perfusion imaging has been in existence as a validated investigational technique for many years, stress echo has a significantly shorter history and is being developed as a new service in many hospitals. Any new service should be carefully and prospectively evaluated before assuming that the diagnostic accuracy is similar to that reported in the literature from institutions with a special interest in the field.

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References


Predictive value of electrocardiographic markers for autonomic nervous system dysfunction in healthy populations: more studies needed

See page 165 for the article to which this Editorial refers

In this issue Whitsel et al.[1] looked at the predictive value for primary cardiac arrest of low heart rate variability and a large QT interval index taken together in a population of enrollees in a large health plan. The rationale behind this nested case-control study is based on the fact that both heart rate variability and QT index are electrocardiographic markers of the autonomous nervous system function and sympathovagal balance.[2–4] Where do we stand on each of these markers with respect to their predictive power and usefulness in both patients and the population at large? Since the pioneering paper from Kleiger et al.[5] showing that depressed heart rate variability increased the risk of mortality in a cohort of 808 patients who survived an
acute myocardial infarction, epidemiological evidence for the involvement of sympathovagal dysfunction has been clearly proven for sustained ventricular tachycardia and sudden death after myocardial infarction before and during the thrombolytic era, by both time domain and frequency domain analyses.

Heart rate variability could add to risk stratification of arrhythmic events after myocardial infarction, depressed heart rate variability being more predictive for arrhythmic death than low left ventricular function although low heart rate variability after myocardial infarction could be a rather short-term predictor (6 months) after discharge from hospital. Recently, non-linear or fractal analysis of heart rate dynamics confirmed the predictive power of heart rate variability in patients with depressed left ventricular function, those with angina but without myocardial infarction as well as those with mild to moderate heart failure. Severity of coronary atherosclerosis correlates with the respiratory component of heart rate variability.

In a general patient population of more than 6000 subjects who underwent a 24-h Holter recording Algra et al. observed an increased risk for sudden death in those with low short-term RR interval variability with an odds ratio of 4:1.

Low heart rate variability is also observed in both alcoholic and idiopathic dilated cardiomyopathy as well as in Type I diabetes with autonomic neuropathy. Whereas the independent predictive value for low heart rate variability is clear in the clinical setting of coronary heart disease, evidence from so-called healthy populations is still scarce.

In the Framingham Heart Study, low heart rate variability assessed by time domain and frequency domain analysis is an independent predictor of all-cause mortality as well as all new coronary heart disease events in a population free of coronary heart disease. Markers of cardiac parasympathetic, sympa-tho-parasympathetic activity and their balance predicted independently from conventional coronary risk factors, incident coronary heart disease defined as myocardial infarction, fatal coronary heart disease or cardiac revascularization procedures in the ARIC Study.

Depressed heart rate variability, assessed by short electrocardiographic recordings, predicted all causes of mortality in an elderly male cohort from the Zutphen Study although in the Rotterdam Study both increased and depressed heart rate variability predicted cardiac mortality, the former being even a stronger predictor. Bias and unknown confounding are both problems in observational field epidemiology, hence the necessity to multiply cohort or nested case-control studies, although publication bias against negative results cannot be totality eliminated.

Heart rate variability is partially genetically mediated, related to age and gender as well as lifestyle and environmental factors, such as endurance sports and exercise training; cigarette smoking decreases heart rate variability whereas dietary consumption of n-3 fatty acids (fish oils) increases heart rate variability and could be protective against sudden cardiac death. Hypercholesterolaemia is associated with decreased heart rate variability in both men with and without coronary heart disease.

Reduced heart rate variability could be the pathogenetic pathway by which some psychosocial variables like anxiety, depression and hostility increase the risk of coronary heart disease. Finally, several drugs increase heart rate variability and could potentially reduce the risk of sudden death in subjects with and without coronary heart disease: scopolamine, beta-blockers, ACE inhibitors, and amiodarone.

The long QT syndromes, like the Jervell-Lange-Nielsen form or the Romano-Ward variant, have a strong unique genetic background, for which several genes are identified. DNA markers make a genetic diagnosis possible, and a molecular basis for this syndrome has already been proposed.

Research on acquired long QT intervals and lately on QT dispersion is scarce. Long QT intervals are predictive of cardiovascular mortality in patients with cardiac disease, in patients referred for Holter monitoring, hypertensive patients and those with diabetic autonomic neuropathy. The prolonged QT interval is a marker for carotid artery atherosclerosis assessed by ultrasonographic measurement of carotid internal-media thickness.

In healthy populations, three prospective studies observed an independent predictive value of the prolonged QT interval for cardiovascular mortality, but not in the Framingham Heart Study. Both heart rate variability and QT interval are influenced by the autonomic nervous system. Whitsett et al. try to combine information from both these markers in an apparent healthy population. The technique is a prospective nested case-control study. Cases were out-of-hospital primary cardiac arrests without prior clinically recognised heart disease, thus in apparent healthy condition; controls were a stratified sub-sample from the same population. Information bias cannot be ruled out when looking retrospectively at baseline data. In this study, distribution of heart rate variability was not statistically significant between cases and controls (Fig. 1 of Whitsett et al.) which is confirmed by results in Table 4 (Witsel et al.): low
heart rate variability in the presence of a low QT index has almost the same predictive value as high heart rate variability combined with a low QT index.

Compared to high heart rate variability and a low QT index, low heart rate variability combined with a long QT index gives an odds ratio of 1:55 when adjusting only for clinical confounders; when adjusting, however, for clinical and ECG characteristics of silent ischaemia the odds ratio is reduced to 1:34 with a P-value of 0.11. Thus, in this population silent ischaemia is a major confounder and most probably an effect modifier. More studies are needed in normal populations analysing the separate and combined effect of these two electrographic markers for autonomic nervous system dysfunction, with a prospective design using computerized recommended techniques for heart rate variability[43] as well as for QT intervals.

In coronary heart disease patients, where the predictive value for depressed heart rate variability and long QT intervals has been demonstrated in clinical observational studies, it is time to start randomized controlled trials in those patients at high risk of premature cardiac death due to an autonomic nervous system dysfunction.

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