Risk Factors for Syncope in a Community-Based Sample (The Framingham Heart Study)

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The epidemiology of syncope has not been well described. Prior studies have examined risk factors for syncope in hospital-based or other acute or long-term care settings. To determine risk factors for syncope in a community-based sample, we performed a nested case-control study. We examined reports of syncope in Framingham Heart Study participants who underwent routine clinic visits from 1971 to 1990. For each syncope case (n = 543) 2 controls were matched for age, sex, and examination period. Mean age of subjects was 67 years (range 25 to 95); 59% were women. History of stroke or transient ischemic attack, history of myocardial infarction, high blood pressure, use of antihypertensive medication, use of other cardiac medication, smoking, alcohol intake, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, atrial fibrillation, PR interval prolongation, interventricular block, and diabetes or elevated glucose level were examined as potential predictors. Using conditional logistic regression analysis, the predictors of syncope included a history of stroke or transient ischemic attack (odds ratio [OR] 2.56, 95% confidence interval [CI] 1.62 to 4.04), use of cardiac medication (OR 1.67, 95% CI 1.21 to 2.30), and high blood pressure (OR 1.46, 95% CI 1.14 to 1.88). Lower body mass index was marginally associated with syncope (OR per 4 kg/m^2 decrement 1.10, 95% CI 0.99 to 1.22), as were increased alcohol intake (OR per 5 oz/week 1.11, 95% CI 0.99 to 1.26), and diabetes or an elevated glucose level (OR 1.29, 95% CI 0.96 to 1.75). To our knowledge, this study represents the first community-based study of risk factors for syncope. **©2000 by Excerpta Medica, Inc.**

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Syncope is an important condition, comprising a relatively common symptom leading to medical attention. The etiologies of syncope vary widely, ranging from benign vasovagal fainting to syncope due to serious arrhythmias. The epidemiology of syncope has not been well described.[1,2] High blood pressure, coronary artery disease, cerebral vascular disease, hypertrophic cardiomyopathies, arrhythmias, and other conditions have been considered risk factors for syncope.[3–9] Previous studies have examined risk factors for syncope in hospital or other health care settings.[10–12] Some studies have examined syncope in nursing home residents, emergency room patients, soldiers, or aviators.[13–16] A previous Framingham study examined the prevalence, morbidity, and mortality associated with isolated syncope, without examining risk factors.[17] To our knowledge, no study has examined risk factors for syncope in a general population sample. This investigation identifies risk factors for syncope in subjects from the Framingham Heart Study.

METHODS

Subjects: The original participants in the Framingham Heart Study were enrolled in 1948. At study inception, the cohort contained 5,209 men and women aged 28 to 62 years from Framingham, Massachusetts. Since then, subjects have undergone biennial examinations to assess factors predisposing these subjects to cardiovascular disease. Details of study design and selection criteria are described elsewhere.[18,19]

A second ongoing study, the Framingham Offspring Study, began in 1971, enrolling 5,124 offspring and spouses of offspring of the original study participants. After their initial evaluation, these individuals underwent repeat examinations at 8, 12, and 16 years thereafter. Details of the Framingham Offspring Study design and selection criteria have been previously described.[20]

At each visit to the Framingham Heart Study, both original participants and Offspring Study participants underwent extensive evaluations. History and physical examinations, blood pressures at rest, body weight and height measurements, and a standard 12-lead electrocardiogram were performed routinely.

Our study sample consisted of original Framingham Heart Study subjects who survived to attend ≥1 examinations (cycles 12 through 20; between June 1971 and June 1990) and Framingham Offspring

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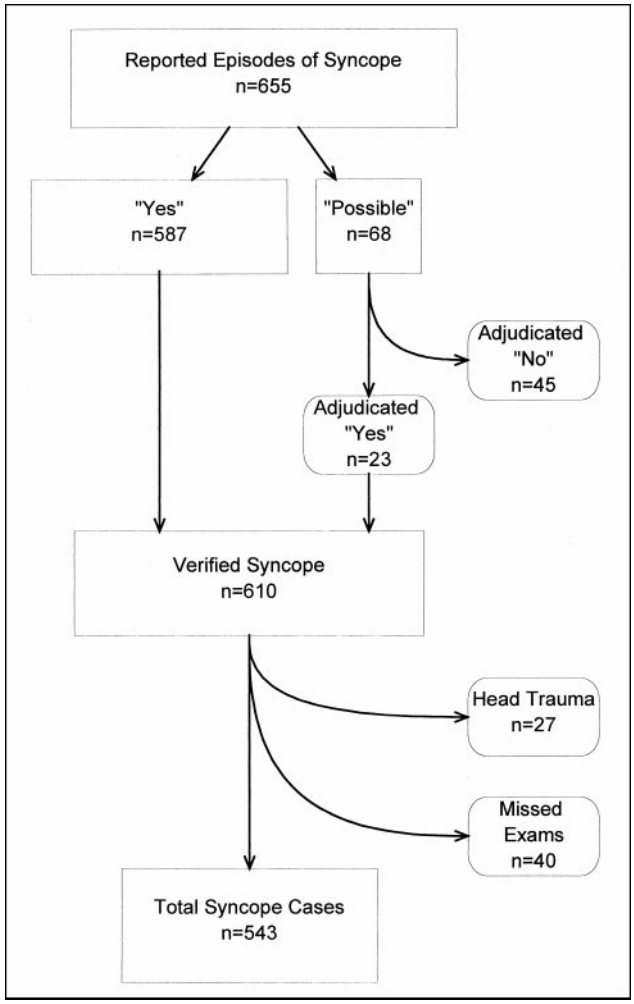

FIGURE 1. Syncope cases.

TABLE I Characteristics of Syncope Cases and Age- and Sex-matched Controls

Characteristic	Cases (n = 543)	Controls (n = 1,086)
Men	41%	41%
Age (mean yrs)	67 ± 15	67 ± 15
History of stroke or transient ischemic attack	9%	3%
History of myocardial infarction	7%	4%
Blood pressure variables:		
High blood pressure	62%	54%
High blood pressure treatment	36%	30%
Systolic blood pressure (mm Hg)	140 ± 24	137 ± 21
Diastolic blood pressure (mm Hg)	78 ± 12	78 ± 10
Cardiac medication	17%	10%
Smoker	29%	26%
Alcohol (oz/wk of ethanol)*	3.5 ± 6	3.0 ± 4.2
Body mass index (kg/m^2)	25.9 ± 4.4	26.2 ± 4.3
Electrocardiographic variables		
Heart rate (beats/min)	72 ± 14	71 ± 13
Heart rate <50 beats/min	3%	3%
Ventricular premature complexes	4%	4%
Atrial fibrillation	6%	3%
PR interval prolongation, PR ≥0.20 s	17%	14%
Interventricular block, QRS ≥0.12 s	7%	6%
Diabetes or elevated glucose level	19%	15%

*Available data for 487 cases and 955 controls.

Study subjects who survived to attend examinations 2 or 3 (October 1979 to September 1987). Each participant was questioned about loss of consciousness (including fainting, seizure, head trauma, stroke, and transient ischemic attack). The examining physician recorded whether a syncopal event had occurred (coded "yes"), had not occurred (coded "no"), or was possible by history (coded "possible"). The physician entered a description of the syncopal event and assigned an etiology when possible. Data regarding number of episodes, duration of loss of consciousness, witnesses, physician visits, hospitalization, and subsequent evaluations were recorded. All hospital and office records were obtained and reviewed when available.

The computer database contained 655 syncopal events (see Figure 1). Of these, 587 were recorded as "yes" and 68 recorded as "possible." The description of each syncopal episode was reviewed by an internist and/or a cardiologist (LC/MHC) for verification. All events recorded as "yes" were verified. The "possible" cases were adjudicated by a panel of 3 cardiologists and an internist (MHC/EB/DL/LC) and changed to "yes" only if there were subsequent confirming information (hospital or office records), which was not available at the time of the examination. Episodes that were definitively not syncope or remained "possible" after adjudication were excluded from the study (n = 45). A total of 610 episodes were verified as definite syncope.

For primary analyses, we excluded 27 cases of syncope caused by direct head trauma, because they represented a distinct subgroup likely to have different risk factors. To limit the recall period, we eliminated 40 reported episodes of syncope when the reporting subject had not been examined within 4 years of the episode. After these exclusions, a total of 543 syncopal episodes (cases) were included in the primary analysis. These represented 470 subjects, some of whom reported syncope at >1 examination cycle. Utilizing a nested-case control method, the 543 cases were matched for age, sex, and examination period with 1,086 controls (2 to 1 matching). Subjects previously reporting syncope were not utilized in the pool for selecting controls.

Subject characteristics: Characteristics of syncope cases and the age- and sex-matched controls are listed in Table I. The mean age was 67 years (range 25 to 95), and 59% were women. Alcohol was the only variable with missing data for more than a few individuals (data available for 487 of 543 cases, and available for 955 of 1,086 controls). High blood pres-

sure was present in 62% of cases and 54% of the controls.

Risk factors: The possible risk factors for syncope that we examined were age, sex, history of myocardial infarction (recognized or unrecognized), history of cerebrovascular disease (transient ischemic attacks, stroke, or intracranial hemorrhage), cardiac medication use, cigarette smoking (current at time of examination), alcohol use (assessed in ounces of ethanol per week), heart rate (beats per minute), ventricular premature beats (presence or absence on clinic electrocardiogram), history of atrial fibrillation, PR interval prolongation (PR interval ≥0.20 seconds), interventricular block (QRS ≥0.12 seconds), and body mass index (kilograms per square meter). Several blood pressure variables were considered, including systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), high blood pressure, and high blood pressure treatment. Diabetes or elevated glucose level was considered present in subjects on hypoglycemic treatment (oral agents or insulin use) or with a fasting blood glucose level ≥110 mg/dl in the Framingham Offspring Study cohort or a casual blood glucose level ≥120 mg/dl in the original Framingham Heart Study cohort.

High blood pressure was defined as a systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥95 mm Hg (based on the mean of 2 blood pressure measurements at the Framingham Heart Study examination) or use of antihypertensive treatment. These blood pressure definitions were used because they represented values of blood pressure likely to result in the initiation of treatment during most of the observation period for our study.

Criteria for other cardiac events have been reviewed.[21] All risk factors were determined using information gathered at the examination before the reported occurrence of syncope.

Statistical analysis: Conditional logistic regression models were used to accommodate matched sets of cases and controls.[22,23] First, separate analyses were run for individual variables to allow the largest possible sample size. Second, stepwise models were run using all potential risk factors, except alcohol intake, due to missing data. Finally, a model was run that included alcohol intake plus variables having a p value of <0.10 in the prior stepwise regression analysis.

Odds ratios (OR) and 95% confidence intervals (CI) are reported, describing the relative risk of syncope in relation to presence versus absence of binary variables, or for a specified increment of continuous variables. A p value of <0.05 is considered significant in each analysis. Statistical analyses were performed on a SUN Sparcstation 2 using SAS version 6.11 (SAS, Inc., Cary, North Carolina).

RESULTS

Risk factors: Univariate analyses (Table II) identified 4 "highly significant" (i.e., p value <0.01) and 2 "nominally significant" (i.e., p value <0.05) risk factors for syncope, namely, history of stroke or transient ischemic attack, high blood pressure, cardiac medication use, and measured systolic blood pressure, as well as high blood pressure treatment and diabetes or elevated glucose level. Alcohol intake, history of myocardial infarction, and presence of PR interval prolongation were of marginal significance.

TABLE II Univariate Analyses of Potential Risk Factors for Syncope

Risk Factor	OR (95% CI)	p Value
History of stroke or TIA (yes vs no)	2.96 (1.85–4.72)	0.0001
High blood pressure (yes vs no)	1.50 (1.17–1.94)	0.002
Cardiac medication (yes vs no)	1.70 (1.22–2.36)	0.002
Systolic blood pressure (per 22 mm Hg)	1.19 (1.06–1.34)	0.004
High blood pressure treatment (yes vs no)	1.37 (1.07–1.76)	0.015
Diabetes or elevated glucose level (yes vs no)	1.39 (1.02–1.88)	0.037
History of myocardial infarction (yes vs no)	1.54 (0.96–2.46)	0.071
Alcohol (per 5 oz/wk of ethanol)	1.12 (0.99–1.26)	0.072
PR interval prolongation (yes vs no)	1.29 (0.95–1.73)	0.099
Smoking (yes vs no)	1.21 (0.93–1.56)	0.15
Body mass index (per 4 kg/m^2)	0.93 (0.84–1.03)	0.18
Heart rate (per 13 beats/min)	1.07 (0.96–1.20)	0.20
Diastolic blood pressure (per 11 mm Hg)	1.08 (0.96–1.21)	0.22
Atrial fibrillation (yes vs no)	1.50 (0.78–2.89)	0.23
Heart rate (<50 vs ≥50)	1.27 (0.68–2.36)	0.45
Ventricular premature beats (yes vs no)	0.91 (0.51–1.61)	0.74
Interventricular block (yes vs no)	1.07 (0.67–1.69)	0.78

TIA = transient ischemic attack.

TABLE III Results of Multivariable Model of Risk Factors for Syncope

Risk Factor	OR (95% CI)	p Value
History of stroke or TIA (yes vs no)	2.56 (1.62, 4.04)	0.0001
Cardiac medication (yes vs no)	1.67 (1.21, 2.30)	0.002
High blood pressure (yes vs no)	1.46 (1.14, 1.88)	0.003

TIA = transient ischemic attack.

In stepwise multivariable analyses, 3 factors were significant simultaneously (history of stroke, high blood pressure, cardiac medication use) and 3 additional factors were of borderline significance (body mass index, diabetes or elevated glucose level, alcohol intake). After accounting for high blood pressure, several variables failed to meet the entry criterion of p <0.10 (systolic blood pressure, blood pressure treatment, history of myocardial infarction, and PR interval prolongation).

The multivariable model results are shown in Table III, including OR with 95% CI and p values. History of stroke was most strongly associated with syncope (OR 2.56, 95% CI 1.62 to 4.04, p <0.0001), followed by cardiac medication use (OR 1.67, 95% CI 1.21 to 2.30, p = 0.002), and high blood pressure (OR 1.46, 95% CI 1.14 to 1.18, p = 0.003). Results were suggestive for 3 additional variables when entered indi-

vidually into the multivariable model. Lower body mass index (OR 1.10 per 4 kg/m^2 decrement, p = 0.072), alcohol intake (OR 1.11 per 5 oz/week, p = 0.079), and diabetes or elevated glucose level (OR 1.29, p = 0.096) were marginally associated with increased risk for syncope.

Additional analyses: An additional analysis was performed including the 27 cases of head trauma-related syncope and their 54 controls. There were no material differences in the OR obtained. The risk of syncope for every 5 oz/week of alcohol remained similar (OR 1.13, 95% CI 1.00 to 1.27 [head trauma included] vs OR 1.14, 95% CI 1.00 to 1.30 [head trauma excluded]).

In an attempt to further examine why a lower body mass index was associated with a trend toward increased risk for syncope, we compared cancer prevalence in cases versus controls. We found similar cancer prevalence (a disease state that may be associated with lower body weight) in 9.9% of cases versus 8.6% of controls.

DISCUSSION

We recognize that syncope is a symptom attributable to different causes, and by itself is not a disease process. Although this study cannot definitely determine etiologies of syncope, several plausible risk factors did emerge from our analyses. Individuals with a history of stroke or transient ischemic attack were >2.5 times as likely to experience syncope. This may be due to recurrence of stroke or transient ischemic attack with loss of consciousness, neurologically mediated hypotension, autonomic insufficiency, or medication side effects.

Subjects using cardiac medications were at increased risk for syncope. The occurrence of syncope in this setting is probably multifactorial. Hypotension or bradycardia can be induced by the medications. The syncope also may be related to the underlying diseases, necessitating the use of the medications. Identification of the cause cannot be ascertained with certainty from this study.

High blood pressure was associated with increased risk for syncope. This was found in most of the subjects (>60%) who had syncope, and was consistent with the advanced age of our study sample (mean age 67 years). Nevertheless, when comparing the cases and controls, after adjustment for other variables, high blood pressure conferred a 39% increased risk for syncope.

Alcohol use was marginally associated with increased risk for syncope. For every 5 ounces of ethanol consumed per week, there was a small (11%) increased risk for syncope. Alcohol may be associated with syncope due to toxic brain effects, dehydration, hypoglycemia, withdrawal seizures, and other mechanisms.[24]

Leaner individuals had a marginally greater risk for syncope. Each decrement of 4 kg/m^2 in body mass index was associated with a 10% greater risk for syncope. The explanation for this finding is not clear. We postulated that individuals with comorbid diseases may be at higher risk for syncope and have leaner body masses due to other diseases. As noted previously, however, there was no significant increase in cancer diagnoses in the individuals having syncope compared with the controls.

Diabetes or elevated glucose level were also associated with marginally increased risk for syncope. There are no reported direct associations in the literature between these factors and syncope. Our definition of diabetes or elevated glucose level was such that individuals with severe diabetes as well as mild glucose intolerance would have been captured. Perhaps individuals with insulin use may have had episodes of hypoglycemia associated with loss of consciousness. The existence of autonomic neuropathy and orthostatic hypotension may contribute to syncope in diabetics.

Electrocardiographic markers were not predictive of syncope in the multivariable model. This may be due to a relatively small numbers of subjects with these markers in our sample. It is possible that some individuals with ventricular premature beats who suffer from malignant ventricular arrhythmia did not attend the next examination to report syncope—after suffering a lethal arrhythmia.

Study limitations and strengths: Recent position papers point out the limitations of the current literature on syncope.[25,26] The classification of syncope is varied.[27] The evaluation and diagnosis of syncope are also varied, and methods undoubtedly have changed over the time period during the study (so called "technology creep").[8,28,29] Syncope is a manifestation of several different disease processes. The risk factors we have identified can only show association—not a direct causal link.

The history of syncope was obtained at a routine clinic visit performed every 2 to 4 years. Underreporting of episodes of syncope may have occurred due to recall bias. Because individuals had to survive to the next examination to report a syncopal event, lethal cerebrovascular accident, myocardial infarction, or ventricular arrhythmia would not have allowed a subject to attend a follow-up examination to report syncope. Hence, we may have underestimated the risks associated with these conditions.

A fundamental advantage of this study was the routine ascertainment of risk factors regardless of the individual's syncope status. Risk factor data were obtained at the examination before the syncopal event; thus, these risk factors were not affected by the occurrence of the event. We have utilized the Framingham Heart Study database to collect a large, community-based sample that is largely free from referral and selection biases. The data were optimized by obtaining hospital and office medical records whenever possible to verify syncope and all clinical events. To our knowledge, no other study to date has been able to examine syncope in such a large, population-based cohort, permitting some generalizability of risk factors for syncope to the general population.

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