Hotline Editorial

Exercise testing: do frequent premature ventricular depolarizations represent a new criterion of positivity?

Exercise testing is widely used to detect coronary heart disease in patients with suspected ischaemic cardiomyopathy, but also in apparently healthy persons, for example before the initiation of sport activity. Exercise testing is also used to assess short- and long-term prognosis. The only current criterion for positivity of the exercise test is an ischaemic ST-segment response to exercise, that has been proven to be a powerful predictor of major coronary events, including death[1–4]. In contrast, the occurrence of premature ventricular depolarizations during exercise has been generally considered as non-informative. The long-term prognostic implications of exercise-induced premature ventricular depolarizations have been debated in patients with known or suspected cardiovascular disease[5–7]. In apparently healthy subjects, the occurrence of premature ventricular depolarizations during exercise was not associated with an increase in cardiovascular mortality[8–11] and was reported to be a normal response of a normal heart during exercise[12].

A new predictive criterion?
Probably yes

The Paris Prospective Study I examined the long-term predictive implications of exercise-induced ventricular depolarizations in a cohort of 6101 men without known or suspected cardiovascular disease after 23 years of follow-up[13].

These subjects were native Frenchmen employed by the Paris Civil Service, aged 42 to 53 years, and included between 1967 and 1972. They underwent a standardized bicycle exercise test during which cardiac rhythm was continuously monitored. Frequent premature ventricular depolarizations were defined as a run of two or more consecutive premature ventricular depolarizations, making up more than 10% of all ventricular depolarizations on any 30 s electrocardiogram.

Frequent premature ventricular depolarizations were present in 0.8% of subjects before exercise, in 2.3% during exercise and in 2.9% during recovery.

There were no serious complications of exercise testing which was positive in 4.4% of subjects.

After 23 years of follow-up, the risk of death from cardiovascular causes was increased by a factor of more than 2.5 among the men who had frequent premature ventricular depolarizations during exercise, similar to that observed in men who had a positive ischaemic response to exercise. This increased relative risk persisted unchanged after adjustment for age, body mass index, basal heart rate, systolic blood pressure, tobacco consumption, participation in sport, diabetic status, cholesterol level, premature ventricular depolarizations before exercise and premature ventricular depolarizations during recovery. When the ischaemic response to exercise and the occurrence of frequent premature ventricular depolarizations were introduced in the predictive model, both of them carried a significant independent predictive value for increased mortality.

Frequent premature ventricular depolarizations at rest or during recovery were not associated with an increase in cardiovascular mortality. Infrequent premature ventricular depolarizations were not associated with an increased mortality whenever they occurred.

A new criterion for coronary heart disease? Maybe no

The occurrence of premature ventricular depolarizations during exercise may be related to exercise-induced myocardial ischaemia. However, subjects with a positive exercise test for ischaemia and subjects with frequent premature ventricular depolarizations during exercise did not apparently share the same pattern of risk factors. An exercise test positive for ischaemia was associated with age, and higher cholesterol and triglyceride levels, whereas the occurrence of frequent premature ventricular depolarizations during exercise was associated with a lower body mass index and a higher tobacco consumption. Moreover, it is striking that among subjects with a positive exercise test for ischaemia (n=271), only 3% had frequent premature ventricular depolarizations during exercise. Conversely, among subjects with frequent premature ventricular depolarizations...
during exercise (n=138) only 6% had a positive exercise test for ischaemia.

It is conceivable that frequent premature ventricular depolarizations during exercise identify a subgroup of subjects with subclinical types of non-ischaemic cardiomyopathy. Based on the findings of the Paris Prospective Study I, hypertensive cardiomyopathy is unlikely to be involved. Hypertrophic cardiomyopathy is usually a familial disorder with a diverse clinical course, frequently including premature ventricular depolarization[14]. Left ventricular hypertrophy may be absent or mild and the disease may be asymptomatic and non-clinically detectable at an early stage. Arrhythmogenic right ventricular dysplasia is characterized by replacement of right ventricular myocardium by fibrous tissue and fat which is usually responsible for frequent premature ventricular depolarizations with a left bundle branch block pattern[15]. Its early diagnosis can be quite difficult with only minor signs on the electrocardiogram. Premature ventricular depolarizations may also be due to dilated cardiomyopathies[16], which may not have been detectable at an early stage, or due to mitral valve prolapse, which has been described to be associated with a higher frequency of premature ventricular depolarizations than controls[17], and usually with a low prevalence of adverse effects in the population[18].

Thus, although the precise mechanisms of the premature ventricular depolarizations during exercise in asymptomatic men remained undefined, they do not appear to be a direct consequence of ischaemia.

Contrasting results

The relatively low prevalence of premature ventricular depolarizations during exercise in the Paris Prospective Study I is consistent with that reported by several studies in subjects without known or suspected cardiovascular diseases. Most of them, however, did not find a worsened prognosis. The Seattle Heart Watch Study followed 2365 subjects considered healthy (mean age 45 years), and found an unaffected cardiovascular mortality in subjects with premature ventricular depolarizations after 5 years of follow-up[8]. Drory et al. reached the same conclusion in 76 healthy young subjects (mean age 22 years) with frequent premature ventricular depolarizations followed for 6 years[9]. In the Veterans Study, 2546 subjects (mean age 59 years) referred for exercise test (probably with a suspicion of coronary disease) were followed for 3 years. Cardiovascular mortality in subjects with premature ventricular depolarizations during exercise was not increased[10]. Fleg and Lakatta followed 922 participants (mean age 54 years) in the Baltimore Longitudinal Study on Aging, free from apparent heart disease, and found no increased mortality in subjects with unsustained ventricular tachycardia during exercise after a mean follow-up period of 2 years[10]. These results, which were at variance with those of the Paris Prospective Study, can probably be explained by the far shorter duration of follow-up.

What clinical consequences?

The higher cardiovascular mortality associated with frequent premature ventricular depolarizations during exercise in asymptomatic men has some consequences for clinical practice. Such subjects should certainly be investigated and treated for cardiovascular risk factors with a strong recommendation to quit smoking. A regular clinical follow-up would be advisable. These results also suggest that additional diagnostic testing should be proposed with at least non-invasive investigations (such as echocardiography, 24 h ECG recording, search for late ventricular potentials and stress myocardial tomoscintigraphy).

More generally, one could envisage proposing that frequent premature ventricular depolarizations might be considered as another positive criterion in the interpretation of the exercise test, beside the positive ischaemic criterion. Further studies are, however, needed to confirm these findings and particularly, to validate the 10% threshold for the definition of frequent premature ventricular depolarizations (which was arbitrarily fixed at the initiation of the study).

Epidemiology: what help for arrhythmia research?

The results of this study exemplify the help that large prospective studies may provide in the progress of knowledge on cardiac arrhythmias. Data issued from cohort studies in patients with defined cardiovascular diseases are also needed in order to complement those obtained in general populations. We anticipate that epidemiological research using modern non-invasive investigations and biological and genetic markers will be as rewarding in arrhythmia research as it has been in the field of ischaemic heart diseases.

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