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Standing at work and progression of carotid atherosclerosis

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Objectives The association between the amount of standing at work and the progression of carotid intima media thickness (IMT) was studied among 584 active working men participating in the Kuopio Ischemic Heart Disease Risk Factor Study.

Methods Ultrasound measurements of atherosclerotic changes in the carotid arteries were performed at the beginning of the study and after 4 years. Analyses of changes in IMT included adjustments for risk factors and stratification by base-line levels of atherosclerosis and prevalent ischemic heart disease (IHD).

Results Significant relationships were found between the amount of standing at work and atherosclerotic progression. After adjustment for the heaviness of the work, psychosocial job factors, income, and biological and behavioral risk factors, the mean change in maximum IMT for those standing not at all, a little, a lot, and very much was 0.24, 0.25, 0.28, and 0.33 mm, respectively. For men with IHD the respective changes were 0.08, 0.15, 0.37, and 0.75 mm — a 9-fold difference between the no-exposure and high-exposure group. For the men with carotid stenosis, the respective difference was 3-fold.

Conclusions These findings provide the first empirical support in a population study for the role of hemodynamic factors in the progression of atherosclerosis induced by long-term standing. Men with carotid stenosis or IHD appear especially vulnerable to the adverse effects associated with standing at work. Reducing the duration of standing at work should be considered both in the occupational rehabilitation of such patients and in the primary prevention of atherosclerosis.

Key terms atherosclerosis, coronary heart disease, hemodynamics, occupational risk factors, rehabilitation, work posture.

Several studies have linked workplace characteristics with cardiovascular disease and mortality (1—5), but the findings have been both positive and negative (2, 6—9). One major difficulty in examining the role of workplace factors in cardiovascular disease is the disease-based selection of persons in and out of specific work environments. Studies of angina pectoris, myocardial infarction, and cardiovascular mortality are especially vulnerable to these selection effects. Studying earlier, asymptomatic stages of the atherosclerotic disease process can help avoid these selection issues. The development of ultrasound measurements of atherosclerotic changes in the carotid arteries allows us now to look at the relationship between work characteristics and the progression of atherosclerosis in earlier, asymptomatic stages before selection effects occur (10, 11). Ultrasound measurement of intima media thickness (IMT) in carotid arteries has been shown to be reliable, to relate to the extent of disease in the coronary arteries, and to have predictive validity with regard to risk of coronary events (11—13).

While a recent study found an association between psychosocial workplace characteristics and the

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progression of IMT (14), no studies have yet examined specific physical characteristics of work with regard to the progression of atherosclerosis. Occupational physical activities such as heavy work or work in a standing position could be possible risk factors for atherosclerosis because of concurrent hemodynamic changes resulting in increased intravascular turbulence (15—17). Increased turbulence and concurrent changes in shear stress to arterial walls are thought to be the main hemorheologic phenomena that induce endothelial damage in human arteries (15—18). The empirical evidence for hemorheologic factors in the etiology of atherosclerosis comes from experimental and human pathology, but to our knowledge there are neither clinical nor epidemiologic studies addressing this issue directly. However, the Framingham study found varicose veins — a condition more common in people standing a lot — to be predictive of atherosclerotic cardiovascular disease, and this finding could not be explained by traditional risk factors (19—21). In this population-based prospective study, long-term standing at work was hypothesized as a potential risk factor for atherosclerosis because of the hemodynamic changes associated with prolonged standing.

Figure 1 summarizes the physiological and hemodynamic concepts behind this investigation. Long-term standing leads to a redistribution of circulating blood into the extremities (22). This hydrostatic or venous pooling

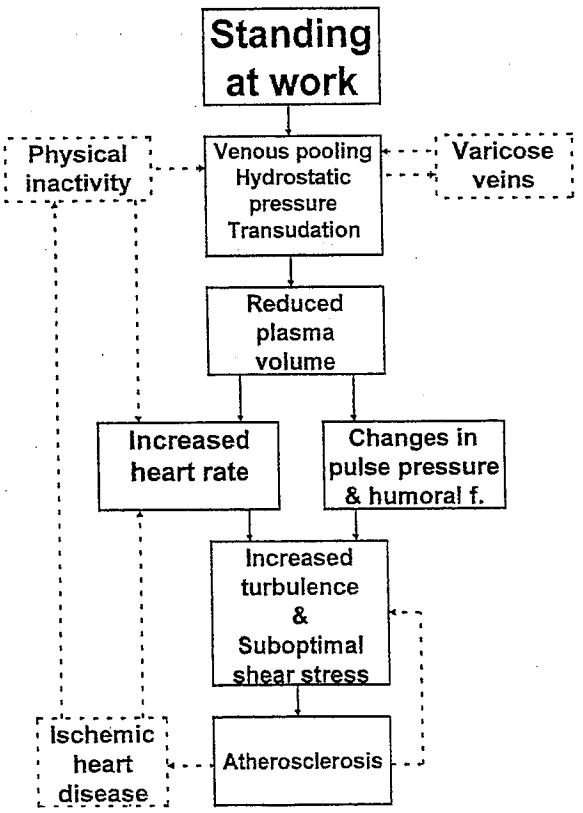

Figure 1. Biological pathways linking prolonged standing at work with the progression of atherosclerosis.

results in a reduction of circulating blood plasma volume. For example, a recent study reports a reduction of plasma volume by 500—550 ml or about 16% after only 15 minutes of quiet standing (23). The reduction in plasma volume, in turn, triggers several changes that can be grouped into hemodynamic and humoral effects, including but not limited to increased hemoconcentration (23, 24), increased release of catecholamines (25), changes in pulse pressure, and increased heart rate (25). For example, one recent study measured a significant increase in heart rate and catecholamines after 10 minutes of standing for men with cardiovascular disease, and also for healthy referents (25). Several hours of standing have been found to be associated with increased plasma renin activity and long-lasting endothelin-1 system activation affecting water-electrolyte balance and plasma volume, which is an important factor in the regulation of hemodynamic flow characteristics (26). Alderman discusses retrospective and prospective studies and suggests that hypertensive patients with increased renin-sodium profiles are at increased risk for coronary events (27). Increased hemoconcentration may lead to a higher concentration and possibly higher toxicity of free radicals and lipid peroxidation products that contribute to the biochemical reactions involved in atherogenesis (28, 29). Increasing amounts of circulating catecholamines have been linked to increased lipid absorption into the arterial walls, increasing levels of clotting factors, and increases in heart rate and systolic blood pressure (30—32). A higher pulse pressure means a tendency for relative intravascular stasis or blood flow reversal during diastole and therefore leads to increased turbulence and suboptimal shear stress at the outer arterial wall near the carotid bifurcation (15). A recent experimental study found that decreased blood flow rate and suboptimal shear stress disrupt endothelial repair (33). Increased heart rate and altered systolic blood pressure both lead to hemodynamic changes resulting in increased turbulence and changes in shear stress (15). Higher systolic blood pressure will increase vascular turbulence per heart beat near bifurcations and near atherosclerotic plaques, and increased heart rate will lead cumulatively to more turbulence over time regardless of blood pressure. Turbulence contributes to the development of endothelial cell injury and atherosclerosis (16, 34—36). The exact mechanisms by which elevated heart rate contributes to atherosclerosis in humans still needs to be explored, but it has been shown in animal models that high heart rate is associated with greater atherosclerosis of the carotid and coronary arteries, and a pharmacological lowered heart rate has been shown to have a retarding effect on atherosclerosis in primates (35, 37, 38). Prospective population-based studies found an independent association between heart rate and cardiovascular mortality after adjustment for other cardiovascular risk factors (39).

This study tested the hypothesis that long-term standing at work is associated with an accelerated progression of atherosclerosis in common carotid arteries of middle-aged men. Ultrasound measurements of atherosclerotic changes in the carotid arteries at base line and after 4 years in the Kuopio Ischemic Heart Disease Risk Factor Study enabled us to study this problem prospectively in a population sample. (10, 11). Base-line information on other physical and psychosocial workplace characteristics, socioeconomic status, prevalent disease, and biological and behavioral atherosclerotic risk factors have been used to adjust for known risk factors and to stratify the analyses by both prevalent ischemic heart disease and the extent of atherosclerosis at the time of the base-line measurements.

Subjects and methods

Subjects

The subjects were participants in the Kuopio Ischemic Heart Disease Risk Factor Study, which was designed to investigate risk factors for ischemic heart disease (IHD), carotid atherosclerosis, and related outcomes in a population-based random sample of eastern Finnish men. Details of the study sample have been published elsewhere (40, 41). Base-line examinations were conducted in 2 series between March 1984 and December 1989 on 2682 men (participation rate 82.9%) who resided in the town of Kuopio or its surrounding rural communities. The 1st series constituted an older age cohort, while the second comprised a random age-stratified sample. Ultrasonic scanning of the carotid arteries was introduced as part of the 2nd series of base-line examinations. Follow-up examinations were conducted on the age-stratified sample of men who underwent ultrasonic scans at base line. On the average, the participants were followed for 4.2 (range 3.8—5.2) years. Of the 1229 participants who were invited to the follow-up examinations, 52 had died, were suffering severe illness, or had migrated away from the area. Of the remainder, 139 could not be contacted or refused to participate. The participation rate calculated for the potentially available subjects at follow-up was 88.2%. Information on the progression of carotid atherosclerosis and covariates was available for 982 men. The analyses presented in this paper were restricted to the 584 men who were actively working at the time of the base-line measurements and had complete information on all variables. Men who were unemployed or who had retired were excluded. There were 197, 180, 169, and 51 men in the 42, 48, 54, and 60-year-old age groups, respectively.

Assessment of carotid atherosclerotic progression

Atherosclerotic progression was assessed in a high-resolution B-mode ultrasonographic examination of a 1.0—1.5 cm section of the left and right common carotid artery (CCA) below the carotid bulb. The images were focused on the posterior (far) wall with the subject supine. Technical details of the ultrasonography have been described elsewhere (11). On the average, 100 estimates of the distance between the lumen-intima and media-adventitia interfaces were recorded over the 1.0—1.5 cm section of each common carotid artery. The IMT of the posterior wall was measured as the distance from the leading edge of the first echogenic line to the leading edge of the 2nd echogenic line, as explained in detail elsewhere (11). Measurements were not conducted of the near wall due to greater measurement variability (42). The present study uses maximum IMT defined as the average of the maximum IMT in the right and left common carotid artery. The progression of carotid atherosclerosis was calculated as the arithmetic difference between the base-line and 4-year follow-up values for maximum IMT. Base-line IMT recordings were also classified by 1 physician into the following 4 categories: (i) no atherosclerotic lesion, (ii) intima-media thickening, (iii) nonstenotic plaque, and (iv) large, stenotic plaque. "Intima-media thickening" (category 2) was defined as more than 1.0 mm between the lumen-intima interface and the media-adventitia interface in the common carotid arterys below the carotid bulb. "Nonstenotic plaque" (category 3) was defined as a distinct area of mineralization or focal protrusion into the lumen. A plaque was defined as stenotic (category 4) if it obstructed more than 20% of the lumen diameter (11).

Assessment of standing at work

Standing at work was assessed with the use of a self-administered questionnaire at the time of the base-line measurements. For the 584 respondents with complete information on all the variables, the amount of working in a standing position was reported in the following 4 ordered categories: "very much" (N=88), "a lot" (N=152), "little" (N=264), and "not at all" (80). (In the Finnish questionnaire the upper 2 categories were called "erittäin paljon" and "paljon").

Assessment of covariates

The following 4 groups of covariates were measured: (i) technical factors possibly influencing measurements of the progression of IMT (IMT in the base-line measurements, sonographer, and participation in an unrelated clinical trial on lipid lowering medication), (ii) heaviness of physical work, (iii) psychosocial job factors (mental strain at work, stress from work deadlines, social support from co-workers and supervisors, and personal income at the time of the base-line measurements), and (iv)

biological and behavioral risk factors (body mass index, apo-lipoprotein B, high-density lipoprotein, blood glucose, fibrinogen, hematocrit, systolic blood pressure, cardiorespiratory fitness, smoking, alcohol, and leisure-time physical activity). A detailed description of the measurement of risk factors has been published elsewhere (43, 44). Cardiorespiratory fitness was measured directly on the basis of respiratory gas exchange during a maximal, symptom-limited exercise tolerance test on a bicycle ergometer (45). Alcohol consumption was assessed for a 4-day period with the use of diaries and for the previous 12 months with a self-administered questionnaire (46). Smoking was measured by a questionnaire and classified for this analysis as "never smoker", "former smoker", and "current smoker" (measured in 3 levels of pack-years). Treatment for hypertension or hyperlipidemia was assessed by a review of medications.

Assessment of prevalent ischemic heart disease

The subjects were considered to have existing ischemic heart disease (IHD) at the time of the base-line measurements if they (i) had any history of prior myocardial infarction or angina pectoris, (ii) currently used antiangina medication, or (iii) had positive findings of angina from the London School of Hygiene Cardiovascular Questionnaire (47).

Statistical methods

The association between the amount of standing at work and the progression of IMT was assessed by estimating the mean change in each measure of IMT (maximum thickness, mean thickness, and plaque height), for each level of standing. The analyses were conducted using the GLM procedure in SAS version 6.12 on a personal computer (48). This procedure allows for age-adjusted, least-square mean values of IMT to be estimated and contrasted for each amount of standing while simultaneously controlling for the base-line IMT and other covariates. In addition to age, base-line levels of IMT, and covariates, all estimates were adjusted for participation in the clinical trial of pravastatin, the zooming depth of the ultrasound scan, and separate indicator variables for the individual technicians who conducted the scans (11).

Table 1. Maximum common carotid intima media thickness (IMT) by amount of standing at work at the time of the base-line measurements — Kuopio Ischemic Heart Disease Risk Factor Study, 1984—1989.[a]

Standing	N	IMT	
		Mean	SD
Not at all	80	0.90	0.15
Little	264	0.91	0.15
A lot	152	0.93	0.27
Very much	88	0.93	0.27

[a] F(3 df)=0.76, P=0.51.

Results

Table 1 shows the unadjusted base-line measurements of IMT by amount of standing at work. Workers standing not at all (N=80) had the lowest mean maximum IMT (0.90 mm), and workers standing a lot or very much (N=240) had the highest mean maximum IMT (0.93 mm). The differences were not statistically significant (P=0.51).

Table 2 shows the adjusted mean 4-year changes in IMT by the amount of standing at work. Model 1 shows

Table 2. Progression of common carotid atherosclerosis[a] by amount of standing at work — Kuopio Ischemic Heart Disease Risk Factor Study, 1984—1989.

Work in standing position	Model 1: adjustment for age and technical factors[b] (N=584)			Model 2: model 1 with additional adjustment for heaviness of physical work[c] (N=584)			Model 3: model 2 with additional adjustment for psychosocial job factors and income[d] (N=584)			Model 4: model 3 with additional adjustment for biological[e] and behavioral factors[f] (N=584)		
	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI
None	0.24	0.10	0.04—0.15	0.24	0.09	0.03—0.15	0.24	0.09	0.03—0.15	0.24	0.09	0.03—0.16
Little	0.25	0.09	0.05—0.13	0.25	0.09	0.04—0.14	0.25	0.09	0.04—0.14	0.25	0.09	0.03—0.14
A lot	0.28	0.06	0.01—0.11	0.28	0.06	0.01—0.11	0.28	0.06	0.01—0.10	0.28	0.05	0.00—0.10
Very much	0.34	-	-	0.34	-	-	0.34	-	-	0.33	-	-

[a] Change in maximum intima media thickness (IMT) in milimeters.
[b] Technical factors included sonographer, depth, participation in clinical trial on lipid lowering medication, maximum carotid intima thickness during the base-line measurements.
[c] Heaviness of physical work included 4 self-reported levels: very light, light, moderately heavy, and heavy physical work.
[d] The psychosocial job factors included a 10-item mental scale, stress from deadlines, social support from co-workers and supervisors, and personal income at the time of the base-line measurements.
[e] The biological factors included cardiorespiratory fitness (maximal oxygen consumption), body mass index, apo-lipoprotein B, high-density lipoprotein, systolic blood pressure, treatment of blood pressure, blood glucose, fibrinogen, hematocrit.
[f] The behavioral factors included former smoking, level of current smoking, alcohol consumption, and leisure-time physical activity.

the age-adjusted mean 4-year change in IMT. There was a significantly greater progression of atherosclerosis among the men who reported the most standing (0.34 mm) when they were compared with the men standing a lot (0.28 mm), little (0.25 mm), or not at all (0.24 mm). The difference in the mean IMT change between standing very much and standing not at all was 0.10 mm (95% CI 0.05—0.15) or 26%. Model 2 adds adjustment for physical heaviness of the work. The results of model 2 are nearly identical with those of model 1. Further adjustment for mental strain at work, stress from deadlines, social support from co-workers and supervisors, and income in model 3 did not change the results. Additional adjustment for biological factors (cardiorespiratory fitness, body mass index, apo-lipoprotein B, high-density lipoprotein, blood glucose, fibrinogen, hematocrit, systolic blood pressure, and treatment of blood pressure) and behavioral factors (former smoking, level of current smoking, alcohol consumption, and leisure-time physical activity) yielded the same results (model 4). There was no significant interaction between the levels of standing and the heaviness of the work ($P_{interaction} = 0.49$).

After additional adjustment for hostility and hopelessness, 2 psychological factors that may be related to the work environment and that have recently been shown to be associated with the progression of atherosclerosis (49, 50), the mean change in IMT for those standing very much was 0.32 mm. The difference in IMT change compared with those of the 2 lower levels of standing at work was 0.07 mm, and it was statistically significant (results not shown).

There was a significant interaction between the levels of standing and prior stenosis of the common carotid arteries when the interaction term was added to model 4 (P=0.002). Similarly, there was significant interaction between standing and the prevalence of IHD (P=0.001), a finding indicating that the rates of progression between the healthy and the diseased subgroups differed significantly.

Table 3 shows the adjusted mean 4-year changes in the intima thickness by the amount of standing at work for the subgroups of men with different health status at the time of the base-line measurements. All the results in table 3 were submitted to the same adjustments for covariates as model 4 in table 2. For the men without prior stenosis of the common carotid artery (model 5), the mean change in the IMT showed a nonsignificant trend for more progression of atherosclerosis in men standing very much (0.30 mm) when they were compared with men standing a lot (0.27 mm), little (0.26 mm) or not at all (0.26 mm). For the men with prior carotid stenosis (model 6), the mean change in the IMT showed significantly more progression of atherosclerosis for the men standing very much (0.45 mm) when they were compared with the men standing a lot (0.28 mm), little (0.19 mm), or not at all (0.14 mm). Among the men with prior stenosis, the progression of atherosclerosis was over 3 times greater for those standing very much at work than for those not standing at work; the absolute difference was 0.31 [95% confidence interval (95% CI) 0.10—0.51] mm.

For the men without existing IHD in the base-line measurements (model 7), the mean change in IMT showed a graded relationship with significantly more progression among the men standing very much (0.30 mm) when they were compared with the men standing a lot (0.26 mm), little, or not at all (0.24 mm). For the men with existing IHD (model 8), the mean change in IMT showed significantly more progression of atherosclerosis among the men standing very much (0.75 mm) when compared with the men standing a lot (0.37 mm), little (0.15 mm), or not at all (0.08 mm). Among the men with prior IHD, the progression of atherosclerosis was 9 times

Table 3. Progression of common carotid atherosclerosis[a] by amount of standing at work in the subsamples defined by health status at the time of the base-line measurements — Kuopio Ischemic Heart Disease Risk Factor Study, 1984—1989. (95% CI = 95% confidence interval)

Work in standing position	Model 5: model 4,[b] restricted to men without stenosis[c] (N=463)			Model 6:model 4, restricted to men with stenosis[c] (N=121)			Model 7: model 4, restricted to men without ischemic heart disease[d] (N=512)			Model 8: model 4, restricted to men with ischemic heart disease[d] (N=72)		
	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI	Adjusted mean change	Difference	95% CI
None	0.26	0.04	-0.02—0.10	0.14	0.30	0.10—0.51	0.24	0.06	0.00—0.12	0.08	0.67	0.22—1.12
Little	0.26	0.04	-0.01—0.09	0.19	0.25	0.09—0.41	0.24	0.06	0.01—0.11	0.15	0.60	0.24—0.96
A lot	0.27	0.03	-0.02—0.08	0.28	0.17	0.03—0.31	0.26	0.04	-0.01—0.09	0.37	0.38	0.09—0.67
Very much	0.30	-	-	0.45	-	-	0.30	-	-	0.75	-	-

[a] Change in maximum intima media thickness (IMT) in millimeters.
[b] See table 1 for a definition of model 4.
[c] Prior stenosis was defined as ultrasonic incidence of ≥20% stenosis or nonstenitic atherosclerotic plaque.
[d] Ischemic heart disease was defined as prevalent at the time of the base-line measurements by (i) any history of myocardial infarction of angina pectoris or (ii) current use of antiangina medication or (iii) angina according to the London School fo Hygiene Cardiovascular Questionnaire.
[e] Reported differences in the adjusted mean change in IMT to the reference category ("very much") vary due to rounding.

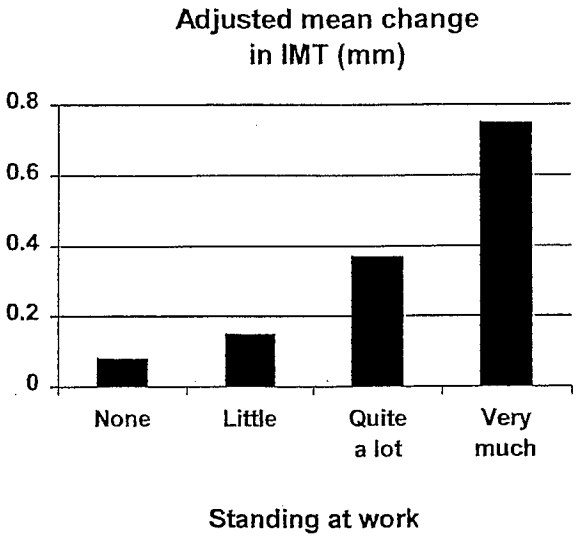

Figure 2. Four-year change in carotid intima media thickness (IMT) in millimeters by standing at work among men with ischemic heart disease at the time of the base-line measurements, adjusted for age, technical factors, physical and psychosocial job factors, income, and biological and behavioral risk factors (model 8, see the text).

greater for those standing very much at work than for those not at all standing at work; the absolute difference was 0.67 (95% CI 0.22—1.12) mm. (See figure 2.)

Discussion

Observed changes in the mean maximum IMT over the 4-year follow-up period ranged from 0.08 to 0.67 mm. Although these changes may appear small, the differences observed in the atherosclerotic progression between the men standing very much at work and the men standing less have potentially important clinical and occupational health consequences. While there is limited information on the relationship between carotid atherosclerotic progression and clinical events, Salonen & Salonen have demonstrated that a 0.1-mm difference in maximum IMT is associated with an 11% increased risk of acute myocardial infarction (95% CI 6—16%, P<0.001) (51). The Atherosclerosis Risk in Communities (ARIC) study group reported comparable risk estimates from the population-based study in 4 communities in the United States (52). In this prospective study, the mean 4-year change in the maximum IMT for men who reported the most standing ranged from 0.30 mm for the men with no carotid stenosis at the time of the base-line measurements to 0.75 mm for the men with pre-existing IHD. In our models these adjusted mean changes in the IMT were bigger than the changes observed for heavy smokers. For the upper tertile of current smokers, the adjusted mean 4-year change in the maximum IMT ranged from 0.30 mm in the total sample to 0.38 mm for the men with IHD at the time of the base-line measurements.

The results showed a strong association between the amount of standing at work and the progression of carotid atherosclerosis. The relationships remained unaltered after adjustments for the physical heaviness of the work, psychosocial job factors, income, and biological and behavioral risk factors. The associations between standing and the progression of atherosclerosis were strongest among the men with prior carotid stenosis or with IHD. Among the men with prior stenosis, the progression of atherosclerosis was 3 times greater for those standing very much at work than for those not standing at all. For the men with prevalent IHD, the progression of atherosclerosis was 9 times greater for the men standing very much than for those not standing at all. These results suggest that men with prior stenosis or IHD are especially vulnerable to the adverse effects of prolonged standing at work. This faster progression of atherosclerosis among men with preexisting atherosclerotic plaques or stenosis is in agreement with our hemodynamic hypothesis because abrupt or irregular changes in arterial lumen diameter — even in the presence of localized compensatory vasodilatation (53—55) — may cause local turbulence. Similarly, wall shear stress is indirectly proportional to the radius to the third power, thus small changes in lumen radius result in marked changes in wall shear stress (15). Since the subgroups of men with IHD and with prior carotid stenosis largely overlap — confirming earlier observations that atherosclerotic changes in the carotid arteries are associated with coronary heart disease (11, 12, 51, 52) — similar hemodynamic mechanisms may be invoked to explain the progression of atherosclerosis in men with IHD.

We also found associations between standing at work and the progression of atherosclerosis in subsamples of healthy men without prior stenosis or without IHD at the time of the base-line measurements, and this finding suggests that long-term standing at work may be a risk factor in the very early subclinical stages of atherosclerosis. For the smaller of the 2 healthy subgroups (men without carotid stenosis at the time of the base-line measurements), the adjusted association did not remain statistically significant due to the reduced statistical power after adjustment for 26 confounders with 30 degrees of freedom in the multivariate analysis.

To our knowledge, the effect of a standing work position on atherosclerosis or any other cardiovascular disease outcome of the arterial branch has not been previously studied. However, prolonged standing (or sitting) has been shown to be associated with the incidence of varicose veins (19, 21, 56). Interestingly, varicose leg veins were in turn associated with a higher incidence of atherosclerotic diseases in several studies, but the researchers provided no specific biological explanation for this co-emergence of varicose veins with arteriosclerotic vascular diseases (19, 20). According to our hemodynam-

ic hypothesis, varicose veins could contribute to atherosclerosis through increased hydrostatic venous pooling during standing and therefore lead to a further reduction in plasma volume and result in arterial flow changes that, in turn, lead to atherogenic turbulence and shear stress changes on the arterial wall, as described in more detail earlier.

It is beyond the scope of this paper to discuss the etiology and pathophysiology of varicose veins, but a hemodynamic theory could probably explain both varicose veins and atherosclerosis on the basis of physiological changes associated with standing. Thus the association of varicose veins with atherosclerotic disease can be viewed as an indirect support of our hemodynamic hypothesis. Together with the evidence from experimental studies and human pathology, our findings suggest that hemodynamic factors triggered by long-term standing play a role in the progression of atherosclerosis. Because there are no direct measurements of shear stress in vivo that could have been employed in this or any other epidemiologic study, the conclusion regarding the involved mechanisms — including altered blood flow characteristics such as changes in turbulence and wall shear stress — rests on indirect evidence. Even if the study cannot rule out alternative unknown mechanisms driving the association between standing and the progression of atherosclerosis, the effect of standing at work on the progression of atherosclerosis seems biologically plausible.

One alternative explanation for our findings could be that work requiring a lot of standing is more prevalent in groups of lower socioeconomic status. Low socioeconomic status is a strong predictor of cardiovascular disease (57), and inverse associations of ultrasonographically assessed IMT have been reported for socioeconomic status in both cross-sectional (58, 59) and prospective (60) studies. Men of lower socioeconomic status exhibit a profile of higher levels of known cardiovascular risk factors (43, 61). However, adjustment for socioeconomic status and adjustment for all major cardiovascular risk factors did not change the observed relationships in our study. This finding suggests that standing has an effect on the progression of atherosclerosis independent of socioeconomic status and the traditional risk factors. Similarly, adjusting for hopelessness and cynicism, factors that have been recently linked with the progression of atherosclerosis in our study population (49, 50, 62) and which are more prevalent among men of lower socioeconomic status (63), did not affect the relationships.

Another alternative explanation of our findings could be that people who work predominantly in a standing position may be concurrently exposed to other adverse work conditions, particularly heavy physical labor and psychosocial stress factors. The latter are often more prevalent in physically demanding jobs (64). Such factors, if present, may account for the difference between men standing very much at work and men who mostly sit during work. However, we also found a significant difference in the progression of atherosclerosis between the 2 highest exposure groups (ie, between men standing very much and men standing quite a lot). One would not expect their jobs to differ as much from each other in terms of heaviness of work or psychosocial work conditions when compared with sitting jobs, and, yet, the differences between these 2 high-exposure groups were nearly as large as the differences between the highest exposure group and the lowest exposure group. On the other hand, psychosocial job factors have been shown to be related to cardiovascular disease outcomes, including myocardial infarction and the progression of artherosclerosis in our study population (14, 65). Therefore we explored this possibility of confounding by additionally adjusting for psychological job demands (mental strain at work and stress from deadlines) and the degree of social support from supervisors and co-workers. The results did not indicate any confounding by these factors. Similarly, adjustment for the physical heaviness of work, which was also related to the IMT in our sample and which may be correlated with work in a standing position, did not affect the results. No interaction effects were found between the heaviness of work and the amount of standing at work. These analyses suggest that the association between standing at work and the progression of atherosclerosis was not confounded by other physical or psychosocial workplace factors.

A limitation of the study was the measurement of the amount of standing at work by self-reports. The correlation between self-reports and direct observations for physical work activities is often only moderate (66—69). However, questions about static postures involving the whole body, such as sitting or standing, have shown fair-to-high reliability and validity in self-reported contexts (68—71). Workers tend to underestimate the amount of standing, and this tendency would introduce a conservative bias (68). The potential for bias due to measurement error has been shown to be lowest for prospective studies (72). No direct job observations were available in this population-based study, but we had the opportunity to check current occupational titles for all the subjects and found that the occupational titles were consistent with reported work positions. For example, men doing administrative work, operating stationary machinery, or driving motor vehicles were the 3 occupational groups most often reporting no standing at work, while physicians, sales people, metal workers, and wood and construction workers typically reported high amounts of work in a standing position. These occupations are heterogeneous in terms of socioeconomic status and other relevant work characteristics. For this reason we believe that it is the standing position at work per se that has an atherosclerotic progression-promoting effect.

Measurement bias is also possible because the amount of standing in our analyses was based on a single base-line measurement, and it did not reflect possible changes in exposure during the 4-year follow-up period. In fact, of those who were still employed at the time of the follow-up and who were standing very much at the time of the base-line measurements, 58% reported standing very much, 26% stated that they stood a lot, 10% did little standing, and 6% did not stand at all at the time of the follow-up. The Pearson correlation coefficient between the 4 categories of standing at the time of the base-line measurement and at the time of the follow-up was 0.63 ($P<0.001$). Although these figures indicate a modest stability of exposure over the follow-up period, some exposure changes had definitely occurred, and these changes probably resulted in an underestimation of the magnitude of the effects associated with prolonged standing (73). Cumulative changes in work conditions during several decades prior to the current job at the time of the base-line measurements were probably responsible for the smaller differences seen in the base-line IMT values.

Selection bias needs to be considered even in this population-based sample because it is possible that men were selected out of jobs requiring excessive amounts of standing because of symptomatic cardiovascular disease. Given the faster progression of atherosclerosis observed among the men with cardiovascular disease, this occurrence would lead to an underestimation of the magnitude of effects. It is noteworthy that we found significant effects even in the healthy subsample of men without any clinically manifest ischemic heart disease.

In conclusion, our findings cannot entirely be explained by any of the established cardiovascular risk factors, and this result suggests a causal role of prolonged standing at work in the progression of atherosclerosis. Our findings also provide the 1st empirical evidence in a population study for the possible role of venous pooling and subsequent changes in pulse pressure, blood flow turbulence, and shear stress (as consequences of long-term standing) in the progression of human atherosclerosis. Our observations warrant further epidemiologic studies to identify occupational and clinical groups at increased risk and clinical or physiological studies to determine the involved hemodynamic and humoral pathways. Especially important is the finding that the progression of IMT was 3- to 9-fold greater among the men who stood the most at work and who had prior carotid atherosclerosis or clinical IHD when they were compared with those who did not stand at work and had no such conditions. This difference may have important implications for the management of patients with such cardiovascular conditions. For example, if these findings are confirmed by others, one might reconsider current practices in counseling and rehabilitating patients who work in occupations requiring excessive amounts of standing while working. One implication might be to advocate vocational rehabilitation and job modification that allows for less standing and more flexibility in work positions. Establishing an opportunity for self-paced and frequent changes of work position and requiring less standing at work is an intervention that might also be helpful in the prevention of other chronic diseases, such as spinal disorders and associated work disability (74, 75). On the basis of the presented data, reducing the amount of standing at work needs to be considered as a new measure in the prevention of atherosclerosis in the carotid arteries. Of course, other studies of different populations and using different methods need to confirm these findings before definite conclusions can be drawn. Future studies should also examine the effects of long-term standing at work on cardiovascular and cerebrovascular disease outcomes, such as myocardial infarction and stroke.

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