
Hotline Editorial

ATRAMI: a mark in the quest for the prognostic value of autonomic markers

The availability of a wide array of therapeutic options, including aggressive and expensive ones, has shifted the early identification of patients at high risk of sudden and non-sudden cardiac death after a myocardial infarction into an area of even more active investigation. The last 15 years have witnessed a growing interest in the possibility that markers of autonomic activity might usefully add to the established risk stratifiers, such as depressed left ventricular ejection fraction and frequent premature ventricular contractions. A few small or retrospective studies have provided encouraging hints in this direction. A few months ago, the first large prospective study aimed at quantifying the potential prognostic value of the two major autonomic markers, heart rate variability and baroreflex sensitivity, was published^[1]. Its results are likely to have a significant impact on the management of post-myocardial infarction patients.

ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) is an international study, involving 25 centres in Europe, U.S.A. and Japan, which enrolled 1284 patients with a recent myocardial infarction. Heart rate variability^[2] was quantified by 24 h Holter recording as the measure of the standard deviation of normal to normal RR interval (SDNN), while baroreflex sensitivity^[3] was calculated from measurement of the rate-pressure response to intravenous phenylephrine.

During the 21 months of follow-up, the primary end-point, cardiac mortality, was reached in 49 patients. Low values of either SDNN (<70 ms) or baroreflex sensitivity (<3.0 mmHg) were independent predictors of cardiac mortality with a relative risk of 3.2 and 2.8 respectively. The association of low SDNN and baroreflex sensitivity further increased risk as the 2-year mortality was 17% when both values were depressed and only 2% when both were well preserved. The association of low SDNN or baroreflex sensitivity with left ventricular ejection fraction below 35% carried a relative risk of 6.7 and 8.7, respectively. Among patients with left ventricular ejection fraction <35%, survival was markedly affected by whether the values of the autonomic markers were depressed. This effect was particularly

evident for the association with low baroreflex sensitivity, which increased the 2 year mortality from 8% to 18%, while for SDNN the increase was only from 9% to 13%.

This large prospective study marks an important transition and warrants several considerations. The transition is represented by the fact that, contrary to long standing views which maintained that survival after a myocardial infarction was almost exclusively determined by pump function (i.e. left ventricular ejection fraction) and by the presence of ventricular arrhythmias on a Holter recording, ATRAMI crowns a series of converging hints^[4] and provides clear evidence that autonomic markers also carry independent prognostic value. The whole post-myocardial infarction risk stratification has to be reconsidered and should no longer ignore the autonomic balance.

The haemodynamic and autonomic data provide important synergistic information. This becomes particularly evident when analysing baroreflex sensitivity, which may be taken to grossly represent the maximal ability of the system to respond with vagal reflexes. Within patients with a similar substrate (i.e. depressed left ventricular ejection fraction), what significantly influences their survival appears to be the preserved ability to reflexly increase vagal activity. The practical inference is that it now becomes appropriate to determine both left ventricular ejection fraction and baroreflex sensitivity in patients with a recent myocardial infarction. This will enhance the possibility for the early identification of high risk patients. Given the high proportion of sudden arrhythmic deaths among this group, these patients are logical candidates for a more aggressive preventive strategy which may range from experimental antifibrillatory drugs to implantable cardioverter defibrillator. Similar considerations are already entering the design of new post-myocardial infarction clinical trials, as exemplified by the ALIVE trial which focuses on patients with a left ventricular ejection fraction between 15% and 35% who also have a depressed heart rate variability^[5].

What are the main practical implications for management that originate from the results of

ATRAMI? In patients with well preserved left ventricular ejection fraction, the analysis of autonomic markers is of modest value because the differences in mortality between patients with and without signs of autonomic imbalance are non-significant, and thus cannot be recommended. By contrast, when left ventricular ejection fraction is depressed the analysis of autonomic markers should be performed because it does discriminate between subgroups at moderate and high risk. Heart rate variability is more easily performed than baroreflex sensitivity and, at first glance, it may appear as the marker of first choice. Reality is, however, more complex because of an interesting interplay between autonomic activity and age. As age increases vagal activity decreases with unequal effects on the two markers, as this affects baroreflex sensitivity much earlier and more severely than heart rate variability. It follows that, within the ATRAMI population, baroreflex sensitivity carried no prognostic value in patients above age 65 but was of extraordinary discriminating power among patients below age 65; at variance, heart rate variability was modestly affected by age and remained of similar value in all age groups. As a consequence, when dealing with patients below age 65 baroreflex sensitivity is markedly more powerful as risk stratifier than SDNN.

We now determine heart rate variability in all post-myocardial infarction patients for whom a Holter recording has already been planned and determine baroreflex sensitivity in all patients with depressed left ventricular ejection fraction and below age 65. As the coexistence of depressed left ventricular ejection fraction and baroreflex sensitivity identifies a subgroup at definite high risk for both sudden and non-sudden cardiac death, this finding should prompt a more aggressive strategy. Unless contraindications are present, it is appropriate to treat these patients with beta-blockers and, if possible, to enter them in an exercise training programme. Indeed, exercise training has been shown to correct autonomic imbalance by increasing baroreflex sensitivity and also to reduce the risk for ventricular fibrillation^[6,7].

The non-invasive variables used in post-myocardial infarction risk stratification are all undergoing critical reassessment, and ATRAMI will contribute to this process. For instance, the significance of QT dispersion is seriously questioned^[8] and that of the signal averaged ECG has diminished in the thrombolytic era. In this regard, it is important to note that the prognostic value of baroreflex sensitivity is still present in thrombolysed patients, who constituted the majority (63%) of the ATRAMI patients.

A novel and intriguing possibility is stimulated by the ATRAMI data. Indeed, the wide scatter in baroreflex sensitivity observed for the first time in dogs with a *normal* heart^[9] and now in the post-myocardial infarction ATRAMI patients underlines the hypothesis that the autonomic balance might be influenced not only by environmental but also by genetic factors. Accordingly, we are currently searching for mutations in the genes involved in the autonomic control of circulation. The death rate for patients admitted to a coronary care unit for an acute myocardial infarction has considerably decreased; what remains painfully high is the mortality, almost always due to ventricular fibrillation, in the pre-hospital phase of the first episode of myocardial ischaemia or infarction. An exciting possibility is that those individuals more likely to die suddenly during their first ischaemic episode do so partly because of a genetically mediated alteration in the neural control of circulation. This concept may open new, and previously unforeseen, strategies for primary prevention.

It is important to recognize the causal relationship existing between altered autonomic balance and increased mortality. A depressed baroreflex sensitivity or heart rate variability are not just innocent bystanders; their presence indicates a reduced ability to release acetylcholine and an increased propensity to release norepinephrine during an ischaemic episode. This has detrimental effects on cardiac electrophysiology and favours the development of ventricular fibrillation; conversely, this lethal arrhythmia can be prevented in subjects with impaired autonomic balance by either beta-blockers or by direct vagal stimulation^[10]. In this regard, ATRAMI contributes to a better understanding of the pathophysiological mechanisms involved in the survival, or demise, of patients who have suffered a myocardial infarction.

ATRAMI represents an unusual link between experimental and clinical cardiology. In the early 1980s, it was unexpectedly shown that a tight relationship existed between depressed vagal reflexes, identified by a low baroreflex sensitivity, and increased susceptibility to ventricular fibrillation during a brief ischaemic episode in dogs with a healed myocardial infarction^[9,11,12]. This led to a pilot clinical study^[13] which found the same relationship in post-myocardial infarction patients and which was soon confirmed^[14]. This sequence of studies led to ATRAMI. It is reassuring, for those who respect the slow but relentless advancement of science, to see that within 20 years from the initial experimental observations it has been possible to translate these novel concepts into clinical application.

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References

- [1] La Rovere MT, Bigger Jr JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; 351: 478–84.
- [2] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Bigger Jr JT, Breithardt G, Camm AJ *et al.*). Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996; 93: 1043–65 and *Eur Heart J* 1996; 17: 354–81.
- [3] La Rovere MT, Mortara A, Schwartz PJ. Baroreflex sensitivity. *J Cardiovasc Eletrophysiol* 1995; 6: 761–74.
- [4] Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992; 85 (Suppl I): I177–I91.
- [5] Camm AJ, Karam R, Pratt CM. The azimilide post-infarct survival evaluation (ALIVE) trial. *Am J Cardiol* 1998; 81 (6A): 35D–39D.
- [6] Billman GE, Schwartz PJ, Stone HL. The effects of daily exercise on susceptibility to sudden cardiac death. *Circulation* 1984; 69: 1182–9.
- [7] Hull Jr SS, Vanoli E, Adamson PB, Verrier RL, Foreman RD, Schwartz PJ. Exercise training confers anticipatory protection from sudden death during acute myocardial ischemia. *Circulation* 1994; 89: 548–52.
- [8] Zabel M, Klingenhoben T, Franz MR, Hohnloser SH. Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction. Results of a prospective, long-term follow-up study. *Circulation* 1998; 97: 2543–50.
- [9] Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988; 78: 969–79.
- [10] Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull Jr SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res* 1991; 68: 1471–81.
- [11] Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: A predictor of sudden cardiac death. *Circulation* 1982; 66: 874–80.
- [12] Schwartz PJ, Billman GE, Stone HL. Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with healed myocardial infarction. An experimental preparation for sudden cardiac death. *Circulation* 1984; 69: 790–800.
- [13] La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. *Circulation* 1988; 78: 816–24.
- [14] Farrell TG, Odemuyiwa O, Bashir Y *et al.* Prognostic value of baroreflex sensitivity testing after acute myocardial infarction. *Br Heart J* 1992; 67: 129–37.