TRIGGERING OF SUDDEN DEATH FROM CARDIAC CAUSES BY VIGOROUS EXERTION

CHRISTINE M. ALBERT, M.D., M.P.H., MURRAY A. MITTLEMAN, M.D., DR.P.H., CLAUDIA U. CHAE, M.D., M.P.H, I.-MIN LEE, M.B., B.S., SC.D., CHARLES H. HENNEKENS, M.D., DR.P.H., AND JOANN E. MANSON, M.D., DR.P.H.

ABSTRACT

Background Retrospective and cross-sectional data suggest that vigorous exertion can trigger cardiac arrest or sudden death and that habitual exercise may diminish this risk. However, the role of physical activity in precipitating or preventing sudden death from cardiac causes has not been assessed prospectively in a large number of subjects.

Methods We used a prospective, nested case–crossover design within the Physicians' Health Study to compare the risk of sudden death during and up to 30 minutes after an episode of vigorous exertion with that during periods of lighter exertion or none. We then evaluated whether habitual vigorous exercise modified the risk of sudden death that was associated with vigorous exertion. In addition, the relation of vigorous exercise to the overall risk of sudden death and nonsudden death from coronary heart disease was assessed.

Results During 12 years of follow-up, 122 sudden deaths were confirmed among the 21,481 male physicians who were initially free of self-reported cardiovascular disease and who provided information on their habitual level of exercise at base line. The relative risk of sudden death during and up to 30 minutes after vigorous exertion was 16.9 (95 percent confidence interval, 10.5 to 27.0; $P<0.001$). However, the absolute risk of sudden death during any particular episode of vigorous exertion was extremely low (1 sudden death per 1.51 million episodes of exertion). Habitual vigorous exercise attenuated the relative risk of sudden death that was associated with an episode of vigorous exertion (P value for trend = 0.006). The base-line level of exercise was not associated with the overall risk of subsequent sudden death.

Conclusions These prospective data from a study of U.S. male physicians suggest that habitual vigorous exercise diminishes the risk of sudden death during vigorous exertion. (N Engl J Med 2000;343:1355-61.)

PHYSICAL activity clearly benefits cardiovascular health.[1-3] In prospective epidemiologic studies, both vigorous physical activity and moderate activity are consistently associated with a reduced risk of coronary heart disease.[4-7] However, it is also recognized that sudden death from cardiac causes seems to occur with an unusually high frequency during or shortly after vigorous exertion.[7] Approximately 6 to 17 percent of all sudden deaths occur in association with exertion,[8-11] and there is evidence to suggest that vigorous exertion simultaneously triggers and protects against sudden death.[11] However, the role of vigorous exertion in precipitating or preventing sudden death has not been assessed prospectively in a large number of subjects. The prospective data compiled in the Physicians' Health Study presented a unique opportunity to determine whether vigorous exertion triggers sudden death and whether habitual vigorous exercise diminishes the risk.

METHODS

Study Population

The methods of the Physicians' Health Study have been described in detail elsewhere.[12] Briefly, 22,071 male physicians who were from 40 to 84 years of age in 1982 and had no history of myocardial infarction, stroke, transient ischemic attacks, or cancer were assigned to receive aspirin, beta carotene, or both, according to a randomized, placebo-controlled, two-by-two factorial design. At base line, the physicians completed questionnaires on their cardiovascular risk factors, intake of selected foods, and frequency of vigorous exercise. In this investigation, we excluded 590 men who reported having angina or having undergone coronary revascularization, or for whom data on physical activity were missing, at base line, leaving 21,481 participants as the base population for the analysis.

Study Design

We used a nested case–crossover design to quantify the relative risk of sudden death from cardiac causes during or up to 30 minutes after an episode of vigorous exertion as compared with the risk during periods of lighter exertion or none (Fig. 1). The case–crossover study design permits the assessment of change in the risk of an event during a brief "hazard period" during and after exposure to a transient risk factor.[13] For each subject who had an event (i.e., who died), the prospectively determined habitual frequency of exertion for that subject served as the control information, and each such subject therefore served as his own control in this "self-matched" analysis.

Frequency and Timing of Vigorous Exertion

Frequency of Vigorous Exertion at Base Line

At base line, the subjects were asked, "How often do you exercise vigorously enough to work up a sweat?" The possible responses were rarely or never, one to three times a month, once a week, two to four times a week, five or six times a week, or daily. This measure of physical activity correlates with maximal oxygen

From the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston (C.M.A., C.U.C., I.-M.L., J.E.M.); the Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston (C.M.A., C.U.C.); the Cardiology Division, Beth Israel Deaconess Medical Center, Boston (M.A.M.); the Department of Epidemiology, Harvard School of Public Health, Boston (I.-M.L., M.A.M., J.E.M.); and the Department of Medicine, Epidemiology and Public Health, University of Miami School of Medicine, Miami (C.H.H.). Address reprint requests to Dr. Albert at the Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave. E., Boston, MA 02215-1204, or at calbert@partners.org.

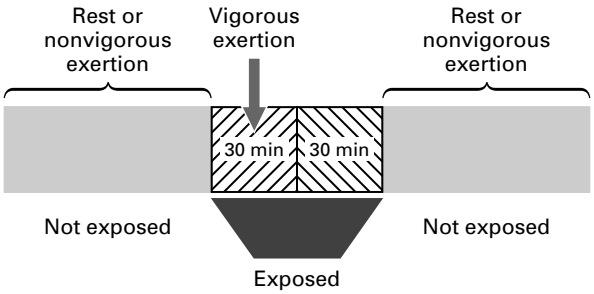

Figure 1. Design of Nested Case–Crossover Analysis.

The hatched portion of the time line represents the 60-minute hazard period (30 minutes during and 30 minutes after vigorous exertion). If a sudden death occurred during this period, there was considered to have been exposure to vigorous exertion. If a sudden death occurred during the shaded portion of the time line, there was considered to have been no exposure to vigorous exertion.

uptake,[14] time on the treadmill during exercise testing,[15] and the high-density lipoprotein cholesterol level.[16] The midpoint value was assigned to each response category and multiplied by 52 to estimate the usual annual frequency. Subjects were not asked about the average duration of exertion at base line, but the question was asked of those who reported engaging in a regular program of exercise in a questionnaire administered at 36 months (59 percent of the total cohort). The median duration reported (30 minutes) was used as an estimate of the usual duration of vigorous exercise at base line. In our primary analysis we assessed the risk of sudden death during and 30 minutes after exertion (Fig. 1). We therefore assumed that each episode of exertion was associated with 60 minutes of exposure time. To calculate the unexposed person-time, the person-time of exposure (in hours) was subtracted from the number of hours in a year.

Activity at the Time of Death

The specific activity in which the subject was engaged at the time of sudden death and for one hour before death was ascertained from the medical record or from the next of kin. The degree of physical exertion was quantified on a scale of 1 to 8 metabolic equivalents (MET).[17] The subject was considered to have been exposed to vigorous exertion if the activity was estimated as 6 MET or more. If the activity was unknown or was at a level of less than 6 MET, there was considered to have been no exposure.

Definitions

An end-points committee of physicians confirmed all events by review of medical records. Deaths for which there was evidence of coronary heart disease at or before death and no evidence of a noncoronary cause were classified as due to cardiac causes. To identify sudden deaths, medical records and reports from the next of kin for all subjects who had died from cardiac causes were reviewed again by two cardiologists, and agreement was reached on whether the death was sudden.

Sudden death was defined as death within one hour after the onset of symptoms or death after a witnessed cardiac arrest or abrupt collapse that was not preceded by symptoms lasting more than one hour. Information from the death certificate was not used to determine the timing of death. To increase the specificity of our method for identifying death from arrhythmia, we excluded anyone who had evidence of circulatory collapse (hypotension, exacerbation of congestive heart failure, or altered mental status) before the disappearance of the pulse.[18]

Absolute Risk during Vigorous Exertion

Each physician's reported frequency of vigorous exertion at base line (episodes per week) was multiplied by the follow-up time in weeks to generate an estimate of the total number of episodes of vigorous exertion in the population, and the absolute risk of sudden death associated with an episode of vigorous exertion was calculated. This risk was then compared with the incidence of sudden death during lighter physical activity, and the difference in absolute risk was estimated.

Case–Crossover Analysis

The analysis of case–crossover data is similar to that of a crossover experiment in which the risk to each subject is assessed during periods of exposure and nonexposure. The ratio of the observed frequency of exposure in the 60-minute hazard period (Fig. 1) to the frequency of exposure expected on the basis of the usual frequency of exercise reported at base line was used to calculate an odds ratio as a measure of relative risk.[13,19] The data were then stratified for each subject and analyzed by methods for cohort studies with sparse data in each stratum.[20] Modification of the relative risk by habitual vigorous exertion was assessed by comparison of the relative risks for three categories of habitual vigorous exertion (less than once, one to four times, and five or more times per week), and a test for linear trend[21] was performed. The effect of the time of day on the relative risk of sudden death was assessed by stratification of the analysis according to the time of death, followed by comparison of the relative risks by means of a test for homogeneity.[22] All reported P values are two-sided.

Sensitivity Analyses

Three sensitivity analyses were performed. First, to examine the sensitivity of the results to the hazard period chosen, we considered only the period during vigorous exertion (the labeled portion in Fig. 1) as the period of exposure and reexamined the relative risk of sudden death during this 30-minute hazard period. Second, we examined the sensitivity of the results to changes in our estimate of the usual duration of vigorous exertion. Third, we examined the sensitivity of the results to our definition of sudden death, which, although specific for death from arrhythmia, excluded most unwitnessed deaths and deaths during sleep. Some of these deaths could have been sudden, and their systematic exclusion could have biased our results toward a positive association between death and vigorous exercise. Therefore, in this analysis, we included unwitnessed deaths with an autopsy result consistent with an arrhythmic cause and those that occurred during sleep without preceding symptoms as sudden deaths.

Overall Risk of Sudden and Nonsudden Death from Cardiac Causes

The base-line information on the usual frequency of vigorous exertion was modeled in four categories (less than once, once, two to four times, and five or more times per week), and the relative risks of sudden death and nonsudden death from coronary heart disease for the base population of 21,481 men were computed with use of Cox proportional-hazards models[23] with simultaneous control for potential confounders.

RESULTS

During 12 years of follow-up, 122 sudden deaths from cardiac causes occurred among the 21,481 participants. The age-adjusted risk factors at base line and the usual frequency of vigorous exertion for those who died suddenly and for the other participants are shown in Table 1. The majority of participants reported exercising vigorously two to four times per week, and the distribution of the categories for usual fre-

TABLE 1. CHARACTERISTICS OF THE SUBJECTS WHO DIED SUDDENLY AND THOSE WHO DID NOT.*

CHARACTERISTIC	NO SUDDEN DEATH (N=21,359)	SUDDEN DEATH (N=122)	P VALUE
	means ±SD		
Age (yr)	53.0±9.42	60.5±9.6	<0.001
Body-mass index†	24.9±3.0	25.2±2.9	0.32
	no. (%)		
Frequency of vigorous exercise			0.41
<1 time/wk	5,890 (27.6)	32 (22.5)	
1 time/wk	3,941 (18.4)	27 (20.1)	
2–4 times/wk	8,063 (37.7)	40 (38.8)	
5 or 6 times/wk	2,328 (10.9)	9 (9.9)	
Daily	1,137 (5.3)	14 (8.6)	
Smoking status			0.05
Current smoker	2,366 (11.1)	20 (19.8)	
Past smoker	8,367 (39.3)	53 (40.3)	
Never smoked	10,592 (49.6)	48 (40.0)	
Medical conditions			
Diabetes	477 (2.2)	13 (10.7)	0.001
High cholesterol level‡	1,264 (6.7)	10 (8.2)	0.73
Hypertension§	2,852 (13.5)	40 (32.5)	0.001
Parental myocardial infarction before 60 years of age	2,761 (13.0)	17 (17.1)	0.18
Alcohol intake			0.05
<Weekly	5,476 (25.8)	48 (37.8)	
Weekly	10,475 (49.3)	36 (37.5)	
Daily	5,277 (24.9)	37 (24.7)	
Fish consumption (<1 serving/wk)¶	1,902 (9.2)	17 (15.0)	0.03
Treatment group			
Aspirin	10,661 (49.9)	59 (54.9)	0.75
Beta carotene	10,678 (50.0)	61 (50.2)	0.98

*Characteristics have been standardized according to age in the entire cohort. Not all questions were answered by all subjects.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡This diagnosis was based on a self-reported high cholesterol level, a cholesterol level ≥260 mg per deciliter (6.7 mmol per liter), or the use of cholesterol-lowering medications.

§This diagnosis was based on a self-reported systolic blood pressure ≥160 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications.

¶Information was ascertained on the 12-month questionnaire.

quency of vigorous exertion did not differ significantly between those who died and those who did not. Complete information on physical activity during the hour before death was available for 80 percent of the sudden deaths. Seventeen such deaths (13.9 percent) occurred during vigorous exertion, and six (4.9 percent) occurred within 30 minutes after vigorous exertion. The majority of the participants were engaged in dynamic exercise, such as jogging or racquet sports (68 percent). The rest were involved in other sports (25 percent) or heavy yardwork or home repairs (7 percent).

Among the 21,481 men, the incidence of sudden death per person-hour was 1 death per 19 million hours. The risk of sudden death associated with an episode of vigorous exertion was 1 per 1.42 million episodes or person-hours at risk. Alternatively, the risk of sudden death during periods of lighter exertion or none was 1 death per 23 million person-hours. From these data, the unadjusted difference in risk associated with exposure to vigorous exertion can be estimated at 1 excess sudden death per 1.51 million episodes of vigorous exertion. On the basis of the case–crossover method, the relative risk of sudden death during the one-hour period associated with vigorous exertion (Fig. 1), as compared with other time points, was significantly elevated at 16.9 (95 percent confidence interval, 10.5 to 27.0; $P<0.001$).

Effect of the Frequency of Vigorous Exercise

The results after stratification according to the usual frequency of vigorous exercise at base line are presented in Table 2. The relative risk of sudden death associated with an episode of vigorous exertion was lower among those who exercised more frequently

TABLE 2. EFFECT OF HABITUAL VIGOROUS EXERCISE ON THE RISK OF SUDDEN DEATH DURING VIGOROUS EXERTION.

FREQUENCY OF HABITUAL VIGOROUS EXERCISE	SUDDEN DEATHS		RELATIVE RISK (95% CI)*
	TOTAL	RELATED TO VIGOROUS EXERTION	
	no.		
<1 time/wk	32	3	74.1 (22.0–249)
1–4 times/wk	67	13	18.9 (10.2–35.1)
≥5 times/wk	23	7	10.9 (4.5–26.2)

*The relative risk is the risk of sudden death during and 30 minutes after an episode of vigorous exertion, as compared with the risk during periods of lighter exertion or none. CI denotes confidence interval.

TABLE 3. RELATIVE RISK OF SUDDEN DEATH ASSOCIATED WITH AN EPISODE OF VIGOROUS EXERTION, ACCORDING TO THE TIME OF DEATH.

TIME OF DEATH	SUDDEN DEATHS		RELATIVE RISK (95% CI)*
	TOTAL	RELATED TO VIGOROUS EXERTION	
	no.		
All times	122	23	16.9 (10.5–27.0)
6 a.m.–noon	33	7	18.5 (7.3–46.6)
Noon–6 p.m.	23	5	19.0 (6.9–52.2)
6 p.m.–midnight	36	6	16.6 (7.0–39.8)
Midnight–6 a.m.	17	1	4.58 (0.55–37.9)

*The relative risk is the risk of sudden death during and 30 minutes after an episode of vigorous exertion, as compared with the risk during periods of lighter exertion or none. CI denotes confidence interval. Subjects were excluded if exact times of death were not known.

(P for trend=0.006). Men who rarely engaged in vigorous exercise (less than once a week) had a relative risk of sudden death of 74.1 in the period during and 30 minutes after exertion. In comparison, men who exercised at least five times per week had a much lower risk (relative risk, 10.9); however, this risk was still significantly higher than that during periods of lighter exertion or none.

Effect of Time of Death

It is well known that the incidence of sudden death varies according to the time of day. If the subjects tended to exercise during the circadian peak in the incidence of sudden death (from 6 a.m. to noon),[24] this fact could account for part of the increased risk associated with exertion. To address this issue, we reexamined the relative risks according to the time of death (Table 3). The relative risk associated with an acute episode of vigorous exertion was not significantly modified by the time of death. In addition, the relative risk associated with vigorous exertion remained significantly elevated at times other than the circadian peak in sudden death, except for the period from midnight to 6 a.m., when exposure to exertion was low.

Sensitivity Analyses

Seventeen of the 23 sudden deaths that were associated with vigorous exertion occurred during the exertion. Using the case–crossover method, we found the estimated relative risk of sudden death during exertion (a 30-minute hazard period) to be higher (relative risk, 44.9; 95 percent confidence interval, 26.7 to 75.4) than that during the 60-minute hazard period, but it was still modified by habitual vigorous exercise (P for trend=0.003). When the usual duration of vigorous exercise was estimated to be 20 minutes, the relative risk of sudden death in the 60-minute hazard period was 20.4 (95 percent confidence interval, 12.7 to 32.7); it was 14.6 (95 percent confidence interval, 9.10 to 23.4) when the duration was estimated to be 40 minutes. Again, modification by usual vigorous exercise remained significant (P≤0.005). Finally, if deaths that occurred during sleep or were unwitnessed were included as sudden deaths, the relative risk of sudden death in the 60-minute hazard period remained elevated (relative risk, 13.8; 95 percent confidence interval, 8.9 to 21.2), and this excess risk was still modified by the frequency of vigorous exercise (P for trend=0.003) (Table 4).

Overall Risk Associated with Vigorous Exercise at Base Line

The base-line level of vigorous exercise was not significantly associated with the risk of subsequent sudden death, either before or after potential confounders had been controlled for. In contrast, the risk of nonsudden death from coronary heart disease was lower among the men who participated in vigorous exercise than among those who did not. However, no further reduction in risk was observed for a frequency of exercise of more than once a week (Table 5).

DISCUSSION

In this prospective, nested case–crossover study of apparently healthy male physicians, the risk of sudden death was transiently elevated in association with an episode of vigorous exertion by a factor of 14 to 45, as compared with the risk during periods of lighter or no exertion. Despite the high relative risk, the

TABLE 4. RESULTS OF THE INCLUSION OF UNWITNESSED DEATHS AND DEATHS DURING SLEEP AS SUDDEN DEATHS.

FREQUENCY OF HABITUAL VIGOROUS EXERCISE	SUDDEN DEATHS		RELATIVE RISK (95% CI)*
	TOTAL	RELATED TO VIGOROUS EXERTION	
	no.		
<1 time/wk	54	3	47.6 (14.6–156)
1–4 times/wk	96	15	14.1 (8.1–24.6)
≥5 times/wk	27	8	10.5 (4.6–23.7)

*The relative risk is the risk of sudden death during and immediately after an episode of vigorous exertion, as compared with the risk during periods of lighter exertion or none. CI denotes confidence interval.

TABLE 5. MULTIVARIATE RELATIVE RISK OF SUDDEN DEATH AND NONSUDDEN DEATH FROM CORONARY HEART DISEASE ACCORDING TO THE FREQUENCY OF VIGOROUS EXERCISE AT BASE LINE.*

FREQUENCY OF VIGOROUS EXERCISE	SUDDEN DEATH (N=109)	NONSUDDEN DEATH (N=146)
	relative risk (95% CI)	
<1 time/wk	1.0	1.0
1 time/wk	1.68 (0.98–2.87)	0.61 (0.37–1.02)
2–4 times/wk	1.13 (0.69–1.88)	0.59 (0.40–0.88)
≥5 times/wk	1.36 (0.76–2.43)	0.61 (0.37–1.02)
P for trend	0.63	0.03

*The multivariate model includes age (as a continuous variable); assignment to aspirin and beta carotene treatment; body-mass index (in quartiles); smoking status (current smoker, <20 cigarettes/day or ≥20 cigarettes/day; past smoker; never smoked); history of diabetes, hypertension, or hypercholesterolemia; consumption of alcohol (pseudocontinuous, linear, and quadratic term), use of vitamin E, vitamin C, and multivitamins at base line; and frequency of consumption of fish at 12 months (<1 time/month, 1–3 times/month, weekly, 2–4 times/week, ≥5 times/week). Only subjects for whom data were available are included. CI denotes confidence interval.

absolute excess risk of sudden death during any particular episode of vigorous exertion was extremely low (1 death per 1.51 million episodes of vigorous exertion), similar to that reported in other populations.[7,9,11]

As expected, the base-line level of habitual exercise significantly attenuated the increase in the risk of sudden death that was associated with an episode of vigorous exertion in both the primary analysis and the three sensitivity analyses. Habitually active men had a much lower risk of sudden death in association with an episode of vigorous exertion than men who exercised less than once a week; however, the most active men's risk remained significantly elevated during and after vigorous exertion in all analyses. These results are similar to those reported for nonfatal myocardial infarction[17,25] and corroborate those previously reported in a population-based, retrospective case–control study of victims of cardiac arrest.[11]

The effect of vigorous exertion on the sympathetic nervous system, plaque vulnerability, or both, could account for the findings. Acute bouts of exercise activate the sympathetic nervous system and decrease vagal activity, leading to an acute increase in susceptibility to ventricular fibrillation.[26] However, habitual vigorous exertion increases basal vagal tone, resulting in increased cardiac electrical stability and in protection against ventricular fibrillation.[27] In addition, sympathetic surges associated with acute exertion may promote plaque rupture,[10,28] and habitual vigorous exercise could modify this risk through favorable effects on lipids or by decreasing the hemodynamic stress at a given workload.

Our finding that there was no relation between the frequency of vigorous exercise as reported by the men at base line and the overall risk of sudden death appears to be at odds with the findings of numerous studies in which regular exercise was associated with reductions in the long-term risk of cardiac events.[4-6,29-32] However, few studies have examined sudden death specifically and rigorously, and the results of prospective studies have been conflicting. The Framingham Study found no relation between physical activity and sudden death during 20 years of follow-up.[33,34] In contrast, the British Regional Heart Study[35] and the Multiple Risk Factor Intervention Trial[6] found significant reductions in the risk of sudden death associated with both moderate and vigorous exercise.

Several factors may explain why we found no association between habitual exercise and the subsequent risk of sudden death. First, we had no information about moderate levels of activity, in which the men in our sedentary category could have been participating regularly. Moderate physical activity is associated with a markedly reduced risk of coronary events[32,36] and cardiac arrest,[37] and therefore it might also protect against sudden death. Second, activity levels may have changed over the course of the study, and misclassification of the exposure could have contributed to the null result. Finally, the effect of vigorous exercise on the risk of sudden death may actually be different from its effect on other cardiovascular end points, such as nonsudden death (Table 5).

Our study has several limitations. First, the measure of physical activity that we used is limited in comparison with more objective measures of physical fit-

ness, which have been shown to correlate with rates of cardiac events.[38] Second, the base-line data on the frequency of vigorous exertion were not updated during the study. Since levels of physical activity tend to vary over time,[39] there is likely to have been misclassification in our assessment of each person's level of habitual exercise; if such errors were random, this factor would tend to bias our results toward a null finding. However, if participation in vigorous exercise either increased or decreased over time, then our estimates of the relative risk during exertion might have been biased toward a positive or negative association, respectively. In addition, we lacked information on the duration of vigorous exertion. For both of these reasons, the magnitude of the relative risk associated with an acute episode of vigorous exertion should be viewed as an estimate.

Third, the rarity of exertion-related sudden death limits the statistical power of the study and tends to produce unstable estimates of risk. However, although the number is still quite small, the 23 sudden deaths that were associated with vigorous exertion in this study make up one of the largest series to date. Finally, our study and the earlier retrospective study[11] included only men, and therefore these data may not apply to women.

In summary, prospective data on U.S. male physicians suggest that bouts of vigorous exertion are associated with a transient increase in the risk of sudden death and that habitual vigorous exercise diminishes this risk. The absolute magnitude of the increase in risk associated with vigorous exertion is extremely small, and the overall risk of sudden death was not increased in association with increasing frequency of vigorous exercise. Therefore, these data should not discourage participation in an exercise program. The benefits of a physically active lifestyle in terms of multiple health outcomes, including the frequency of all cardiovascular events, clearly outweigh the small risks described above. However, further research directed at the mechanisms underlying sudden death during vigorous exertion may lead to innovative strategies to prevent this rare but devastating event.

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