the pulmonary veins\cite{11} is quite compatible with any vagal or adrenergic profile. Ectopic foci in fact form the arrhythmia trigger, the behaviour of which may be sensitive preferentially to vagal or to adrenergic influences. It is our experience that vagal arrhythmias can be cured by a focal ablation. These foci, however, are more often sensitive to adrenergic than to vagal stimulation.

Waxman et al.\cite{12} made some interesting observations some years ago on the mechanism of the occurrence of AF as a consequence of paroxysmal reciprocating tachycardias. They nicely demonstrated that AF was the result of strong adrenergic stimulation evidenced by the rise in blood pressure and the acceleration of the rate of the tachycardia. Both reflected the sympathetic reaction to the initial fall in blood pressure resulting from sudden tachycardia onset. This type of AF can be efficaciously prevented by beta-blockers, which can, however, have a counter-productive corollary: by preventing blood pressure peak and its vagal consequences via the baroreflex, beta-blockers also prevent the vagal mechanism which allows the reciprocating tachycardia to block the atrioventricular node. No treatment is perfect.

Sport in general, and strong exercise in particular, are dangerous from the cardiologist's point of view, although their reservations about excessive sporting activities may not be popular and are frequently ignored. Usually the danger comes from ventricular tachyarrhythmias in the context of cardiac disease, such as cardiomyopathy, right ventricular dysplasia or the long QT syndrome, in apparently healthy young people. Compared to such severe accidents, AF looks benign but should not be neglected: its recurrence may be extremely disabling, but it is now well established that the risk of ischaemic cerebral accidents is always present.

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Tilt-induced asystole: a useful prognostic marker or clinically irrelevant finding?

See page 483, doi:10.1053/euhj.2001.2900 for the article to which this Editorial refers

Vasovagal syncope (also called neurocardiogenic syncope) is a common clinical problem. It may occur at any age and accounts for more than one third of all causes of syncope\cite{1}. The diagnosis of vasovagal syncope is relatively easy in the presence of characteristic triggering factors (fear, severe pain, medical instrumentation, tiredness, prolonged standing, crowded places, warm environment) and prodromal symptoms.

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(diaphoresis, nausea, abdominal discomfort, yawning)\[2\]. When the aetiology of loss of consciousness remains uncertain after the initial (history, physical examination, electrocardiogram) and subsequent evaluation (carotid sinus massage, Holter monitoring, neurological assessment and, if indicated, electrophysiologic study and other examinations) head-up tilt testing alone or with drug challenge enables a vasovagal origin of syncope to be detected in a high proportion of patients with a sufficient degree of specificity\[3,4\]. A shortened oral nitroglycerin test and low-dose isoproterenol test are the most accurate head-up tilt protocols for this purpose (positivity rate \(\sim 60\%\) in patients with unexplained syncope and \(<10\%\) in control subjects)\[5–10\] and their use has been recently recommended by the Task Force on Syncope of the European Society of Cardiology\[2\].

Regarding prognosis, vasovagal syncope is generally considered a benign condition that does not represent a threat to life or to significantly impair quality of life. Although theoretically possible\[11\], sudden death is surely exceptional as a direct consequence of a vasovagal reaction\[2\]; moreover, syncopal spells are likely to be an isolated or sporadic phenomenon; finally, when loss of consciousness occurs, the frequent presence of typical precipitating events and premonitory symptoms (in about 70\% of cases)\[11\] allows the patient to assume a supine position or other evasive action and avoid physical injury. For these reasons, no specific treatment is indicated in patients with vasovagal syncope and recurrences are easily prevented by patient reassurance, education and counselling\[12,13\]. In a limited number of subjects, however, especially elderly people, syncopal episodes are much more frequent and often occur in the absence of predictable circumstances and warning symptoms. These episodes may be accompanied by serious injury (in 9\% of cases)\[14\] and sometimes are so prolonged as to require cardiopulmonary resuscitation\[15–17\]; this is the so-called atypical or malignant vasovagal syndrome\[18,19\]. In these cases, as well as in patients with high occupational risk (pilots, truck drivers, commercial painters, roofers), specific treatment (drugs, tilt training or pacemaker) is generally recommended\[12,13\], although the real efficacy of the available therapies has not been confirmed yet (with a few exceptions) by prospective, randomized, placebo-controlled trials\[20\].

The pathophysiological mechanism underlying spontaneous and tilt-induced vasovagal syncope is still not completely known\[21\]. According to the most popular hypothesis, the abnormal reflex is triggered, in predisposed patients, by the activation of the ventricular mechanoreceptors caused by the vigorous contraction of the heart around a relatively empty cavity as a consequence of the increase in sympathetic tone and the reduction in venous return that occurs in upright posture (especially with passive orthostatism, as during head-up tilt testing)\[22,23\]. There are two main components of vasovagal reaction, vasodepression and cardioinhibition. The former is produced by the sudden withdrawal of the adrenergic drive that leads to generalized arterial vasodilatation; the latter is due to the reflex enhancement of vagal tone responsible for bradycardia and/or asystole. Whereas profound vasodilatation is constantly observed before and at the time of syncope development, bradycardia does not occur systematically and sometimes represent only a slight and secondary phenomenon\[24,25\]. Occasionally, however, very prolonged ventricular asystole lasting for several seconds has been described during vasovagal syncope\[15,18\]. We do not know the exact clinical and prognostic significance of this finding. Is it expression of a more severe disease? May it cause sudden death in some patients under particular circumstances? Does its documentation necessarily require pacemaker implantation?

In this issue, Barón-Esquivias and colleagues\[26\] try to answer these questions. These authors retrospectively reviewed the results of head-up tilt testing performed in their institution in 1322 patients with syncope of unknown origin during a ten-year period. An abnormal response was observed in 330 patients (25\%). Fifty-eight of these patients (17.5\%) showed a ventricular asystole \(\geq 3\ s\) (range, 3–90) at the time symptoms developed. An asystolic pause occurred more frequently during high-dose isoproterenol test than during passive tilting test (three out of 198 cases, 6.5\% vs 45 out of 1124 cases, 4\%, \(P<0.04\)). A dual-chamber pacemaker was implanted in seven patients with asystolic response, whereas 12 patients were treated with drugs (eight with metoprolol, three with etilefrine and one with paroxetine) and 39 did not receive any specific therapy. During the follow-up, the rate of syncopal recurrences was not significantly different in the 58 patients with ventricular asystole and in the 118 tilt-positive controls without asystole (20.6\% during a mean follow-up of 3.4 years vs 27\% during a mean follow-up of 4.3 years, \(P=ns\)). No patient of any group died suddenly or from cardiac cause during the follow-up. The type of treatment did not influence the clinical outcome. In particular, two of the seven (29\%) patients with pacemakers had syncopal recurrences compared to four of the nine (44\%) patients receiving drugs and six of the 39 (15\%) patients who were not treated. The authors conclude that (1) the incidence of ventricular asystole during head-up tilt testing is correlated to the type of tilt protocol used; (2) a tilt-induced asystole does not imply a poor prognosis in terms of syncopal
recurrences or sudden death; and (3) implantation of pacemaker or drug treatment in patients with asystolic response is not associated with a lower syncopal rate during the follow-up. The paper of Barón-Esquivias and colleagues[26] is a significant step towards a better understanding of the real clinical and therapeutic relevance of the cardioinhibitory component of vasovagal reaction. Although the methodology of the study can be criticised in some aspects (retrospective analysis, different types of head-up tilt protocol used, non-uniform treatment, selection criteria of control group) the results and conclusions are sufficiently credible and have important practical implications.

Up to now only a few papers have examined the topic of a tilt-induced asystole[15–18,27–32]. On the whole, 714 patients with a positive response to head-up tilt testing have been studied. Of these, 108 showed a ventricular asystole (>3–5 s) mainly due to sinus arrest and only rarely due to atrioventricular block. The mean incidence of a tilt-induced asystole observed in these specific studies (15%, with a range from 4% to 33%) is similar to that extrapolated from other more general studies on tilt-table test (18%, 141 patients out of 794; range, 6%–48%)[5,6,8,10,25,33–45]. The incidence was higher during nitrate provocation test (21%, 103 out of 489 patients)[6,10,40,43–45] than during passive head-up tilt test (14%, 78 out of 568 patients)[25,27–29,33–35,39] and isoproterenol test (13%, 34 out of 265 patients)[8,15,16,30,36,37,44]. The mean duration of asystole ranged from 7 to 30 s (mean, 14 s)[6,8,10,15–17,25,27–31,34,36,38,40–45]. The longest reported pause was 73 s[18]. The reproducibility of an asystolic response at repeat tilt varied from 54% in the experience of Brignole et al[29] to 67% and 100% in the experience of Foglia Manzillo et al[45] and Grubb et al[10], respectively. In our experience, in two patients with asystole at first tilt examination this response was not reproduced at a second tilt[25]. Although rarely, prolonged asystole (from 6 to 32 s) also occurred in healthy control subjects, in 5% of cases during an unmedicated tilt test (three out of 75 subjects)[20] and in 4% of cases during isosorbide dinitrate test (one out of 20 subjects)[41]. The vasovagal reaction during head-up tilt testing tended to develop earlier in patients with ventricular asystole than in patients with vasodepressor or mixed response[27,30]. Patients with prolonged asystole during head-up tilt testing were usually younger than patients without[27,30]. In a few papers[16,30] a greater severity of symptoms (as assessed by the frequency of seizures or injury during spontaneous episodes) was observed before the initial evaluation in patients with tilt-induced asystole. However, in many other studies this finding was not confirmed and the clinical outcome of asystolic patients after tilt evaluation appeared to be not different from that of non-asystolic patients[27–30,31,32]. Indeed, the incidence of new syncopal events, in a pooled analysis, was 12% among 105 patients with tilt-induced asystole during a follow-up of 9 to 25 months (mean, 19)[16–18,27–32] compared to 35% among 218 control patients without asystole during a follow-up of 16 to 36 months (mean, 24)[28,29]. Moreover, no case of important trauma, cardiopulmonary resuscitation or sudden death was observed in asystolic patients after initial evaluation[16–18,27–32].

As regards the correspondence between induced and clinical episodes of asystole, only limited information is available. In the paper of Milstein et al[15], asystole was reproduced by means of head-up tilt testing in only two of six (33%) patients with fortuitous documentation of asystole during spontaneous vasovagal reaction mimicking sudden death. In contrast, Menozzi and colleagues[46] showed, by means of a specially designed pacemaker able to detect and store in its memory ventricular pauses >3 and >6 s, the frequent occurrence of spontaneous asystole (often asymptomatic) during the follow-up of patients with neurally mediated syncope and ventricular pause induced by vagal manoeuvres. However, only two patients with tilt-induced syncope were included in this study, whereas the majority of patients were affected by carotid sinus syndrome. In a very recent study, the ISSUE trial, a poor correlation was found between the results of tilt testing and the findings observed during spontaneous syncope by means of an implantable loop recorder[47]. In particular, it seems that the clinical manifestation of loss of consciousness is much more frequently associated with prolonged asystole than the vasovagal reaction induced in the laboratory[47]. These data confirm the impression that the outcome of tilt testing is not useful in predicting the type of response during a spontaneous attack and, therefore, cannot be used to select chronic therapy for patients with tilt-induced syncope[2,20]. In particular, the implantation of a pacemaker based on the occurrence of a profound cardioinhibition during tilt testing, although repeatedly suggested[48–51], appears not justified by currently available data. Indeed, electrical treatment with pacemaker in patients with tilt-induced asystole was not shown to be superior to drug or no therapy in preventing new syncopal episodes[15–17,27–32]. This is in contrast with the results of recently published prospective randomized trials that have apparently shown the value of pacemaker therapy in patients with vasovagal syncope and documented bradycardia/asystole during head-up tilt testing[49–51]. These studies, however, were not controlled and a
‘placebo’ effect of pacemaker implantation cannot be excluded [52].

To conclude, it is clear, from the above mentioned data, that literature results on tilt-induced asystole are substantially concordant with those reported by Barón-Esquivias in this issue [26]. Thus, ventricular asystole observed during head-up tilt testing, even when prolonged, is usually not indicative of a more advanced disease and/or serious future clinical events, such as frequent syncopal recurrences, important syncope-related injuries and sudden death. Consequently, at present, an aggressive treatment with pacemaker should not represent the standard therapy of tilt-induced asystole, but should be reserved only for selected cases, on a single patient basis [50, 52]. Of course, this clinical judgment and therapeutic approach is not the definitive answer to the question of the real meaning of prolonged asystole during head-up tilt testing and the role of pacemaker in patients with such a response. To clarify these points, further prospective research exploring the correspondence between tilt-induced and spontaneous asystole, and randomized, placebo-controlled trials on the value of pacemaker therapy in vasovagal syncope are mandatory.

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