SECULAR TRENDS IN CORONARY ATHEROSCLEROSIS — ANALYSIS IN PATIENTS WITH VALVULAR REGURGITATION

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ABSTRACT

Background Between 1980 and 1989, mortality due to coronary artery disease decreased considerably in the United States, suggesting a possible decrease in the prevalence of coronary atherosclerosis. We examined this possibility in patients with valvular regurgitation who, often in the absence of angina, underwent coronary angiography before valve-replacement surgery.

Methods We studied 601 patients with isolated, nonischemic valvular regurgitation who were operated on between 1980 and 1989 and who had undergone preoperative coronary angiography. From the angiograms we determined the prevalence of clinically significant coronary artery disease and of multivessel disease, assessed the mean degree of stenosis, and analyzed the trends in the data over the years of the study.

Results The prevalence of coronary artery disease (35 percent in 1980–1981, 37 percent in 1982–1983, 34 percent in 1984–1985, 37 percent in 1986–1987, and 35 percent in 1988–1989; $P = 0.97$) did not change significantly during the study period. We found no significant change in the prevalence of multivessel disease (24 percent in 1980–1981 and 23 percent in 1988–1989, $P = 0.99$) or in the mean ($\pm$SD) degree of stenosis (11$\pm$13 percent in 1980–1981 and 13$\pm$14 percent in 1988–1989, $P = 0.07$). When these measures of coronary atherosclerosis were adjusted for age and sex, there were still no significant changes over time ($P = 0.39$ for the prevalence of coronary artery disease, $P = 0.81$ for that of multivessel disease, and $P = 0.57$ for the mean degree of stenosis). The patients' mean total cholesterol level decreased from 219$\pm$48 mg per deciliter (5.66$\pm$1.24 mmol per liter) to 206$\pm$44 mg per deciliter (5.33$\pm$1.14 mmol per liter) between 1980 and 1989 ($P = 0.04$).

Conclusions From 1980 to 1989, no significant change was observed in angiographic measures of coronary atherosclerosis in patients with nonischemic valvular regurgitation, in contrast to the marked decrease in mortality due to coronary disease in the general population. These findings suggest that the well-documented reduction in mortality due to coronary disease may not be due to a reduction in the prevalence of coronary atherosclerosis. (N Engl J Med 1996;335:316-22.)

DURING the 1980s, the age-adjusted mortality due to coronary artery disease decreased considerably in the United States[1,2] and other countries.[3] This favorable trend was related partly to a decrease in the rate of fatal myocardial infarction,[2,4-7] but it was also associated with a decline in the prevalence of risk factors for coronary artery disease.[1,2,8] These risk factors strongly influence the severity of coronary atherosclerosis,[9-13] a major predictor of survival in patients with coronary disease.[14] These observations suggest that the decline in mortality from coronary artery disease is related to a parallel decline in coronary atherosclerosis. However, because such a trend has yet to be demonstrated, there is a need for anatomical studies.[15]

It is difficult to analyze trends over time in the prevalence of coronary atherosclerotic lesions on the basis of autopsies. Such studies are potentially biased[16] and have produced conflicting data.[17-19] Although coronary angiography makes possible the diagnosis of obstructive coronary atherosclerosis in living patients,[20] it is performed almost exclusively in patients with symptoms of coronary artery disease. To analyze secular trends in the pattern of obstructive coronary atherosclerosis, it is desirable to examine a population not subject to selection bias, in which coronary angiography, although routine, is not performed primarily because of a suspicion of coronary disease. Patients with severe nonischemic valvular regurgitation, who rarely present with angina[21] and who undergo coronary angiography for preoperative evaluation,[22] constitute such a population.

We therefore examined the coronary angiograms of a group of patients operated on between 1980 and 1989 for isolated, nonischemic, valvular regurgitation to determine whether there was a decrease over time in the prevalence and severity of obstructive coronary atherosclerosis that paralleled the decrease in mortality due to coronary disease in the general population.

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METHODS

Patients

This study was based on a retrospective review of patients who underwent surgical correction of valvular regurgitation at the Mayo Clinic. Patients were included if they had organic (nonischemic) isolated mitral regurgitation or aortic regurgitation, as confirmed by echocardiographic and surgical assessment; underwent surgical correction between January 1, 1980, and December 31, 1989; and had coronary angiography in the six months before their operation. We excluded otherwise eligible patients who had associated cardiac disease, such as congenital heart disease, constrictive pericarditis, or disease of the tricuspid valve necessitating its replacement. Also, patients with ischemic mitral regurgitation were explicitly excluded.

During the period studied, 778 patients underwent surgery for isolated mitral regurgitation or aortic regurgitation; of these, the 601 who had preoperative coronary angiography formed our final study group. In the group of 601 patients (mean [±SD] age, 63±13 years), 385 had isolated mitral regurgitation, 216 had isolated aortic regurgitation, 410 (68 percent) were men, 225 (37 percent) had atrial fibrillation preoperatively, 355 (59 percent) were in New York Heart Association (NYHA) class III or IV, and 135 (22 percent) had chest pain. The mean ejection fraction, measured before surgery in 566 patients, was 56±12 percent.

Coronary Angiography

Coronary angiography was performed at the Mayo Clinic in 473 of the patients and at another institution in the other 128. All the angiograms were interpreted at the Mayo Clinic by two experienced observers. The degree of coronary-artery stenosis was estimated visually as the obstructed proportion of each vessel, given as a percentage of the vessel's diameter.[23] The three indicators of atherosclerosis examined in the study were the presence or absence of clinically significant coronary artery disease (analyzable in all 601 patients), defined as stenosis of ≥70 percent of a coronary artery or stenosis of ≥50 percent of the left main coronary artery[24]; the presence or absence of multivessel disease (analyzable in 584 patients), defined as two or more vessels with clinically significant stenosis or stenosis of the left main coronary artery[24]; and mean segmental stenosis, defined as the average of the percentages of obstruction of 11 proximal segments[24] of the right and left coronary arteries, as analyzed in the 473 patients in whom coronary angiography was performed at the Mayo Clinic.

Statistical Analysis

Values are expressed as means ±SD. Groups were compared with the use of a standard t-test or chi-square test, as appropriate. The associations among the calendar years of intervention, the extent of coronary atherosclerosis, and the patients' preoperative characteristics were analyzed for discrete variables with logistic regression and for continuous variables with linear regression. Multivariate stepwise analysis was performed with the three end points of the study as dependent variables. To assess secular trends, the calendar year of surgery was considered as an independent variable and entered in the final multivariate models. With use of a model including only age and sex, age- and sex-adjusted prevalences of coronary atherosclerosis were calculated and the trends over time were analyzed. Our explanatory models treated risk factors for coronary disease (age, sex, total cholesterol level, diabetes mellitus, history of smoking, hypertension, and family history of coronary disease) as independent variables. The possibility of referral bias was examined by adjusting for potential confounding variables (age, sex, atrial fibrillation, NYHA functional class, distance of the hospital from the patient's residence, serum creatinine level, type of valvular regurgitation, and left ventricular ejection fraction) both in models that included the risk factors and in models that did not. The possibility of a type II error was as-

TABLE 1. SECULAR TRENDS IN CORONARY ATHEROSCLEROSIS AND BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

VARIABLE	1980–1981 (N=98)	1982–1983 (N=107)	1984–1985 (N=108)	1986–1987 (N=139)	1988–1989 (N=149)	P VALUE FOR TREND
Angiographic findings†						
Coronary artery disease (%)	35	37	34	37	35	0.97
Multivessel disease (%)	24	17	21	21	23	0.99
Degree of obstruction (%)	11±13	9±12	12±14	12±12	13±14	0.07
Other characteristics						
Age (yr)	62±13	60±14	65±12	64±13	64±12	0.03
Male sex (%)	79	67	64	61	72	0.25
Serum creatinine (mg/dl)‡	1.2±0.2	1.2±0.4	1.3±0.5	1.2±0.3	1.2±0.6	0.88
Atrial fibrillation (%)	41	42	35	35	36	0.23
NYHA class III or IV (%)	67	54	67	60	50	0.05
Distance <190 km (120 mi) (%)§	46	38	43	36	38	0.23
History of smoking (%)	48	46	45	45	48	0.89
Diabetes mellitus (%)	3	7	7	7	5	0.55
Family history of coronary artery disease (%)	34	40	34	37	35	0.93
History of hypertension (%)	27	22	21	32	32	0.08
Serum cholesterol (mg/dl)¶	219±48	214±45	217±42	210±43	206±44	0.04
Ejection fraction (%)	55±13	57±13	55±12	55±11	58±12	0.21

*Plus–minus values are means ±SD.

†See the Methods section for definitions.

‡To convert values to micromoles per liter, multiply by 88.4.

§This variable refers to the distance from the patient's residence to Rochester, Minnesota.

¶To convert values to millimoles per liter, multiply by 0.02586.

sessed by calculating the confidence intervals for the trends over time in the three indicators of atherosclerosis and by calculating a simple average of the three trends and a weighted average of these trends, taking into account the covariance matrix of the three estimates.

The possibility of bias due to exclusion of patients who did not undergo coronary angiography was analyzed by assigning to these patients for each time period values for the three indicators of coronary atherosclerosis on the basis of multivariate models (defined in patients who had undergone angiography). These numbers were then added to the known data and tested for trend over time. In all analyses, a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

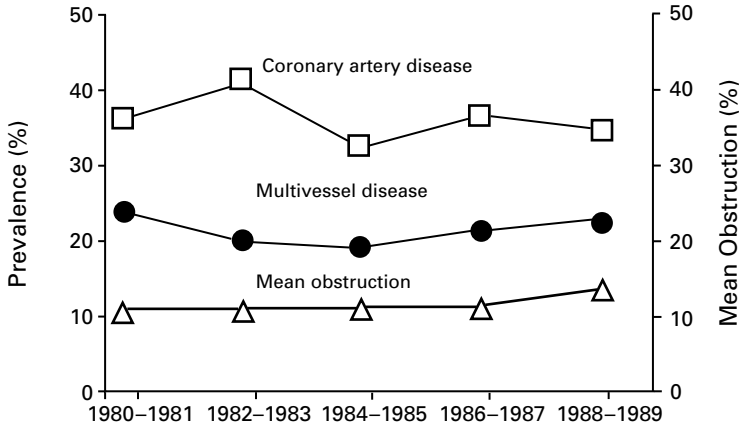
The prevalence of coronary artery disease in the 601 patients in the study group was 35.6 percent (214 patients); the prevalence of multivessel disease was 21.2 percent (124 of 584 analyzable patients); and the mean segmental stenosis in the 473 studied patients was 12±13 percent.

Changes over Time

The changes over time in various characteristics of the patients are presented in Table 1. There were no significant trends in the indicators of coronary atherosclerosis during the study period. There was also no significant secular trend in the prevalence of coronary atherosclerosis after adjustment for age and sex (Fig. 1). The odds ratio associated with each consecutive calendar year was 0.97 (95 percent confidence interval, 0.92 to 1.035; P=0.39) for coronary artery disease and 0.99 (0.92 to 1.07; P=0.81) for multivessel disease; the change in the degree of obstruction for each consecutive calendar year was an increase of 0.12 percent (95 percent confidence interval, −0.29 to 0.52; P=0.57).

Although we found significant secular trends in the severity of symptoms, in the patients' ages, and in their total cholesterol levels, our multivariate analysis revealed no significant association between the year of surgery and the prevalence of coronary atherosclerosis (Table 2). The independent factors that were positively associated with the three indicators of coronary atherosclerosis in the models that included all variables are also shown in Table 2. These classic risk factors were the strongest predictors of each of the three indicators of coronary atherosclerosis.

Although their confidence intervals are relatively large, the changes observed in the three indicators are minimal (Tables 1 and 2 and Fig. 1). Two of the trends represent a slight decrease in atherosclerosis, and one a slight increase, suggesting a low probability of a type II error. If we combine the three indicators, we find a mean decrease in the prevalence of coronary atherosclerosis from 1980 to 1989 of 2 per-



Indicator	1980–1981	1982–1983	1984–1985	1986–1987	1988–1989
Prevalence of coronary artery disease (%)	36	41	32	36	34
Prevalence of multivessel disease (%)	24	20	19	21	22
Mean (±SD) obstruction (%)	11±4	11±4	11±4	11±4	12.7±4

Figure 1. Indicators of Coronary Atherosclerosis Expressed as the Percentage of Patients with Clinically Significant Coronary Artery Disease, the Percentage of Patients with Multivessel Disease, and the Mean Obstruction (Mean Percent Stenosis in 11 Proximal Coronary-Artery Segments).

Values have been adjusted for age and sex.

TABLE 2. ASSOCIATION OF SELECTED VARIABLES WITH INDICATORS OF ATHEROSCLEROSIS IN THE MULTIVARIATE ANALYSIS.*

VARIABLE	CORONARY ARTERY DISEASE		MULTIVESSEL DISEASE		MEAN OBSTRUCTION	
	OR (95% CI)	P VALUE	OR (95% CI)	P VALUE	MEAN PERCENT CHANGE (95% CI)	P VALUE
Calendar year of operation (per yr)	0.97 (0.90 to 1.05)	0.49	0.99 (0.91 to 1.09)	0.86	0.078 (−0.402 to 0.558)	0.58
Age (per yr)	1.08 (1.05 to 1.10)	0.001	1.08 (1.05 to 1.12)	0.001	0.39 (0.26 to 0.52)	0.001
Cholesterol (per 10 mg/dl [0.3 mmol/liter])	1.14 (1.07 to 1.20)	0.001	1.12 (1.05 to 1.18)	0.001	0.62 (0.32 to 0.92)	0.001
Diabetes mellitus	3.90 (1.54 to 9.87)	0.004	—	—	7.46 (2.26 to 12.66)	0.004
History of hypertension	1.95 (1.18 to 3.21)	0.009	1.81 (1.04 to 3.16)	0.036	4.74 (1.72 to 7.76)	0.002
History of smoking	1.74 (1.10 to 2.75)	0.018	—	—	—	—
Male sex	—	—	2.23 (1.22 to 4.09)	0.009	3.40 (0.40 to 6.40)	0.02

*OR denotes odds ratio, and CI confidence interval. For dichotomous variables, odds ratios are for patients with the factor in question, as compared with those without it. For other variables, odds ratios are for each increase of the unit specified (for calendar years, each subsequent year). The dashes indicate that the variables were not significant in the final model.

cent in the unweighted average and an increase of 2.3 percent in the weighted average. These findings are not commensurate with the decrease in mortality from coronary causes in the general population during the same period.

Analyses Including Patients without Preoperative Coronary Angiography

Among the 778 patients who underwent surgery in the study period, 177 were excluded from our final study group because they did not undergo preoperative coronary angiography. These 177 patients were younger and had fewer risk factors than those in the study group (Table 3). We checked for possible bias in our results by imputing data on the prevalence and severity of coronary atherosclerosis, derived from our study group, to the patients without angiography and then combining the imputed data with the known data (Table 4), but the only significant trend over time we found was a small increase in the observed degree of mean segmental stenosis.

Referral Patterns

From the beginning to the end of the study period, there was a trend for the yearly cohorts of patients to be slightly older ($P=0.03$) and to have fewer symptoms at the time of surgery ($P=0.05$). Except for a decrease in the total cholesterol level ($P=0.04$), no other changes in the characteristics of the patients were noted (Table 1). Functional class was not associated with the presence or severity of coronary atherosclerosis in the study group ($P>0.50$), and in our multivariate models, which adjusted for age, as well as other variables potentially affected by referral patterns, we found no significant trends over time in the prevalence or severity of coronary atherosclerosis. Finally, the geographic distribution of the patients — in terms of the proximity of their residences to our institution — did not change significantly ($P=0.23$) (Table 1). Given these data, we could find no effects of the pattern of referral for surgery on secular trends in the prevalence or severity of coronary atherosclerosis.

DISCUSSION

Although there was a marked decline in mortality due to coronary disease in the general population between 1980 and 1989, we found that the prevalence and degree of coronary atherosclerosis did not

TABLE 3. CHARACTERISTICS OF PATIENTS WITH VALVULAR REGURGITATION WHO UNDERWENT CORONARY ANGIOGRAPHY AND THOSE WHO DID NOT.*

CHARACTERISTIC	CORONARY ANGIOGRAPHY (N=601)	NO CORONARY ANGIOGRAPHY (N=177)	P VALUE
Age (yr)	63±13	53±17	0.001
Male sex (%)	68	67	0.70
Serum creatinine (mg/dl)†	1.2±0.4	1.2±0.6	0.54
Ejection fraction (%)	56±12	59±11	0.002
NYHA class III or IV (%)	59	46	0.001
Distance <190 km (120 mi) (%)‡	40	39	0.96
Serum cholesterol (mg/dl)§	212±44	199±43	0.006
Family history of coronary artery disease (%)	36	20	0.001
History of hypertension (%)	27	16	0.004
History of smoking (%)	46	36	0.014
Diabetes mellitus (%)	6	3.4	0.18

*Only patients who underwent angiography were included in the final study group. Plus–minus values are means ±SD.

†To convert values to micromoles per liter, multiply by 88.4.

‡This variable refers to the distance from the patient's residence to Rochester, Minnesota.

§To convert values to millimoles per liter, multiply by 0.02586.

TABLE 4. ESTIMATED VALUES FOR INDICATORS OF CORONARY ATHEROSCLEROSIS IN PATIENTS WITH VALVULAR REGURGITATION.*

VARIABLE	1980–1981	1982–1983	1984–1985	1986–1987	1988–1989	P VALUE FOR TREND
			percent			
Prevalence of coronary artery disease						
Estimated	30	19	16	14	17	
Total	33	31	30	34	32	0.97
Prevalence of multivessel disease						
Estimated	15	7	11	11	10	
Total	21	14	18	19	21	0.58
Mean obstruction						
Estimated	8.6	3.6	4.6	3.2	4.7	
Total	10±11	7.8±10.5	10±12	10.7±11.8	11.9±12.8	0.04

*Estimated values for indicators of coronary atherosclerosis were obtained in patients who had not undergone preoperative coronary angiography (n = 177 overall) on the basis of the final multivariate models (defined in patients who had undergone angiography) and combined with the known data in the final study group (n = 601 overall) to obtain the total estimated indicators.

decrease significantly in patients with isolated valvular regurgitation during this period.

Trends in Mortality Due to Coronary Disease and the Prevalence of Atherosclerosis

A recent investigation of data covering an interval similar to our study period revealed a 23 percent decrease in the age-adjusted rate of death from coronary artery disease in the general population.[1] This decrease has been continuous and is not related to a shift in the classification of the causes of death.[25] Although the validity of such a decrease is widely accepted, its causes are not fully understood.[1,3] The prevalence of risk factors for coronary artery disease that are strongly associated with mortality[26] and coronary atherosclerosis[9-13] has also decreased in recent years.[1,2] Because the severity of coronary atherosclerosis is an essential determinant of mortality from the disease,[14] a causal relation between a reduction in risk factors, a decrease in coronary atherosclerosis, and a decreased mortality rate appears implicit, but this assumption has never been tested.[15]

The only available anatomical data come from autopsy studies and are inconsistent.[17-19] In our study, no significant secular trend in the adjusted and unadjusted prevalence of coronary atherosclerosis was observed in patients in the age range known to be most affected by coronary disease. Moreover, the trends that were found in the adjusted data are minimal, inconsistent with each other, and incommensurate with the marked change in coronary mortality in the general population during the same period.

The extension of findings in a selected group to the general population is always questionable. However, the fact that at the time of coronary angiography most of the patients in our study had no clinical evidence of coronary artery disease and were similar to the general population in their pattern of risk factors for coronary disease[1,2,27,28] underscores the relevance of the present data.

As unexpected as these results may appear, they are consistent with other data. During a similar time period, no decrease in the prevalence of coronary disease[29] or in the nonfatal manifestations of coronary disease[30] was detected in the general population. The absence of a significant decrease in indicators of coronary atherosclerosis in our study group, despite a decrease in total cholesterol levels comparable to that in the general population,[1] is also consistent with the results of studies showing that lowering lipid levels produces an important decrease in mortality but only minimal changes in the degree of coronary-artery obstruction.[31] Together, these results suggest that a decrease in the prevalence and severity of coronary atherosclerosis may not be the chief reason for the decline in mortality from coronary disease and that the decline needs to be explained by other potential mechanisms.

The rupture of atherosclerotic plaques and the formation of thrombi can cause acute coronary syndromes and death; these processes can be triggered by a number of factors[32] and may occur in only minimally stenotic atherosclerotic lesions.[33,34] A decrease in the frequency of plaque rupture, possibly due to a decrease in lipid content,[35] may minimize the complications of atherosclerosis, especially sudden death.[36] A decreased rate of sudden death[37] thus may partly explain the general reduction in mortality from coronary disease and may have been influenced by favorable trends in the prevalence of risk factors.[38]

Interestingly, as compared with the decrease in mortality, the decrease in the incidence of myocardial infarction has been less conspicuous[39,40] and slower to come about.[1] However, the proportion of myocardial infarctions that are fatal has decreased,[2,4-7] possibly because of improved therapy,[2] and this may partly explain the decrease in mortality from coronary causes.[1]

Coronary Atherosclerosis and Risk Factors

The risk factors associated with coronary atherosclerosis in our study were the same for the three chosen indicators and similar to those described in autopsy[9,12] and angiographic[13] studies. Although a causal relation between these risk factors and coronary atherosclerosis has been disputed,[15] the retarding effect a reduction in risk factors has on the progression of atherosclerosis[41,42] argues in favor of the connection. Our study confirms the relation between accepted risk factors and coronary atherosclerosis in a relatively representative group of living patients, most of whom did not have angina.[43]

Coronary Artery Disease in Patients with Valvular Regurgitation

In previous studies, mostly involving data collected before 1980, nonischemic valvular heart disease was frequently associated with coronary artery disease[44-46] and had a poor prognosis[47,48]; these findings led to a recommendation that routine preoperative coronary angiography be performed in patients with valvular disease.[44-46] Recently, noninvasive methods have become available to quantify the valvular defects,[49,50] and coronary angiography, which has a small but definite risk associated with it,[51,52] is often the only reason to perform cardiac catheterization. Moreover, the decrease in mortality from coronary causes[1] in the general population raises the possibility of a lower prevalence of coronary disease in patients with valvular disease than has previously been described. In our study, however, the prevalence of coronary atherosclerosis was not significantly decreased during the study period; we believe that coronary angiography should continue to be performed routinely before surgery for valvular disease, especially in older patients.[53]

Limitations of the Study

The wisdom of generalizing the results of research on a selected population is debatable, but no random samples of the general population undergo coronary angiography. Consequently, our study group of patients who were alive and mostly without angina at the time of angiography represents a unique opportunity to look at data from a population that is similar to the general population in the distribution of risk factors for coronary disease and also lies in the age range in which obstructive coronary atherosclerosis is usually observed. Although referral bias cannot be ruled out completely, the clinical and geographic patterns of referral were examined, and no biasing effects on secular trends in the prevalence of coronary atherosclerosis could be identified.

Coronary calcifications can be measured noninvasively,[54] but only with coronary angiography can we reliably assess obstructive coronary atherosclerosis in living patients.[55] Coronary angiography is not a perfect technique,[56] but its results are acceptably replicable[57] and potential variations in interpretation are not likely to alter the analysis of secular trends in the prevalence of coronary atherosclerosis.

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