease and hemodynamic factors as well as endothelial function.9 A decrease of vagal tone may also be of pathophysiological importance.9

Hypertension is associated with an increased risk of cardiovascular disease10 and is often accompanied by abnormalities in lipid and the carbohydrate metabolism and smoking habits.11-13 The coexistence of several risk factors in hypertensive subjects considerably increases the risk of cardiovascular disease.14,15

Noninvasive techniques such as B-mode ultrasound can more directly assess intima-media thickness, thereby giving an opportunity to study early phases in the atherosclerotic disease process.14-16 In the present study of treated hypertensive men with at least one additional cardiovascular risk factor (hypercholesterolemia, tobacco smoking, diabetes mellitus), the intima-media thickness of the common carotid artery was examined in a prospective study during a follow-up period of 3.3 years.

The aim was to examine whether quality of life, as measured by the minor symptoms evaluation profile,17-19 was associated with progress of the intima-media thickness in the common carotid artery in this group of treated hypertensive men at high risk of cardiovascular disease.

SUBJECTS AND METHODS

Five hundred and eight male patients with treated hypertension were included in a risk factor intervention study.19 The inclusion criteria for the patients in this study were, apart from treated hypertension and male sex, aged between 50 and 72 years, and one or more of the following: hypercholesterolemia (serum cholesterol ≥ 6.5 mmol/L), tobacco smoking (one or more cigarettes per day), or diabetes mellitus.20

The serum cholesterol criterion was based on the mean of two measurements. The diagnosis of hypertension had been established according to previously reported routines.11 Exclusion criteria were unwillingness to participate or malignant or other serious chronic disease. The background population was representative of high-risk hypertensives in Gothenburg because the majority (of 90%) was earlier recruited by screening a random third of all men in their respective age groups in Gothenburg.22

From this group of 508 men one-third of the patients were randomly selected to take part in an ultrasound study of the carotid region. Of 169 patients randomized to the ultrasound study, 164 patients agreed to take part and in 142 men good quality measurements of the intima-media thickness in the common carotid artery were achieved. The results from the baseline examination have been published earlier.14 Out of these 142 patients, 112 patients filled in the minor symptom evaluation profile. After 3.3 years of follow-up, 97 of these patients were reexamined with ultrasound. The entry characteristics in the drop-out group did not in any way differ from the group of 97 patients included in the present study (data not shown).

In the risk factor intervention study, the patients were either randomized to an intervention program directed towards hypercholesterolemia, smoking, and diabetes mellitus, or to conventional treatment.20 The aims of the program were to lower total cholesterol below 6.0 mmol/L, help smokers to quit smoking, and to reduce glycosylated hemoglobin (HbA1c) to below 6% in patients with diabetes mellitus. The details of the intervention program and the effects of the intervention in the total study group have been reported previously.20 Because the change in intima-media thickness was similar in the intervention and the usual care groups during follow-up (unpublished data), the patients have been handled as one group in the present study.

All subjects gave informed consent after written and oral information and the study was approved by the Ethical Committee of the Faculty of Medicine, Göteborg University.

Measurements Resting blood pressure was measured phonographically (Korotkoff sounds recorded on electrocardiogram (ECG) paper) in the right arm after a 5 min rest in connection with the ultrasound examination as earlier described.14 Blood pressure was calculated to the nearest 1 mm Hg and the mean of two recordings was used. Body mass index was measured according to recommended principles.20 Venous blood was drawn after an overnight fast and after 5 min of rest in the recumbent position for determination of blood glucose and serum concentrations of total cholesterol and triglycerides using established methods.20 Smoking was assessed by a questionnaire.20 Established criteria for stroke, intermittent claudication, myocardial infarction, and angina pectoris were used.11

Ultrasonography Examination Procedure Subjects were examined in a supine position with an ultrasound scanner (Acuson 128, Mountain View, CA) equipped with a linear 5 or 7 MHz transducer, as earlier described in detail.14,15 The distal part of the right common carotid artery was scanned by modifying the ultrasound beam to pass perpendicular to the vessel wall in order to achieve the typical two-line image of the vessel wall structures from both the anterior and posterior wall. At the position of the thickest part of the far wall intima-media complex, three separate images were captured by ECG triggering20 and recorded on videotape.

Measurements of Intima-Media Thickness The videorecorded frozen images were analyzed offline in a computerized analyzing system along a 10 mm-long section
just proximal to the carotid bulb.\textsuperscript{20} Intima-media thickness was defined as the distance from the leading edge of the lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the far wall. The computer program calculated the maximal and mean values of intima-media thickness.

Interobserver variability (including variation in data collection and measurements) studied in our laboratory with repeated recordings by two independent observers has shown a coefficient of variation for mean wall thickness of 10.2% and 8.9% for maximal intima-media thickness.

Minor Symptoms Evaluation Profile Subjective experiences of the patients were evaluated using a standardized questionnaire\textsuperscript{17-19} at entry of the study and after 3.3 years of follow-up. The Minor Symptoms Evaluation Profile (MSEP) is a self-administered questionnaire with 24 questions based on a visual analog scale (VAS), which has been shown to be valid, reproducible, and sensitive to the effects of treatment.\textsuperscript{17} Low values on the visual analog scale indicate positive feelings and high values indicate negative ones. The MSEP has been shown to discriminate between symptoms induced by different classes of drugs, as well as differences in the subjective well-being of normotensives, borderline hypertensives, and hypertensives.\textsuperscript{18,19} In addition, construct validity has been established by calculating the correlation coefficients between dimensions of MSEP and those of other questionnaires, e.g., the Nottingham Health Profile.\textsuperscript{18} Compared with equivalent dimensions of other questionnaires for measurement of health-related quality of life, the dimensions of the MSEP were found to be relevant.

Instead of using the answers to the individual questions as effect variables, the questions that have similar factor loadings in a principal component analysis are combined. Three dimensions are thus created from 15 of the 24 questions in the MSEP profile.

These three dimensions are assumed to reflect the patient's condition as regards contentment, vitality, and sleep: contentment (seven items: happiness, tranquility, self-control, decisiveness, self-confidence, mental fatigue, and general well-being); vitality (five items: enthusiasm, initiative, endurance, concentration, and responsiveness); and sleep (three items: nocturnal sleep, quality of sleep, and insomnia). By using the three dimensions as primary variables for evaluating subjective symptoms, the variability in the answers can be reduced and the multivariate problem is avoided.

Statistical Methods The results are presented as means and standard deviations. Pearson's correlation coefficient was calculated after verification of normal distribution of the variables in focus. Variables significantly associated in correlation analyses with contentment at baseline were entered as independent variables in a multiple regression analysis with the change in intima-media thickness as the dependent variable. In the next step, presence of cardiovascular organ damage was used as a dummy variable in the multiple regression analysis. A two-sided $P < .05$ was considered as statistically significant.

RESULTS

Clinical characteristics and drug treatment at entry are given in Table 1 (n = 97). Patients with any cardiovascular disease (myocardial infarction, angina pectoris, intermittent claudication, or stroke) at entry felt more discontent at entry, compared with patients without signs or symptoms of cardiovascular disease. The first group had a higher value of contentment at entry, indicating more negative feelings, 31 ± 18 and 23 ± 10, respectively (95% confidence interval for the difference: 2 to 14, $P < .05$). The other two dimensions of the minor symptom evaluation profile, vitality and sleep, did not differ significantly between patients with and without concomitant cardiovascular disease (for vitality, 28 ± 19 and 25 ± 13, respectively, and for sleep 26 ± 23 and 23 ± 24, respectively).

Serum cholesterol was significantly associated with contentment at entry ($r = 0.21$, $P < .05$). The dimensions sleep and vitality were not associated with any of the measured variables at entry.

There were no associations between the mean and maximum intima-media thickness at entry and the three measured dimensions of the minor symptom evaluation profile (data not shown).

\begin{table}[h]
\centering
\caption{Patient Characteristics at Entry (n = 97)}
\begin{tabular}{lcc}
\hline
\textbf{Age (years)} & 66.4 (6.1) \\
\textbf{Body mass index (kg/m²)} & 26.8 (3.1) \\
\textbf{Blood pressure (mm Hg)} & \\
\textbf{Systolic} & 150 (20) \\
\textbf{Diastolic} & 91 (10) \\
\textbf{Serum total cholesterol $\geq$ 6.5 mmol/L [number (%)]} & 78 (80) \\
\textbf{Serum total cholesterol (mmol/L)} & 6.7 (1.0) \\
\textbf{Serum-triglycerides (mmol/L)} & 2.1 (1.3) \\
\textbf{Diabetes mellitus [number (%)]} & 71 (72) \\
\textbf{Blood glucose (mmol/L)} & 5.8 (2.3) \\
\textbf{Smokers [number (%)]} & 30 (31) \\
\textbf{Carotid mean intima-media thickness (mm)} & 0.89 (0.17) \\
\textbf{Myocardial infarction [number (%)]} & 9 (9) \\
\textbf{Angina pectoris [number (%)]} & 14 (14) \\
\textbf{Interventricular claudication [number (%)]} & 8 (8) \\
\textbf{Stroke [number (%)]} & 3 (3) \\
\textbf{Any cardiovascular disease [number (%)]} & 22 (23) \\
\textbf{Drug treatment [number (%)]} & \\
\textbf{Diuretic} & 45 (46) \\
\textbf{β-Blocker} & 72 (74) \\
\textbf{Calcium antagonist} & 13 (13) \\
\textbf{ACE inhibitor} & 4 (4) \\
\textbf{Hydralazine} & 17 (18) \\
\hline
\end{tabular}
\end{table}

Values are means (SD), unless otherwise is stated.
The change in mean and maximum intima-media thickness during the follow-up period was associated with contentment at entry ($r = 0.20$, $P = .06$ and $r = 0.23$, $P = .03$, respectively) (Figure 1). Vitality and sleep showed positive, but nonsignificant, associations with the change in intima-media thickness during the follow-up period. The relationship between the change in maximum intima-media thickness and contentment at entry remained significant ($P = .018$) after adjusting for serum cholesterol at entry. Including previous cardiovascular disease (myocardial infarction, angina pectoris, intermittent claudication, and stroke) as a dummy variable did not change the significant relationship ($P = .008$) between the change in maximum intima-media thickness and contentment at entry.

The mean change in maximum intima-media thickness during the follow-up period was 0.052 ± 0.255 mm. If outliers, defined as a change in intima media thickness more than two standard deviations ($n = 4$), were excluded from the analysis, the relationship between contentment at entry and the change in intima-media thickness remained significant ($r = 0.24$, $P = .026$).

No significant relationship was observed between intima-media thickness at entry and the change in intima-media thickness during the follow-up ($r = 0.09$).

There was a close relationship between the measurements of the three MSEP dimensions at entry and at follow-up ($P < .0001$); for contentment $r = 0.71$, for vitality $r = 0.70$, and for sleep $r = 0.73$.

**DISCUSSION**

The results of this study indicate that a measure of discontent was associated with an increased progression rate in maximum intima-media thickness in the common carotid artery, which may indicate a more rapid progress of atherosclerosis.

This finding has to be considered from some methodological aspects. First, quality of life has emerged as an important outcome in evaluating medical care and to evaluate this issue the minor symptom evaluation profile was used. There is no gold standard to measure quality of life. The method used in the present study, the minor symptoms evaluation profile, is based on a questionnaire for self-assessment using a visual analog scale. However, this instrument has been evaluated by assessing the effects of different drugs on well-known symptom profiles. In addition, construct validity has been established by calculating the correlation coefficients between dimensions of MSEP and those of other questionnaires, e.g., the Nottingham Health Profile. Compared with equivalent dimensions of other questionnaires for measurement of health-related quality of life, the dimensions of the MSEP were found to be relevant.

Furthermore, a fundamental requirement is that the instrument used produce the same results in repeated use. This matter has previously been evaluated by the test/retest reliability and has been shown to be acceptable. The close relationship between the measurements of the MSEP dimensions at entry and at follow-up, which was observed for all the three dimensions of MSEP in the present study, confirmed the reliability of the method used in the study.
Patients with cardiovascular disease felt more discontent compared with patients without concomitant cardiovascular disease. This was an expected finding which supports the validity of the MSE profile to estimate the quality of life.

Hence, all these observations taken together make us believe that the MSE profile is a valuable tool to estimate aspects of quality of life that are of clinical importance.

Second, two out of three dimensions of the minor symptoms evaluation profile were not significantly associated with progress of the intima-media thickness. This raises the suspicion that the association between discontent at entry and progress of the maximum intima-media thickness might be a random finding, ie, a type I error. However, contentment may be the most relevant dimension of the three, since this, but not the other two dimensions of the MSE profile, was significantly associated with cardiovascular disease at entry. In addition, as previously discussed, the observation that there was a strong correlation between the measurements of the MSE dimensions at entry and at follow-up makes it unlikely that the finding in focus was by chance.

Third, our study group was not a randomly selected sample of untreated hypertensive men with high coronary risk, even though most of the patients originally were recruited by screening a random third of all men in their respective age groups in Göteborg. This study concerns mostly elderly, treated hypertensive men and we cannot generalize the conclusions to the entire hypertensive population.

Only measures of the right common carotid artery were done and this cannot be claimed to be an overall measure of the atherosclerotic process. Previous studies have shown that different arterial regions seem to differ in relation to different established risk factors for atherosclerotic disease.

With the reservations discussed above, the observations in the present study support some previous observations. A poor social network was associated with an increased mortality, even when the effects of other risk factors like smoking habits, serum cholesterol, and blood pressure were taken into account. It was also shown that the socioeconomic status is related to cardiovascular mortality. Animal studies have clearly shown that social structure and different stressors are associated with atherosclerosis. However, the mechanism by which increased social support may prevent atherosclerotic disease is not clear.

The type A behavior pattern is characterized by competitive drive, time urgency, hostility, and a strong job involvement. This behavior pattern has been suggested as a risk factor for developing heart disease. In a small cross-sectional ultrasound study an index to measure anger was significantly associated with the plaque score in patients with signs of atherosclerosis or with risk factors for atherosclerosis. In the present study no cross-sectional associations between ultrasound measurement of the common carotid artery and the three dimensions of the minor symptoms evaluation profile were revealed.

As discussed above, discontent was associated with presence of cardiovascular disease. Therefore, one might believe that the significant association between the change in maximum intima-media thickness in the common carotid artery and discontent at entry was due to the presence of cardiovascular disease in those who both felt discontent and had a high rate of progress of intima-media thickness during follow-up. However, in the multiple regression analysis this association remained significant after adjusting for concomitant cardiovascular disease.

In conclusion, discontent in treated hypertensive men at high cardiovascular risk was significantly and independently associated with an increase in maximum intima-media thickness in the common carotid artery. This finding suggests that the experience of subjective well-being may influence the atherosclerotic process. The causal relationship is, however, not yet known.

REFERENCES


