Epidemiology of reflex syncope

N. Colman
K. Nahm
K. S. Ganzeboom
W. K. Shen
J. B. Reitsma
M. Linzer
W. Wieling
H. Kaufmann

N. Colman · K. S. Ganzeboom ·
W. Wieling (✉)
Dept. of Internal Medicine, Room F4-221
Academic Medical Centre
P. O. Box 22700
1100 DE Amsterdam, The Netherlands
Tel.: +31-20/5665990
Fax: +31-20/6914904
E-Mail: w.wieling@amc.uva.nl

N. Colman
Dept. of Cardiology
Academic Medical Centre
Amsterdam, The Netherlands

K. Nahm · H. Kaufmann
Dept. of Neurology
Mount Sinai School of Medicine
New York (NY), USA

W. K. Shen
Division of Cardiovascular Diseases and
Internal Medicine
Mayo Clinic
Rochester (MN), USA

J. B. Reitsma
Dept. of Clinical Epidemiology and
Biostatistics
Academic Medical Centre
Amsterdam, The Netherlands

M. Linzer
Dept. of Medicine
University of Wisconsin
Madison (WI), USA

■ **Abstract** Cost-effective diagnostic approaches to reflex syncope require knowledge of its frequency and causes in different age groups. For this purpose we reviewed the available literature dealing with the epidemiology of reflex syncope.

The incidence pattern of reflex syncope in the general population and general practice is bimodal with peaks in teenagers and in the elderly. In the young almost all cases of transient loss of consciousness are due to reflex syncope. The life-time cumulative incidence in young females ($\cong 50\%$) is about twice as high as in males ($\cong 25\%$). In the elderly, cardiac causes, orthostatic and postprandial hypotension, and the effects of medications are common, whereas typical vasovagal syncope is less frequent. In emergency departments, cardiac causes and orthostatic hypotension are more frequent especially in elderly subjects. Reflex syncope, however, remains the most common cause of syncope, but all-cause mortality in subjects with reflex syncope is not higher than in the general population. This knowledge about the epidemiology of reflex syncope can serve as a benchmark to develop cost-effective diagnostic approaches.

■ **Key words** reflex syncope · epidemiology · incidence · prevalence · setting · prognosis

Introduction

Reflex syncope is a transient loss of consciousness caused by systemic arterial hypotension resulting from reflex vasodilatation or bradycardia or both. The condition is mediated by changes in afferent and efferent autonomic neural traffic. Reflex syncope includes vasovagal syncope, carotid sinus syncope and situational syncope (for details see manuscript about Definitions and Classification by van Dijk in this supplement).

Reflex syncope is extremely common. Almost everybody seems to have either experienced or witnessed an episode. However, few studies have addressed its frequency in the general population particularly in comparison to other causes of transient loss of consciousness.

Identifying reflex syncope and distinguishing it from other conditions may be difficult particularly when reviewing epidemiological data. Moreover, the definition of syncope frequently varies or may be lacking altogether, so that comparing data across studies is laborious and not always possible. Here we review published studies examining the epidemiology of syncope in the general population and in different health care settings.

We focus on the frequency and causes of reflex syncope at different ages.

General population studies

■ Definitions

There are two basic ways of describing the occurrence of disease in a population: incidence and prevalence [49]. Incidence is a rate, indicating how many new cases of a disease occurred in a given population during a specified time interval. Cumulative incidence is the number of persons in a population free of disease that acquire the condition in a certain time period (average risk to get the event) [49]. Prevalence is the proportion of people in a given population found to have the disease at a certain point in time (sometimes called "point prevalence"). When a disease is episodic, as reflex syncope, the prevalence does not reflect the total number of people who have ever had the disease up to that point in time. Lifetime prevalence or life-time cumulative incidence can be used to denote the proportion of individuals who had at least one episode of reflex syncope during their lives. In this review, we use life-time cumulative incidence measures where possible to express the frequency of occurrence of syncope.

■ Framingham studies

The first epidemiological study of syncope based on the Framingham cohort published in 1985 reports on a cohort of 5209 subjects (2336 men and 2873 women, mean age of 46, range 30–62 years at the start of the study) [52]. During 26 years of follow-up (from 1952 to 1978), 3 % of the men (71 of 2336) and 3.5 % of the women (101 of 2873) reported at least one episode of syncope. Of these, 79 % of the men (56 of 71) and 88 % of the women (89 of 101) had "isolated syncope" defined as "syncope in the absence of prior or concurrent neurological, coronary or other cardiovascular disease stigmata", suggesting that a high percentage of this "isolated syncope" was likely to have been reflex syncope.

The mean age of the first episode of isolated syncope was 52 years (range 15 to 78) for men and 50 years for women (range 13 to 87). Only 2 % of the men and 11 % of the women experienced their first episode before the age of 20. Only eight subjects had their first episode of isolated syncope as "a child" with a mean age of 15 years for first episode. Seven out of the eight subjects were women. Thirty per cent of men (16 of 56) and 27 % of women (24 of 79) had more than one episode of isolated syncope.

The cumulative incidence of syncope by age was similar in men and women until the age of 75 years. After the age of 75 the incidence of isolated syncope was significantly greater in men than in women: 56 per 1000 person exams in men versus 36 per 1000 person exams in women. Most importantly, isolated syncope was not associated with increased mortality of any cause, nor with an increase in morbidity from cardiovascular disorders such as stroke and myocardial infarction.

The cumulative incidence of isolated syncope of 2–3 % during 26 years of follow-up is low compared to data from younger populations (see below). The most likely explanation is that the Framingham Heart Study focused on the incidence of syncope during follow-up although this is not completely clear from the study. It seems that subjects with incident cases of isolated syncope reported after entry into the study were included. Subjects who did not faint after entering the study, but had experienced syncope before the study, were probably not counted. Moreover, the population analyzed consisted of subjects 35 years or older while most episodes of reflex syncope occur in younger subjects [25]. An additional factor may be the procedure of data collecting; a syncope specific questionnaire might reveal more information than a single question on syncope in a more extensive list [26, 27].

In an offspring cohort of the Framingham study (3491 subjects, 1845 women, mean age 55 years, range 26 to 84 years), the cumulative incidence of syncope (not further defined) during a 4 year period (from 1991 to 1995) was 3 % and thereby much higher than in the first report. An obvious difference is the much broader age range in the latter report [23].

In the latest report of the Framingham Heart Study and the Framingham Offspring Study, syncope was defined differently from the first report, and included subjects with seizures, strokes and transient ischemic attacks (together 9 % of all syncopal episodes) [53]. Over a mean period of 17 years follow-up, 10 % of 7814 participants (mean age 51 years, range 20 to 96) reported at least one episode of syncope. The incidence rate of a first report of syncope was 6.2 per 1000 person-years.

There was a sharp rise in incidence after the age of 70 years, from 5.7 events per 1000 person-years in men aged 60–69, to 11.1 in men aged 70–79 (Fig. 1). Assuming a constant incidence rate over time, the authors calculated a crude 10-year cumulative incidence of syncope of 6 %.

Reflex syncope (labeled as vasovagal in this report) was the most common identifiable cause of syncope responsible for 21.2 % of all episodes, followed by cardiac syncope with 9.5 % and orthostatic hypotension with 9.4 %. Overall, 44 % of participants with a syncopal episode reported that they did not see a doctor or visit a hospital for evaluation.

In 37 % of all episodes history, physical exam and ECG were not indicative of a specific cause, and the patient was classified as having unexplained syncope. Most
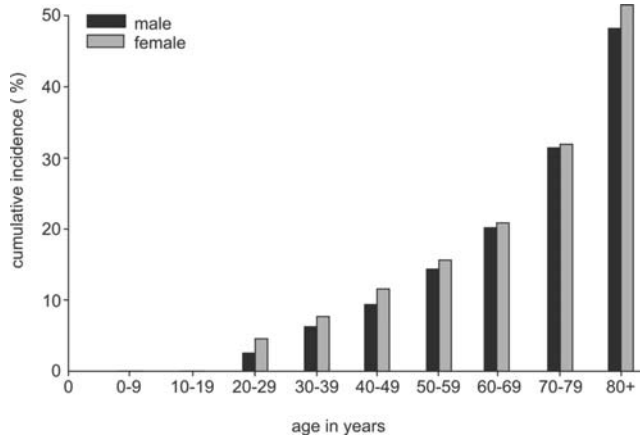
Fig. 1 Cumulative incidence of syncope in the Framingham study. All participants in this study were older than 20 years and episodes of syncope were followed prospectively (revised after Soteriades et al.)

Fig. 2 Cumulative incidence of syncope according to age in medical students in the Academic Medical Center in Amsterdam: 253 female (118 (47 %) with at least one episode of syncope) and 124 male (30 (24 %) with at least one episode of syncope) (revised after Ganzeboom et al.)

Fig. 3 Histogram of the syncope study by Ganzeboom et al. (Ganzeboom et al. unpublished)

investigators agree that at least 40 % of patients with "unexplained" syncope have reflex (vasovagal) syncope [30, 31]. Patients diagnosed with vasovagal syncope had the highest survival equal to those who had not suffered syncope.

■ Syncope in the young

Studies in young populations show a strikingly high incidence of syncope. Ganzeboom et al. found that over one third of medical students (39 % of 394 students, median age 21 years) reported having experienced at least one syncopal episode in their life [25]. The majority of the syncope-triggers identified by the students involved stresses or conditions that affect orthostatic blood pressure regulation. Reflex syncope was therefore a very likely cause of the symptoms in these young subjects (see manuscript by Colman et al. about History taking in this supplement). The lifetime cumulative incidence of syncope in women was almost twice that of men, 47 % versus 24 % (Fig. 2). The median age at the first episode of reflex syncope was 15 years (Fig. 3). A peak around 15 years with predominance in females was also observed in the Framingham cohort [52]. A recent study suggests that this gender difference is due to a decreased cardiac filling in women during orthostatic challenges [24].

Reflex syncope was rare before age 10, but there was a steady increase in first occurrence between ages 10 and 20. After the initial episode, 64 % of females and 53 % of males experienced a recurrent event. Although the study of Ganzeboom et al. involved a specific small population, the cumulative life-time incidence is in agreement with data of older studies, involving similarly young, but almost exclusively male populations [34, 45, 58]. The reported lifetime cumulative incidence in these studies
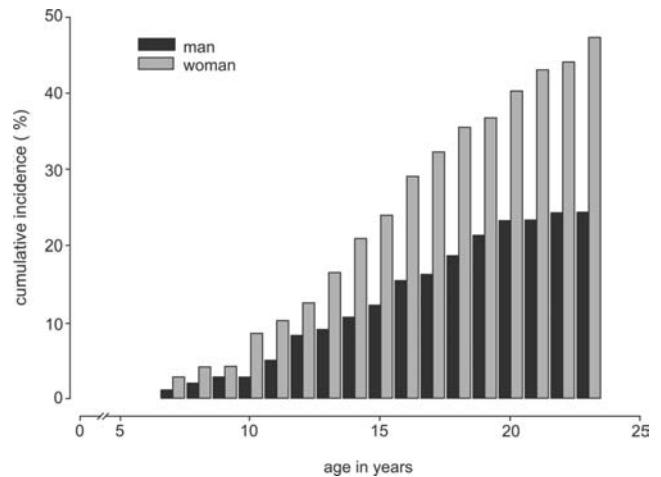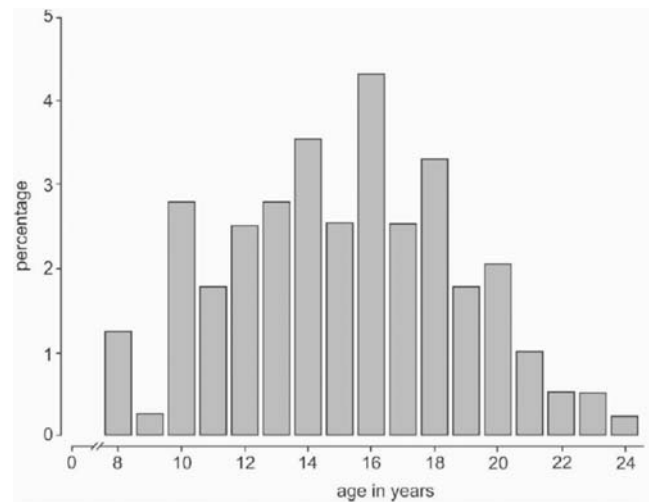
ranged from 17 % to 34 %. Table 1 summarizes the key features of these studies.

The lifetime cumulative incidence of reflex syncope in young subjects (< 25 years) of 18–47 % is much higher than that of epilepsy (0.5 %) or cardiac syncope [45]. Long QT syndrome has an estimated prevalence of 1 gene carrier in 10,000 persons and the rate of sudden deaths from cardiac causes in subjects younger than 35 is reported between 1.3 and 8.5 per 100,000 patient-years [35, 56]. No data are available about the incidence of psychiatric causes of transient pseudo loss of consciousness in young subjects. Data from young subjects coming to medical attention in a general medical setting because of transient loss of consciousness suggest that the prevalence of psychiatric causes is likely to be low [18].

Table 1 General population: relatively small selected young populations

Study	Population	Age in years (mean, range)	No. of males/ females	Persons with syncope (%)
Lamb et al. Study A	USAF	33 (24–45)	1033/0	20%
Lamb et al. Study B	USAF	19 (17–22)	402/0	24%
Lamb et al. Study C	USAF	34 (21–47)	225/0	18%
Lamb et al. Study D	USAF	32 (20–46)	320/0	20%
Williams et al.	chemistry students	Average 21 (17–44)	776/95	34%
Murdoch et al.	military recruits	20 (17–26)	389/0	25%
Ganzeboom et al.	medical students	21 opzoeken SPSS	124/253	47% (females), 24% (males)

USAF United States Air Force

The differences in the incidence of reflex syncope between gender, ethnic, and perhaps cultural groups is highlighted by a study among student blood donors showing that the incidence of syncope was higher in Caucasian (8% of 1076) than in Afro-Caribbean students (1% of 225) [46]. First-time donors were at higher risk of syncope as were female students. An interesting finding was that when students weighing less than 59 kg were excluded from the analysis, the difference in frequency of syncope between females and males disappeared.

■ Syncope in the elderly

Surveys in the elderly often report much lower lifetime cumulative figures than the 39% reported by Ganzeboom et al. For instance, Chen et al. reported a lifetime cumulative incidence of 19% in 1925 subjects aged 45 years or older (905 males) [13]. Recall bias may explain this. When a survey is done at an older age, subjects have to delve deeper in their memories [6]. A study from the National Center for Health Statistics in the USA showed that approximately 1 year after discharge 42% of the subjects failed to report their hospital admission on questioning [48]. A true increase in incidence over time is another possibility.

Another source of data from elderly people are studies performed in nursing homes. In the study of Lipsitz et al. 23% of 711 subjects (54% female) with a mean age of 87 years (range 67–107 years) reported at least one syncopal episode in the past 10 years, and 7% (47 patients) in the previous year [37].

During 2 years of follow-up, 67 patients developed syncope, 44 in the first year. This corresponds to an annual incidence of 6% (compared to almost 2% annual incidence of syncope for those older than 80 in the latest report from the Framingham study) for subjects living in the community. A recurrence rate of 30% was found during the 2 year follow-up. A high incidence of syncope was also found in a study involving older nursing home residents: a total of 72 episodes of syncope were counted over 29 months in 499 persons [5]. The frailer nature of institutionalized populations and the more accurate reporting in institutional settings may explain the considerably higher incidence of syncope among institutionalized elderly populations [50].

In Lipsitz's study fourteen patients (21%) had cardiac syncope and thirty-two patients (48%) non-cardiac syncope. Frequent causes of noncardiac syncope included situational syncope (n = 7), postural hypotension (n = 4) and drug-induced hypotension (n = 8). Typical vasovagal syncope was relatively rare (n = 3).

There was no significant difference in mortality rate between patients with cardiac, non-cardiac, or syncope of unknown origin in this cohort. The lack of significant difference may be attributable to the small sample size or to the advanced age and high mortality rate of patients in the study, irrespective of the underlying illness [32].

Other reports also document that typical vasovagal syncope is less common in older subjects. It is not unusual that an older patient experiences an atypical episode of vasovagal syncope after the patient has suffered from typical vasovagal syncope at a younger age [14, 21, 54]. Cardiac causes of syncope, orthostatic and postprandial hypotension are more frequent in the elderly [7, 29, 32, 44, 59]. This can be attributed to diminished efficiency of cardiovascular regulatory systems, the effects of medications impairing orthostatic blood pressure control and increased prevalence of organic disease (structural heart disease, cardiac arrhythmias, carotid-sinus syndrome) [10, 43]. In the elderly, multiple potential causes of syncope are often present and the medical history may be less reliable than in the young,

for example, syncope may be reported as a fall [8, 12, 32, 33, 40].

In summary, almost all episodes of transient loss of consciousness in the young are due to reflex syncope. A peak in incidence is observed around 15 years of age and the lifetime cumulative incidence in young adult females is about twice as high as in males. Recurrences occur in more than half of the subjects. In the elderly, cardiac causes, situational syncope, orthostatic and postprandial hypotension and the effects of medications are common, whereas typical vasovagal syncope is less frequent.

Studies in health care settings

■ Syncope in general practice

A large database with reasons for encounters of general practitioners in the Netherlands revealed that 2 to 9 per 1000 encounters are due to blackouts or fainting [1]. Based on their definition reflex syncope is the most likely underlying condition [38, 47, 57]. The age distribution of these patients visiting a general practitioner shows a peak in females around 15 years of age and a second peak in older patients (Fig. 4), a similar pattern to that observed in the general population [52, 53]. A population-based study on the incidence of syncope in children and adolescents that sought medical attention in the USA showed a similar peak in 15–19 year old females [18].

The frequency of epilepsy in general practice in The Netherlands is about 10 times lower than for reflex syncope (0.2–0.8 per 1000 patients/year) [22, 25]. Cardiac syncope in general practice in The Netherlands is rare (Wieling unpublished).
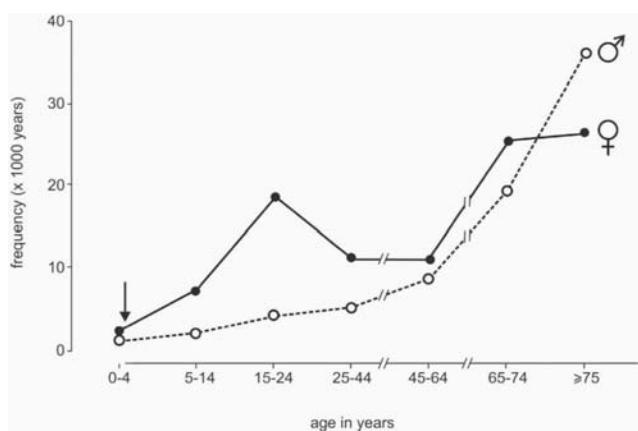

Fig. 4 Frequency of the complaint fainting as reason for encounter in general practice in the Netherlands. Data are obtained from the general practitioners' transition project. It concerns an analysis of 93,297 patient-years. The arrow around 1 year is to indicate that a small peak occurs between 6–18 months (breath-holding spells) (Wieling et al. 2003, with permission)

General practitioners in The Netherlands refer only 10% of the patients with reflex syncope to a specialist for further evaluation or reassurance. In most cases referrals are made to a neurologist or cardiologist [57]. The reasons for referral are atypical fainting, suspicion of a cardiac cause, patient preference and recurrent syncope (Wieling personal communication).

In summary, reflex syncope is a common reason for encounter in general practice. The bimodal age pattern of the incidence of syncope observed in the general population (Figs. 1–3) is mirrored in general practice (Figs. 4 and 5). The frequency of syncope-related encounters is higher in teenagers and adolescents, in particular females, and in the elderly.
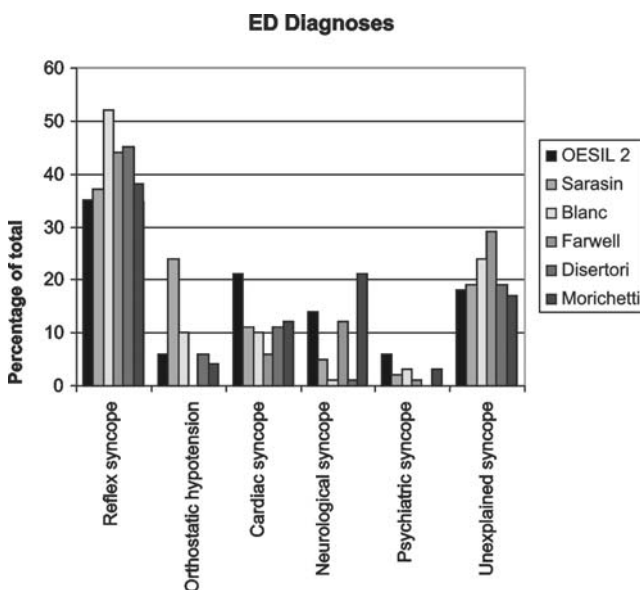
■ Syncope in emergency departments

Recent studies from Europe report that 0.9 to 1.2% of the visits to community-based emergency departments are due to syncope [3, 9, 17, 42, 51]. The remarkably consistent fraction of about 1% in emergency departments in Europe is lower than the 3% from an older study by Day et al. that is often quoted for the frequency of syncope in emergency departments in the USA [11, 15, 20]. However, the frequency of 3% in the study by Day et al. is based on 786 out of 25,000 patients visiting an emergency department over a 1-year period because of transient loss of conscience. The causes included syncope but also seizures, head trauma and cerebrovascular accidents [15]. Only 198 of these 25,000 patients (0.8%) were thought to have syncope and included in the actual analysis. This figure is almost identical to the recent reports from Europe. In one study from Italy a much higher (3.4%) frequency of TLOC is reported [11]. The explanation is unclear. Morichetti reported a large range in presentations with syncope from 0.8–2.4% in several retrospective studies from six Italian hospitals. They suggested that the organization of the emergency department, the criteria used and the available tests at an emergency department might influence these figures [42].

The breakdown of the different causes in the recent European studies reveals that reflex syncope is the most common cause and found in 30–40% of the patients, while orthostatic hypotension occurs on average in 6–24%, cardiac syncope in 10–20% and psychogenic syncope in 1–5% (Fig. 5). In about 20% of the patients syncope remains unexplained [4, 9, 42, 51].

Cardiac causes of syncope and orthostatic hypotension were more common in elderly patients. This age difference in causes of syncope is in accordance with an older study that prospectively evaluated 210 elderly and 190 young patients accrued from an emergency room, inpatient and ambulatory service [29]. It might explain why elderly seem to be admitted more to the hospital af-

Table 2 Emergency departments; recent European studies

Study group	Department	Pts with TLOC/ total ED pts (%)	Age (years)	Male (%)	Protocol	Patients admitted to hospital	Unexplained syncope
Ammirati 1999 OESIL	ED	781/85,102 (0.9%)	55 ± 23	48	Usual care/ observational	450 (58%)	54%
Ammirati 2000 OESIL 2	ED	195/unknown	62.5 ± 22.3 (13–95)	44	Diagnostic algorithm	132 (68%)	18%
Blanc 2002	ED	454/37,475 (1.2%)	57 ± 23	43	Usual practice	285 (63%)	24%
Casini-Raggi 2002	ED	1290/38,330 (3.4%)	72 (15–99)	47	Retrospective	443 (34%)	Not registered
Disertori 2003	ED	996/105,173 (1.0%) 980 enrolled	60 ± 23	47	Usual practice	454 (46%)	19%
Farwell 2002 EaSyAS	ED + inpatient database	660	64 ± 23	49	EaSyAS protocol	Not registered	29%
Morichetti 1998	ED	684/52,387 (1.3%)	58 (15–93)	53	Retrospective	530 (76%)	17%
Sarasin 2001	ED	788 (1.1%) 650 enrolled	60 ± 23 (18–93)	48	Standardized evaluation	Not registered	14%

Fig. 5 Frequency of causes of syncope in European emergency departments

ter presentation at the emergency department. Farwell found a significant difference in age between admitted (66 ± 19 years) and discharged patients (43 ± 23 years) [19]. In one of the other ED studies 59% of the patients > 64 years were admitted versus 22% in the group of 45–64 years and only 6.6% in the < 15–44 years group [11].

In summary, in emergency departments there is a shift towards more serious cardiac causes and, in older subjects, towards more orthostatic hypotension compared to the general population. Reflex syncope, however, remains the most prevalent cause of syncope.

■ Specialized syncope units

There are three types of syncope units depending on the specialists who manage the unit. One can differentiate cardiac syncope units, syncope units specialized in elderly patients and autonomic specialized syncope units. Mostly patients who have a negative neurological and cardiological evaluation will be referred to one of the syncope units. Most studies come from cardiac syncope units.

Alboni et al. studied 341 adult patients (mean age 61 years) referred in a 6 month period from inpatient, outpatient and emergency services, to three specialized cardiac syncope units [2]. After extensive evaluations, including echocardiography, Holter monitoring, tilt-table testing, carotid sinus massage and electrophysiological study, 23% of patients were diagnosed with cardiac syncope, 54% with reflex syncope and only 2% with orthostatic hypotension. Patients with cardiac syncope were older (72 versus 59 years) and more often male (62% versus 47%). In a later study about presentation of syncope in cardiac syncope units in Italy a similar pattern was documented. A marked age difference was found with more cardiac causes in the elderly (34%) compared to the young (12%) [16].

Patients presenting with syncope of unknown etiology or recurrent symptoms refractory to therapy are often referred to cardiac and electrophysiology specialists. In a selected patient population referred to a cardiac clinic, Chen and colleagues reported age-dependent causes of syncope [12]. Among 1180 consecutive patients referred for evaluation of syncope for over three years, 571 patients were less than 65 years of age and 619 patients were older than or equal to 65 years. Age-dependent causes of syncope are shown in Fig. 6. It is interesting to note (but not unexpected), in this referred
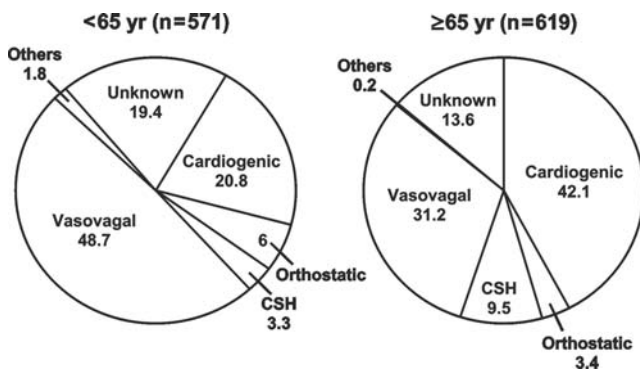
Fig. 6 Age-dependent causes of syncope in a selected patient population referred to cardiac and electrophysiologic evaluation. Data are modified from Chen et al. (reference 12). Discussion is provided in the text

population at a tertiary care center, cardiac causes of syncope were prevalent in the entire study cohort and more frequent in the older than in the younger patients. Vasovagal syncope was the most common cause of syncope in the younger patients while it was not uncommon in the older patients. Carotid sinus syndrome was observed in nearly 10 % of the older population. The low prevalence of orthostatic causes in the elderly could be explained by the nature of patient selection. Most patients with orthostatic intolerance or autonomic dysregulation are usually referred to neurology and autonomic neurology clinics. Despite undergoing the clinically recommended evaluation, 19.4 % and 13.6 % of younger and older patients', respectively, causes of syncope remained undiagnosed. Observations from this study highlighted the importance of recognizing the impact of patient selection on clinical outcomes, while it confirmed that vasovagal syncope remains the most common cause of syncope in the younger patient population.

Cardiac causes become even more prominent when looking at data from specialized cardiac syncope units. Several studies reported that 45 to 80 % of unexplained syncope in this setting could be assigned to a cardiac cause [28, 36, 41, 55].

In syncope clinics specialized in investigating elderly subjects with syncope there is a high frequency of carotid sinus syndrome (17–45 %) [39, 40, 59] while in a tertiary referral center specialized in autonomic disorders an exceptionally high frequency of chronic autonomic failure (4.8 %) was diagnosed [39].

In summary, the causes of syncope in syncope units are highly influenced by the referral process and the particular expertise and the amount and type of testing of the unit.

Conclusions

Syncope is common in the general population. Its age distribution is bimodal with a peak in teenagers and adolescents, and in the elderly (Fig. 3). Several studies have been performed in young subjects, but the incidence of syncope in the elderly in the general population has been studied less. The life-time cumulative incidence of syncope is much higher in young females than males. Caucasians seem to be more affected than blacks. The reasons for these differences are unknown [25, 53, 57].

Reflex syncope is much more frequent than all other causes of syncope especially in the young. Cardiac syncope, orthostatic and postprandial hypotension and the effects of medications are common causes for syncope in the elderly. Reflex syncope is benign. No increased mortality from any cause has been found in subjects that had suffered reflex syncope.

In health care settings reflex syncope remains the most frequent cause of syncope in young subjects. In the elderly cardiac causes become increasingly important in particular in specialized cardiac units. Information about the epidemiology of syncope in combination with information about its triggers can serve as a benchmark to develop cost-effective diagnostic approaches in the evaluation of patients with syncope in different clinical settings.

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