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Type A Behavior Pattern and Coronary Atherosclerosis

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SUMMARY Previous research has demonstrated an increased rate of clinical coronary heart disease (CHD) events among people who exhibit a "coronary prone" (Type A) behavior pattern. This study was undertaken to determine whether the association between behavior pattern Type A and CHD might be extended beyond clinical CHD events to include also the coronary atherosclerotic process. In addition to usual clinical evaluation, 156 consecutive patients referred for diagnostic coronary angiography were independently assessed on the basis of a structured interview and assigned a rating of Type A, Type B, or Type X (indeterminate).

Traditional physiologic factors — age, sex, cholesterol and cigarette smoking — were found to correlate with atherosclerotic disease. Type A patients were found in increasing proportions among groups of patients with coronary occlusions of moderate to severe degree compared with patients with only mild occlusions. This increasing proportion of Type A patients with increasing disease severity remained significant, even when age, sex, blood pressure, serum cholesterol level and cigarette smoking history were all simultaneously covaried.

These findings suggest that, independently of traditional risk factors, behavior pattern Type A may contribute to the risk of clinical CHD events via effects on the atherosclerotic process.

MANY INVESTIGATORS HAVE SHOWN that increased levels of risk factors such as cholesterol, blood pressure and cigarette smoking are prospectively associated with increased subsequent expression of the clinical manifestations of coronary heart disease (CHD). Despite such findings among large groups of subjects, the best combination of these traditional risk factors fails to identify most new cases of CHD. Noting that traditional risk factors account for only about half of the CHD incidence in middle-aged American men, Keys et al., concluded that other variables may contribute significantly to CHD incidence.

In the search for other contributing causes of CHD, a large body of research has been undertaken to identify psychosocial factors that increase the risk of experiencing clinical CHD events. The most promising work in this area has been that of Rosenman, Friedman and coworkers with regard to the Type A (coronary prone) behavior pattern. The behavior of Type A individuals is characterized by excessive achievement striving, time urgency and hostility, while the Type B person shows a relative absence of these characteristics. Followup over an eight and one-half year period has shown Type A men to have about twice the rate of new CHD events as compared to their Type B counterparts. Furthermore, the significantly higher incidence of CHD events among Type A subjects was not found related to any differences in age, height or weight; and it was statistically independent of smoking, family history of CHD, blood pressure and various indices of lipid metabolism.

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A central issue for the understanding of the association between the Type A behavior pattern and the clinical manifestations of CHD concerns the mechanism underlying this association. One point of view in this regard is expressed in a publication of the Public Health Service:

Stress and strain, especially of an emotional nature or for prolonged periods of time, may play a part in some heart attacks. Many medical men think, however, that the role of such pressures probably becomes important only after already hardened arteries have created the setting for an attack.7

An alternate view postulates that Type A behavior plays a role in accelerating the atherosclerotic process itself. It is important to assess the differential role of these two mechanisms. If the former is the only means whereby Type A behavior contributes to risk of CHD, then primary prevention efforts might best be confined to attempts to alter the traditional risk factors involved in atherogenesis, rather than attempting to modify Type A behavior. However, if Type A behavior pattern can be shown to be associated with the atherosclerotic process itself, then it would appear that its influence is exerted over an extended period of time, along with other factors contributing to atherogenesis, and early preventive efforts should also be aimed at reducing the level of Type A behavior.

The evidence can be interpreted as supporting either of the above mechanisms. Type A men have been found to show a greater increase than Type B men in blood or urinary catecholamines when challenged by the stress of an ordinary working day8 or a puzzle solving task,9 but not under resting conditions. The suggested heightened sympathetic discharge among Type A men could contribute to risk of an acute CHD event via effects upon blood clotting mechanisms, cardiac arrhythmias or direct and indirect effects upon cardiac muscle metabolism.10 On the other hand, repeated sympathetic activations could play a role in promoting "endothelial injury," which has been suggested by Ross and Glomset11 as an important event in atherogenesis. The latter possibility is supported by the observation that men prospectively identified to be Type A show increased coronary atherosclerotic deposition compared to Type B men when studied at autopsy.12 While suggesting increased atherosclerosis among Type A individuals, this finding might also be interpreted as showing that, given an advanced level of atherosclerotic disease premortem, Type A men are more likely than Type B men to experience a fatal coronary event — that is, a selection process determining entry into the autopsy study could have favored Type A men independently of their degree of coronary atherosclerosis.

To resolve this issue, we have attempted in the present study to relate behavior pattern Type A to actual arterial lesions demonstrated in vivo by coronary arteriography. This approach permits demonstration of the relationship between Type A behavior and severity of the atherosclerotic process as indexed by objective measurement while controlling for prior coronary events as a selection factor which may bias the findings.

Methods

One hundred fifty-six consecutive patients referred for diagnostic coronary arteriography at Duke University Medical Center, ranging in age from 15–69 (mean 47 years), participated in this study. Fourteen of these patients were deleted from the sample either because of an inadequate study or because they were found after behavioral evaluation to have been referred only for valve disease. Of the 142 patients with completed arteriograms remaining, 80 (56%) were male and 62 (44%) were female.

On the morning after the catheterization procedure, but before the results of the arteriogram were available to the patients, a behavioral evaluation was conducted utilizing the structured interview technique developed by Friedman and Rosenman.13 Permission was obtained to audiobracket each interview. Three independent judges reviewed a random sample of 21 of the 156 interviews. One of these judges had been trained in the techniques of behavior pattern assessment at the Harold Brunn Institute in San Francisco. Paired ratings of the three judges and the primary interviewer, J. Blumenthal, were in agreement 84% of the time. This high level of agreement supports the validity of the primary interviewer's ratings. These latter were the ones used in all data analyses.

In addition, each patient completed a battery of psychological tests designed to measure different components of the Type A behavior pattern. The analysis of this additional testing is in progress and will be reported subsequently.

All other clinical data were collected independently by the cardiology staff without any knowledge of the results of the psychological assessment. Serum cholesterol on present admission, history of cigarette smoking, previous documented myocardial infarction, family history of coronary heart disease and previous history of hyperlipidemia were obtained before coronary angiography. History of hyperlipidemia was documented by abnormal findings before present admission on a lipid panel consisting of serum cholesterol, triglyceride and lipid electrophoresis. We felt it important to include history of hyperlipidemia in addition to the current serum cholesterol level in order not to miss evidence of disordered lipid metabolism among patients in whom dietary or other therapy before the present admission may have normalized lipid indices. To assess chronic levels of sympathetic nervous activity,14 serum dopamine-beta-hydroxylase (DBH) levels were determined using the method of Nagatsu and Udenfriend.15 Aortic blood pressure and cardiac index were measured during the left and right heart catheterization.

Selective coronary cineangiograms in multiple projections were obtained with the Judkins technique16 using a Picker cinefluorographic unit with zoom lens and Kodak 35 mm double X cine films. The respective
Table 1. Comparison of Several Risk Factors (X ± SEM) in Patients Grouped According to Severity of Coronary Atherosclerosis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Mild (TOTCI &lt; 3)</th>
<th>Moderate (TOTCI = 3–6)</th>
<th>Severe (TOTCI &gt; 6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg%)</td>
<td>221 ± 6.5 (46)*</td>
<td>247 ± 6.2 (33)</td>
<td>256 ± 0.8 (26)</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Blood pressure, systolic (mm Hg)</td>
<td>123 ± 2.6 (78)</td>
<td>126 ± 3.9 (36)</td>
<td>118 ± 3.3 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure, diastolic (mm Hg)</td>
<td>70 ± 1.1 (78)</td>
<td>70 ± 1.9 (36)</td>
<td>69 ± 1.4 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>90 ± 1.4 (27)</td>
<td>92 ± 6 (36)</td>
<td>88 ± 2.0 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3169 ± 87 (78)</td>
<td>3104 ± 127 (36)</td>
<td>3304 ± 126 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>History of cigarette smoking</td>
<td>42% (54)</td>
<td>74% (31)</td>
<td>50% (28)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Serum DBH (I.U.)</td>
<td>37.5 ± 3.9 (41)</td>
<td>30.7 ± 2.7 (26)</td>
<td>35.6 ± 6.1 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Behavior pattern (% Type A)</td>
<td>44% (78)</td>
<td>69% (36)</td>
<td>93% (28)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to number of patients for whom data on the variable in question was available. No group had a significant disproportion of missing data for any variable.

Abbreviation: TOTCI = total coronary index.

angiograms were interpreted by a panel of three cardiologists experienced in evaluating coronary cineangiograms, who reached a consensus judgment as described below. To quantify the degree of coronary atherosclerosis, the coronary artery system was divided into four major vessels: the left main artery, the left anterior descending artery, the left circumflex artery and the right artery. Each major vessel was graded on a four-point scale: three points for total occlusion, two points for a stenosis of 75–99% decrease in luminal diameter, one point for a stenosis of less than 75% stenosis, and zero points for no stenosis. An index of severity (total coronary index, or TOTCI) for each patient was determined by taking the sum of the scores for all four vessels. For purposes of analysis, three groups were formed, representing a partitioned gradient of anatomic severity: mild = TOTCI < 3 (N = 78); moderate = TOTCI = 3–6 (N = 36); and severe = TOTCI > 6 (N = 28). This approach makes it possible to examine the levels or prevalence of various risk factors in patients grouped according to severity of arteriographically documented anatomic involvement.

Neither patients nor staff knew the results of the evaluation until all data were collected. This concurrent double blind approach was designed to minimize some of the methodological inadequacies that are often associated with retrospective research designs. That is, the assessment of both behavior pattern and coronary anatomy was conducted concurrently, with neither the behavioral assessment team nor the cardiologists being aware of the findings of the others’ assessment. Thus, the relationship under study is not that between Type A behavior and some prior event such as myocardial infarction, but that between behavior pattern and present status of the coronary vasculature.

Statistical analysis of the data was carried out using the chi-square approach for categorical data and analysis of variance to compare various groups (e.g., those with mild, moderate or severe coronary atherosclerosis). To ensure that any significant group differences are not due to such mediating variables as age and sex, analyses of covariance were performed using the multiple regression/correlation approach. This approach involves a first step of regressing onto a dependent variable (e.g., TOTCI), and a set of independent variables (e.g., blood pressure, age, sex, etc.), to which another set is added, carrying group membership information (e.g., Type A vs Type X and B). If the requirement of homogeneity of regression between groups is met, the relationship between the dependent variable and the group membership variable can be interpreted as an analysis of covariance in which the first set of independent variables entered are simultaneously covaried.

Results

Relationship of Behavior Pattern Type A and CHD

Behavior pattern Type A was found to be related to indices of lipid metabolism previously found related to increased risk for CHD. Whereas Type B patients had a mean serum cholesterol level of 211 mg%, Type A patients had a mean level of 248 mg% (P < 0.01). This difference remained significant when means were adjusted for age and sex. Similarly, behavior pattern Type A was related to a positive history of hyperlipidemia. Among those with a prior lipid panel, 25 patients (36%) classified as Type A had a history of hyperlipidemia, compared to only two patients (5%) classified as Type B (P < 0.001).

There were no statistically significant differences between Type A and Type B patients with respect to history of cigarette smoking, blood pressure, mean aortic pressure, cardiac index or serum DBH level.

In addition to its association with increased serum lipids, behavior pattern Type A was also found related to arteriographically documented atherosclerosis (table 1, fig. 1). Whereas only 44% of those patients with mild (TOTCI < 3) coronary occlusions were classified as Type A, 69% of those with moderate (TOTCI = 3–6) and 93% of those with severe (TOTCI > 6) occlusions were classified Type A (P < 0.001). This relationship between behavior pattern and TOTCI remained significant (P < 0.003) when age, sex, blood pressure, cholesterol and history of cigarette smoking were all simultaneously covaried as described in the Methods section. Thus, the increasing proportion of Type A patients observed with progression from the group with mild to that with moderate to that with severe coronary atherosclerosis...
cannot be explained by increased levels of traditional risk factors among the Type A patients in our sample. Whereas behavior pattern as determined by the interview method was strongly related in the present study to angiographically documented levels of coronary atherosclerosis, behavior pattern as determined by a paper and pencil test, the Jenkins Activity Survey (JAS), bore no relation to TOTCI. This lack of relationship held whether the analysis was based on categorical data or utilized a correlational approach. It also held even when the analysis was confined only to the men in our sample.

Relationship of Traditional Risk Factors and CHD

In addition to behavior pattern, the present study found many of the traditional risk factors for CHD to be related to the arteriographic indices of coronary atherosclerosis.

Sex

Sex must be considered a major risk factor, since the average incidence of CHD in middle-aged men is roughly five times that of middle-aged women. In the present study, men had significantly greater arteriographically demonstrable coronary atherosclerosis than women, even when the mean TOTCIs were age-adjusted. The mean TOTCI for men was 3.8, compared with 1.5 for women (P < 0.001).

Cholesterol

Serum cholesterol was found to bear a significant association to the severity of coronary disease, even when age and sex were covaried. As shown in Table 1, the mean serum cholesterol level in the group with severe artery disease was 256 mg%, while the mean level for the group with moderate disease was 247 mg% and only 221 mg% for the group with mild stenosis (P < 0.002).

Blood Pressure

There were no significant differences among the ordered gradient groups with respect to blood pressure, even when age and sex were covaried. There were also no differences among these groups with regard to mean aortic pressure and cardiac index, as measured at the time of catheterization (Table 1).

Smoking

An association between smoking and CHD was observed in the present study (Table 1). When present or past cigarette smokers were considered together, as compared to those who had never smoked cigarettes, smokers were found in significantly greater proportions in the groups with moderate (74%) to severe (50%) coronary occlusions than in the mild (42%) group (P < 0.02).

Sympathetic Nervous System

Sympathetic nervous activity as indexed by serum DBH levels, did not differ as a function of severity of atherosclerotic occlusions (Table 1).

Discussion

The present findings represent the first report of an association between Type A behavior pattern, as determined by the standardized interview method, and the extent and severity of atherosclerotic coronary involvement as demonstrated in vivo by coronary arteriography. Thus, they lend added weight to the conclusion from the earlier autopsy study that Type A behavior pattern is not only associated with increased risk of specific CHD events, but is also found with increasing prevalence among patient groups with more severe coronary atherosclerosis. Further extension of our knowledge concerning the relationship between Type A behavior pattern and CHD is provided by the fact that nearly half of the present sample were female and by the fact that when sex was covaried the relationship between behavior pattern and TOTCI remained highly significant. The present findings thus provide the first evidence that behavior pattern is related to the atherosclerotic process among women as well as men.

Despite several analyses, no relationship was found between behavior pattern as determined by the JAS questionnaire and arteriographically documented coronary atherosclerosis. Thus, we do not confirm the recent findings of Jenkins et al. of a relationship between scores on the JAS and extent and severity of arteriographically determined coronary disease. We believe that differences between our patient population...
and that studied by Jenkins et al. may account for our failure to replicate their findings. Our sample consisted of a large proportion of individuals from a rural rather than an urban setting. The JAS was originally standardized on a male, urban population, similar to that included in the recent study of Jenkins et al.\textsuperscript{19} It is probable, therefore, that the questions on the JAS, relating as they do to experiences likely to be encountered by men working in an urban setting in close proximity to substantial numbers of other men, would not be relevant to the life style and personal experiences of much of our sample. Thus, an added conclusion to be drawn from the current findings is that the standardized interview method is the most appropriate and valid means of determining behavior pattern in studies of heterogenous populations containing significant numbers of female and/or rural subjects.

Since the presently reported association between Type A behavior pattern and coronary arterial involvement statistically is independent of traditional risk factors, we conclude that this association cannot be explained by higher levels of such risk factors (e.g., cigarette smoking and cholesterol) among Type A patients. Such a conclusion is supported by recent multivariate analyses of the West Collaborative Group data showing that only a small proportion of the increased risk of clinical CHD events among Type A individuals can be explained by presence of increased levels of traditional risk factors in Type A individuals.\textsuperscript{1} Thus, we are unsure of the mechanism underlying the association between Type A behavior and CHD, defined in terms of either clinical CHD events or anatomically demonstrable atherosclerotic coronary arterial involvement.

One hypothesis that appears promising is the possibility of increased sympathetic nervous system discharge among Type A persons. There has been mounting evidence that alterations in serum DBH levels reflect prolonged changes in sympathetic nervous activity.\textsuperscript{18,19} Despite such evidence, the present study did not find any association between high DBH concentrations and CHD on arteriography, nor was any association seen between DBH levels and behavior pattern. These findings fail to provide support for a role of chronic, sustained increases in sympathetic nervous activity as a mediator of the relationship between Type A behavior and CHD. However, any relationship between sympathetic nervous activity and CHD may be so complex that it would not be revealed by such a chronic index of sympathetic function as blood DBH level. Friedman et al.,\textsuperscript{9} for example, have shown that Type A men show higher levels of plasma norepinephrine during stress periods, but not during resting conditions — suggesting that any differences between Type A and Type B individuals in terms of sympathetic nervous function may be strictly phasic, and therefore, not of sufficient degree to increase blood DBH levels.

Ross and Glomset\textsuperscript{11} have noted that any attempt to explain the pathogenesis of atherosclerosis must take into account all three fundamental phenomena involved in the focal lesions of atherosclerosis: proliferation of smooth muscle cells, deposition of intracellular and extracellular lipid, and accumulation of extracellular matrix components, including collagen, elastic fibers and proteoglycans. They further propose that endothelial "injury" may be a key event in the initiation of these phenomena. The phasic increases in sympathetic discharge among Type A individuals which are suggested by the cited findings undoubtedly are associated with changes in hemodynamic function, such as increased shear stress and turbulence, which could be important factors in causing such endothelial injury. Whether such effects of frequent sympathetic activations among Type A individuals represents the mechanism responsible for the current finding of increased coronary atherosclerosis among the Type A patients must be investigated. One means of testing this hypothesis would involve relating the degree of coronary atherosclerosis on arteriography to the magnitude of hemodynamic responses of Type A compared with Type B individuals during experimental stress situations which are challenging to the Type A person.

Recent animal experimentation provides evidence that repeated acute stresses could be responsible for effects upon arterial endothelium which could play a role in the pathogenesis of coronary atherosclerosis. Bassett and Cairncross\textsuperscript{20} report the presence of junctional gaps in the endothelial lining, large lipid-filled vacuoles in the arterial walls and platelet aggregation in the coronary vascular system of rats exposed over a prolonged period to daily 35-minute stress (unavoidable footshocks) sessions.

It should be emphasized that the results of this investigation in no way detract from the possible etiologic significance of such traditional risk factors as cholesterol, blood pressure and smoking. In the present study, age, sex, cigarette smoking and cholesterol were also found to bear a relationship to arteriographically demonstrated atherosclerotic disease. The failure of blood pressure to distinguish disease and non-disease groups may reflect the fact that our sample represents a unique population of physically ill patients.

It must also be noted that our sample population may not be representative of the general population. Those patients who are finally evaluated at a tertiary medical center have, in many cases, survived an extensive screening process. It well may be that Type A persons are represented disproportionately in our study sample as a result of their putting more pressure on their local physicians to refer them to the medical center. Nevertheless, the observation remains that those Type B or Type X patients who made it through the screening process are found in significantly smaller proportions in the groups with progressively greater atherosclerotic involvement.

The findings of this study have practical implications. It is generally agreed that the causation of CHD is multifactorial, and that efforts to reduce the annual cost of this disease should be aimed at reduction of not just single but multiple risk factors when
they are present. The Multiple Risk Factor Intervention Trials (MRFIT) program is a massive attempt to accomplish such a goal with regard to physical risk factors such as smoking, cholesterol and blood pressure. By showing that Type A behavior pattern may be playing a role in the atherosclerotic process itself, the present study suggests that the behavior pattern is exerting its influence upon CHD risk over an extended period, perhaps beginning as early as childhood or young adulthood — much the same as the traditional physical risk factors. The recent demonstration that it is possible to distinguish the Type A behavior pattern as early as the fifth grade22 combines with the present findings to suggest that, as with the traditional risk factors, attempts at primary prevention at an early age should also include efforts to modify Type A behavior.

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