New Methods for Risk Stratification in Patients After Myocardial Infarction

Autonomic Control and Substrate Sensitivity*

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Risk stratification after myocardial infarction (MI) is important to select greater-risk patients who warrant more aggressive strategies for prevention of future serious events such as reinfarction or sudden death. The results of the MADIT II (Multicenter Automatic Defibrillator Implantation) trial (1) suggested that patients with an ejection fraction (EF) <30% benefited from an implanted cardiac defibrillator. However, this costly procedure has not been universally adopted (2).

In this issue of the Journal, 2 important papers address different aspects of risk stratification after MI but in contrasting patient populations. The Canadian study by Exner et al. (3) from 6 hospitals in the Province of Alberta (i.e., REFINE [Risk Estimation Following Infarction, Non-invasive Evaluation] study) looked at the role of T-wave alternans (TWA) and averaged QRS duration (as markers of an arrhythmic substrate), together with markers of autonomic tone (baroreflex sensitivity [BRS], heart rate variability [HRV], and heart rate turbulence [HRT]) in 322 patients who had survived an MI but with left ventricular (LV) impairment (an EF of <40%, measured after 48 h, or <50% measured after 48 h). The 322 eligible patients (of 5,699 MI patients screened) were followed up for 4 years at hospitals where the majority of MI patients were cared for by cardiologists; they received appropriate medical therapy with antiplatelet agents (approximately 95%), beta-blockers (90%), angiotensin-converting enzyme inhibitors (90%), and statins (87%). Approximately one-third of the patients received revascularization within 24 h and approximately 10% underwent later revascularization. This aggressive treatment might partly account for the relatively low percentage of patients who met the entry criteria for reduced EF. To avoid bias caused by alteration in treatment, the results of the initial testing were withheld from their responsible physicians.

Markers of poor autonomic control plus an arrhythmic substrate identified patients at increased risk of sudden death (and of all cause death). None of these markers reliably identified future high-risk patients when tested in the first 2 to 4 weeks after MI but did so when retested 10 weeks or more after MI, when the combination of a receptive substrate, together with impaired autonomic control, identified a group (20% of the 322) who had a relative risk of 5.2 times that of patients without these markers (p ≤ 0.001).

In contrast, in a simpler Italian study from a single center, De Ferrari et al. (4) examined the value of BRS testing alone, at 4 to 6 weeks after the MI, in stratifying risk over 5 years in 244 consecutive ST-segment elevation myocardial infarction (STEMI) patients with better preserved cardiac function (EF of >35%, average 54 ± 8%), selected from 468 consecutive survivors with STEMI. In this different population with relatively preserved LV function, depressed BRS was present in 14% but identified patients with a relative risk of cardiovascular mortality of 11.4, compared with those without impaired BRS (cardiovascular mortality 26% vs. 2.4% over 5 years). In this population with preserved EF, EF itself was (unsurprisingly) not predictive. These results, from some of the same group that had earlier performed the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study (5), extend the ATRAMI study findings to a longer follow-up (5 years vs. 21 months for the ATRAMI study).

Before discussing these important results in more detail, it is necessary to comment on the methodological aspects, which differ importantly between the 2 studies with regard to the autonomic markers chosen. Both studies used the Oxford phenylephrine method (6,7). In brief, an intravenous injection of this alpha-adrenergic agent constricts vascular smooth muscle and increased arterial blood pressure (BP). This increased BP is sensed by the arterial baroreceptors and results in reflex slowing of the heart. Plotting the systolic pressures of consecutive beats (measured noninvasively from the finger by the Finapres machine [Ohmeda, Louisville, Colorado]) against the reflex cardiac slowing (measured from the electrocardiogram as the following pulse interval) results in a linear plot. The steepness of the slope of this regression line in milliseconds per millimeter of mercury (ms/mm Hg) gives an index of vagal response to the increase in BP. This response is impaired with age and with hypertension (8) and several other disease states. In the past (and still persisting in 9 of 10 in a random survey of current textbooks of physiology), it was believed that the arterial baroreflex was concerned only with short-term
correction of BP changes but had no influence on longer-term BP (9). Recent experiments by a number of investigators, such as Thrasher (10), have shown that the baroreflex does indeed influence long-term BP by sympathetically mediated control of sodium excretion by the kidney. I have long advocated (11,12) that the older, erroneous view was a result of the misinterpretation of experiments on sino-aortic denervated dogs, carried out by Cowley et al. (9). This influence of impaired BRS in increasing longer-term BP might be another factor in worsening the prognosis, in addition to the loss of vagal protection against sudden arrhythmic death (13).

In the ATRAMI study (5), it was found that a BRS value of <3.1 ms/mm Hg was highly predictive of an adverse prognosis after MI; this value was that used in the current Italian study (4) to dichotomize responses into impaired BRS and relatively preserved BRS. However, the Canadian REFINE study (quoting the same ATRAMI study results) used a cutoff of <6.1 ms/mm Hg. The reason for the choice by the REFINE Investigators of a cutoff of 6.1 ms/mm Hg is not clear, although these authors do quote Redwood et al. (14), who found that dichotomy values for a determined single variable were not always applicable where that variable was used as one of a combination of risk factors. However, Redwood et al. (14) did find that HRV dichotomy values (which are closely related to BRS) were little altered when combined with other factors. In my opinion, this cutoff at 6.1 mm Hg is too high, because many elderly subjects will have a normal BRS around this level (8); this choice may account for their finding that another method, also related to BRS assessment (namely heart rate turbulence), was marginally more predictive than conventional BRS in their study. The use of HRT measures the acceleration of heart rate, which follows the BP decrease after an ectopic beat, together with the subsequent deceleration as BP increases again (15). Less change (less turbulence) is predictive of a poor prognosis. There have been few previously noted correlations of BRS and HRT in the same populations; it seems a pity, therefore, that the REFINE study used an unconventional value for dichotomization of BRS. The developers of the HRT method acknowledge that the arterial baroreflex is one of the important determinants of HRT (16). The assessment of autonomic function is also highly dependent on environmental factors such as exercise (17) or arousal (18); comparisons should therefore be conducted in the same steady state. Finally, one should add that all methods of assessing autonomic function are highly variable; it is therefore better to repeat these measurements a number of times in any patient to obtain an average value. Neither of these studies reveals how many tests were done to assess BRS, HRT, or HRV. Furthermore, the Italian study (4) is confined to patients surviving STEMI with preserved left ventricular function, whereas it appears that the Canadian study (3) encompasses both STEMI and non-STEMI survivors with impaired left ventricular function.

Despite these technical considerations, there is much to be learned from these 2 studies. The REFINE study showed (understandably) that a combination of an autonomic measure with a measure of cardiac vulnerability to arrhythmia (TWA), in a higher-risk population with impaired LV function, gave better prognostic discrimination than either measure alone. Their exercise protocol (testing for TWA) omitted the immediately preceding dose of the beta-blocker to obtain a faster heart rate response. However, in an earlier study of the effects of beta-blockade on exercising heart rate, we found persisting blunting of the rate response even after a week or more without drug (19).

The REFINE study authors (3) acknowledge that their findings need to be validated in a larger population. In the REFINE study, there were only 24 serious arrhythmic events. The finding that these tests were better long-term predictors when measured after the acute phase after MI is also important, because most risk stratification is performed in the acute (and unstable) phase. Another problem is that the combined end point (autonomic + substrate + EF) was present in only 20% of the already highly selected 322 patients in this study.

The Italian study (4) is equally important because it stratifies the risk of a group with well-preserved left ventricular function, which is normally classed as low risk. In this population, BRS <3 ms/mm Hg identified subgroups with markedly different risks, both in younger (<65 years) patients (relative risk 19.6, p = 0.0002) and older patients (relative risk 7.2, p = 0.02). Furthermore, the proportion of the population with well-preserved left ventricular function after MI is larger than that of the REFINE study. But in both populations the survival curves based on these relatively new prognostic measures continued to diverge during the 4 or 5 years of follow-up. Schwartz et al. (13) speculate that BRS may not only act by way of susceptibility to arrhythmic death (and perhaps by determining long-term BP) but also by a type of genetic “autonomic fingerprint” that is applicable over the longer term. Each of these studies was in patients who were given contemporary gold standard treatment; therefore, the results are applicable in today’s clinical context.

These new measures have a sound pathophysiological basis. The measurement of BRS in these studies used BP changes produced by injection of phenylephrine, but it is now possible to measure autonomic function using spontaneous variability of BP and pulse interval, or indexes of heart rate variability, which may be more widely applicable. Finally, both BRS and protection against serious arrhythmia may be improved with exercise training (20), or by drugs (21), both of which may help long-term outcome. Vagal tone also can be increased by the slow breathing induced by repetitive recitation of the Rosary (Ave Maria) prayer, or by Mantras (22), which might be an alternative aid if better studied in MI survivors in future.
References


