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Baroreflex Sensitivity Determined by Spectral Method and Heart Rate Variability, and Two-Years Mortality in Patients After Myocardial Infarction

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Summary

Sympathetic overactivity and low parasympathetic activity is an autonomic dysfunction (AD) which enhances cardiac mortality. In the present study, the impact of AD on the mortality in patients after myocardial infarction was evaluated. We examined 162 patients 7-21 days after myocardial infarction, 20 patients of whom died in the course of two years. Baroreflex sensitivity (BRS) was estimated by spectral analysis of spontaneous fluctuations of systolic blood pressure and cardiac intervals (Finapres, 5 min recording, controlled breathing 20/min). The heart rate variability was determined as SDNN index (mean of standard deviations of RR intervals for all 5-min segments of 24-hour ECG recordings). BRS < 3 ms/mm Hg and/or SDNN index < 30 ms were taken as markers of AD. The risk stratification was performed according to the number of the following standard risk factors of increased risk of cardiac mortality (SRF): ejection fraction < 40 %, positive late potentials and the presence of ventricular extrasystoles > 10/h. No difference in mortality between patients with AD (4 %) and without AD (4.5 %) was found in 92 patients without SRF, the mortality in 6 patients with three SRF was 66.6 %. Five of these patients had AD. Out of 64 patients with one or two SRF, 32 had AD. The mortality of patients without AD was 6.25 % and 31.2 % of those with AD ($p<0.025$). It is concluded that AD enhanced two-years mortality five fold in our patients with moderate risks.

Key words

Baroreflex sensitivity • Spectral analysis • Myocardial infarction • Cardiac death • Risk stratification

Introduction

Patients surviving acute myocardial infarction (MI) are at risk of cardiac death (CD). The increased risk of CD in patients after myocardial infarction (post-MI patients) is caused by a number of factors, namely: 1) increased automaticity of ventricular myocytes, representing a triggering factor; 2) ischemia-induced non-uniform conduction velocity in different myocardial cells, representing arrhythmogenic substrate; 3) decreased contractility leading to heart failure, and 4) increased sympathetic and/or decreased parasympathetic autonomic nervous activity, which decreases the gain of autonomous reflexes protecting the heart. The risk of CD in post-MI

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patients is estimated by means of critical values of several indexes of these heart functions: 1) presence of ventricular premature complexes – VPCs > 10/h (The ESVM Investigators 1993); 2) presence of late potentials – LP (Denniss *et al.* 1986); 3) ejection fraction (EF) below 40 % (The Multicenter Postinfarction Research Group 1983), and 4) baroreflex sensitivity (BRS) below 3 ms/mm Hg (La Rovere *et al.* 1988, 1998, Honzíková *et al.* 1997a,b) and decreased heart rate variability, e.g. SDNN index (mean of 5-min standard deviations of RRs in 24 h – below 30 ms (Pedretti *et al.* 1993). The above reports may serve as a few examples of numerous prospective studies. These indexes have been shown to have a prognostic value for the prediction of CD or total cardiac mortality and the majority of them belong to standard clinical examinations of longer duration. The BRS determination is an exception.

In the last few years, BRS has been evaluated as an independent prognostic index, measured mostly as the rate-pressure response to intravenous phenylephrine administration. The ATRAMI multicenter prospective study proved that low values of BRS carried a significant risk of cardiac mortality, independent of standard markers (La Rovere *et al.* 1998). The possibility of introducing the phenylephrine method of BRS determination as a standard clinical method is being intensely discussed because of the necessity of administering the drug. Therefore, BRS determination by phenylephrine is compared with other, more natural non-invasive methods. Inconsistent data were found using the alpha-low frequency and alpha-high frequency spectral technique (Maestri *et al.* 1998, Pitzalis *et al.* 1998a) or the sequence technique (Pitzalis *et al.* 1998a). The most promising results were found by Robe spectral analysis technique (Fišer *et al.* 1997, Honzíková *et al.* 1997c, Semrád *et al.* 1998, 1999). It is recommended to use 0.1 Hz spectral component for BRS determination by the spectral method during regular controlled breathing at higher frequency of respiration (e.g. 0.33 Hz) for the following reasons: 1) respiratory sinus arrhythmia is respiratory-frequency dependent, and 2) the correlation of BRS, determined at 0.1 Hz and at respiratory frequency, is insignificant (Honzíková *et al.* 1992). This might be explained by a multifactorial origin of the respiratory sinus arrhythmia. BRS is only one of at least four factors, which causes the respiratory sinus arrhythmia (Honzíková 1992). 3) The comparison of the spectral characteristics of 24-hour blood pressure variability estimated invasively and non-invasively by Portapres should also be taken into account (Castiglioni *et al.* 1999). At around 0.1 Hz, invasive and non-invasive spectra were similar. At the respiratory frequencies, the power spectra were overestimated during daytime, and underestimated at night.

The critical value of BRS determined by spectral method was tested; the critical value of risk for post-MI patients was found to be 3 ms/mm Hg (Honzíková *et al.* 1997b) similarly to the phenylephrine method.

It was clearly shown in previous studies that autonomic dysfunction assessed as a decrease of BRS and/or heart rate variability has a predictive value for risk estimation in post-MI patients. But there are no available data, based especially on non-invasive BRS determination, quantifying the additional value of autonomic dysfunction in the assessment of post-MI risk. The stratification procedure, which identifies patients after MI at increased risk of CD, is more important at present than in the past because of the possibility of treating the patients with implantable cardioverter-defibrillator devices. The patients to be treated must be selected very carefully. It is therefore important to decide whether the clinical determination of autonomic dysfunction might improve the stratification procedure.

In the present study, the impact of autonomic dysfunction (AD) on two-years mortality in patients after myocardial infarction was evaluated. BRS determined by the spectral method was used as an index of AD together with an index of heart rate variability – the SDNN index. These indices were evaluated as auxiliary factors in the risk stratification based on the measurement of standard clinical examinations as risk factors. The presence of increased frequency of ventricular premature complexes (VPCs), late potentials and low ejection fraction were taken as standard clinical risk factors of increased risk of cardiac mortality.

Methods

Subjects

We repeatedly followed all patients (162) discharged from the coronary care unit during a period of two years. The diagnosis of acute myocardial infarction was based on conventional clinical, electrographic and enzymatic criteria. The mortality of this group during two years after MI was 12.35 % (20 patients died, seven of sudden cardiac death, 13 died for other cardiac causes). Detailed characteristics of patients included in our statistics can be found in Table 1.

Table 1. Patient characteristics

Characteristics	Survivors (n=142)	Deceased patients (n=20)	
Age (years)	56.4±8.9	63.1±5.4	$p < 0.05$
Males	109 (77 %)	15 (75 %)	ns
Inferior MI	70 (49 %)	10 (50 %)	ns
Anterior MI	58 (41 %)	8 (40 %)	ns
Q-wave	110 (77 %)	20 (100 %)	ns
History of MI	20 (14 %)	4 (20 %)	ns

MI – myocardial infarction; n – number of patients; ns – non-significant.

The aim of our study was to evaluate the feasibility of a non-invasively assessed autonomic dysfunction and of other non-invasive indices of the risk of sudden cardiac death as a standard clinical regimen. Thus, the patients were examined under appropriate treatment: therapy – number (%) of survivors, number (%) of deceased patients, significance determined by chi square; antiarrhythmics – 9 (6), 5 (25), $p<0.01$; beta-blockers – 75 (53), 2 (10), $p<0.01$; digoxin – 27 (19), 5 (25), insignificant; calcium entry blockers – 35 (25), 0 (0), $p<0.01$; angiotensin-converting enzyme inhibitors – 66 (46), 7 (35), insignificant; nitrates – 105 (74), 13 (65), insignificant; diuretics – 46 (32), 8 (40), insignificant; aspirin – 123 (88), 15 (75), insignificant. Patients were treated by appropriate combined therapy.

The Ethics Committee approved the study and each patient gave his/her informed consent.

Protocol

The majority of Holter monitoring, BRS determination, echocardiogaphic investigation and signal averaged ECG recording was done between day 7 and 14, before discharging the patients from the hospital. If the disease required longer hospitalization, the investigation lasted up to 21 days in a few instances.

Holter monitoring

A two-channel, 24-hour ECG recording (Oxford Excell) was performed. The recordings were manually edited, the artifacts were removed. Arrhythmias were evaluated and classified (ventricular ectopic beats – simple, bigeminal, multiform, repetitive or R on T), and the count of ventricular ectopic beats was determined. Heart rate variability was expressed as the SDNN index – the mean of standard deviations of normal-to-normal RR intervals determined in 5-min periods during 24-hour ECG recording.

Baroreflex sensitivity assessment, spectral analysis

Indirect continuous blood pressure recordings from finger arteries (Finapres, Ohmeda) lasting for 3 min, were performed in sitting, resting patients between 9:00 and noon. Recordings were taken during spontaneous and synchronized breathing. During the latter, only the rhythm of breathing was controlled at 20 per min by metronome (0.33 Hz); the subjects were allowed to adjust the tidal volume according to their own needs.

Beat-to-beat values of systolic pressure and of pulse intervals were measured for further analysis. For spectral analysis, the parameters were linearly interpolated and equidistantly sampled at 2 Hz. The linear trend was deleted. The auto-correlation and cross-correlation functions, relative power spectra (the relative division of the power into frequency ranges in arbitrary units) and absolute power spectra (the relative power multiplied by the squared standard deviation) as well as cross-spectra, coherence and modulus between pulse intervals and systolic pressure were calculated (Honzíková 1992, Honzíková *et al.* 1992). The gain factor, e.g. modulus H[f] of the transfer function between variations in systolic blood pressure and pulse intervals was taken as the index of BRS in the frequency range [f]:

$$Gxy[f] = H[f] \,.\, Gx[f],$$

where Gxy[f] corresponds to the cross-spectral density between systolic pressure and pulse intervals; Gx[f] corresponds to the spectral density of systolic pressure.

The value of modulus at the frequency of approximately 0.1 Hz was taken as the measure of BRS. The 0.1 Hz spectral peak is often shifted to the lower frequencies in post-MI patients. Therefore, the value of modulus was assessed in the frequency range of 0.07 to 0.12 Hz at the highest coherence.

Ejection fraction

A two-dimensional echocardiogram was obtained using an Acuson 128 XP/10 unit. The left ventricular ejection fraction was evaluated.

Late potentials

Late potentials were evaluated using the HIPEC-analyzer ECG Averaging System. Filtering at 40 Hz was

used and 200 beats were averaged to achieve a final noise level lower than 0.3 μV. The presence of late potentials was defined as positive if two of the three criteria were met: the filtered QRS complex longer than 120 ms, root mean square voltage of the last 40 ms of the filtered QRS complex less than 25 μV and duration of low-amplitude signals less than 40 μV in the terminal portion of the QRS complex longer than 40 ms. A prolonged QRS was not considered a positive criterion if the QRS duration measured from the standard ECG was greater than 120 ms.

Statistics

The patients were divided into two groups, comprising survivors and patients deceased during two years after myocardial infarction. BRS lower than 3 ms/mm Hg (La Rovere *et al.* 1988, Honzíková *et al.* 1997b), the SDNN index lower than 30 ms (Pedretti *et al.* 1993), ejection fraction lower than 40 % (The Multicenter Postinfarction Research Group 1983), presence of late potentials (Denniss *et al.* 1986) and 10 or more ventricular ectopic complexes per hour (The ESVM Investigators 1993) were taken as criteria of high-risk patients.

To decide whether it is of practical significance to determine autonomic dysfunction for the assessment of risk stratification of post-MI patients, we used the following approach. The patients were divided into groups with 0, 1, 2 or 3 standard risk factors, which were determined by standard methods, EF, VPCs and LP. Each group was subdivided into two subgroups – with and without autonomic dysfunction. Autonomic dysfunction (AD) was considered in those patients whose BRS and/or SDNN index were lower than the critical value.

Differences between the groups were compared by means of the chi square test. The relationships between continuous variables were examined by means of Pearson's correlation coefficient, $p<0.05$ was considered significant.

Results

The follow up of two-years mortality for each particular index, we found that the presence of each risk factor significantly increased the mortality (see Table 2).

Table 2. Two-years mortality

Risk factor present	n	M (%)	Risk factor absent	n	M (%)	
LP +	36	22.2	LP –	126	9.5	$p < 0.025$
VPCs > 10/h	26	30.8	VPCs ≤ 10/h	136	8.1	$p < 0.01$
SDNN index < 30 ms and/or BRS < 3 ms/mm Hg	62	22.5	SDNN index ≥ 30 ms and BRS ≥ 3 ms/mm Hg	100	6.0	$p < 0.01$
EF < 40 %	36	33.3	EF ≥ 40 %	126	6.3	$p < 0.01$

BRS – baroreflex sensitivity; EF – ejection fraction; LP – late potentials; M – mortality; n – number of patients; SDNN index – mean of 5-min standard deviations of RRs in 24 h; VPCs – ventricular premature complexes.

We compared the groups of patients with a different number of risk factors of increased risk of cardiac mortality (0-4, i.e. three standard risk factors and AD). If the patient had more risk factors, his/her risk increased progressively (Fig. 1). The majority of patients (72.12 %) had no or one risk factor (Fig. 1, left) and their risk was low (Fig. 2, right), 4.48 % and 4 %, respectively. A small group of patients (9.26 %) had 3 or 4 risk factors (Fig. 1, left) and the mortality of these patients was high, i.e. 40 % and 60 %, respectively. The remaining 18.5 % of patients with two risk factors and 26.67 % mortality appeared to be far less important from the clinical point of view. The next step of our study was to decide whether it is of practical significance to introduce methods of AD determination for assessing the risk stratification of the patients. We therefore divided the patients into groups with 0, 1, 2, or 3 standard risk factors, e.g. EF, VPCs and LP (Fig. 2, left, empty columns). Each group was subdivided into two groups – with or without autonomic dysfunction. The number of patients with autonomic dysfunction in each group is presented in Figure 2 (left, hatched columns). The relative number (in %) of these patients in each group is presented in Figure 2, on the right. The data show that the absolute number of patients

with autonomic dysfunction is inversely proportional to the number of standard risk factors, but their relative number increases with the number of standard risk factors. The correlation coefficient between the number of risk factors and the probability that the patient had additional AD was 0.98 ($p<0.05$). This result is not surprising because, with greater damage to the heart by myocardial infarction, the sympathetic nervous activity also increases while the parasympathetic activity decreases.

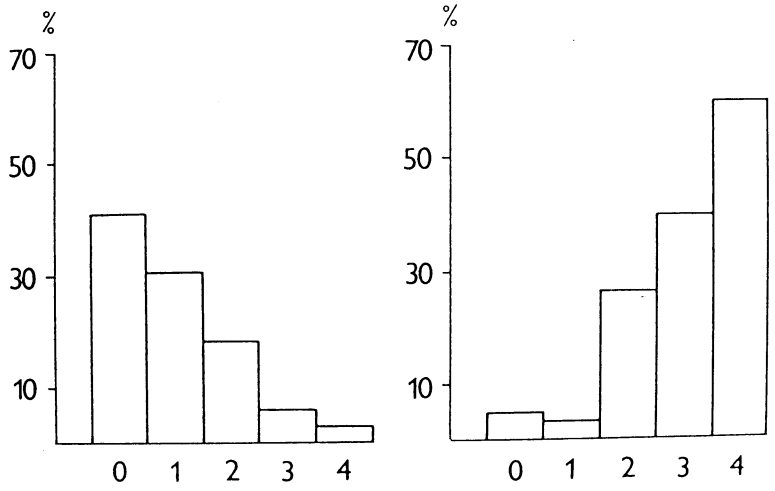

Fig. 1. *Distribution (left) and two-years mortality (right) of 162 patients according to the number of positive risk factors (0-4). Risk factors: ejection fraction < 40 %; positive late potentials; presence of ventricular extrasystoles > 10/h; autonomic dysfunction as baroreflex sensitivity < 3 ms/mm Hg and/or SDNN index < 30 ms.*

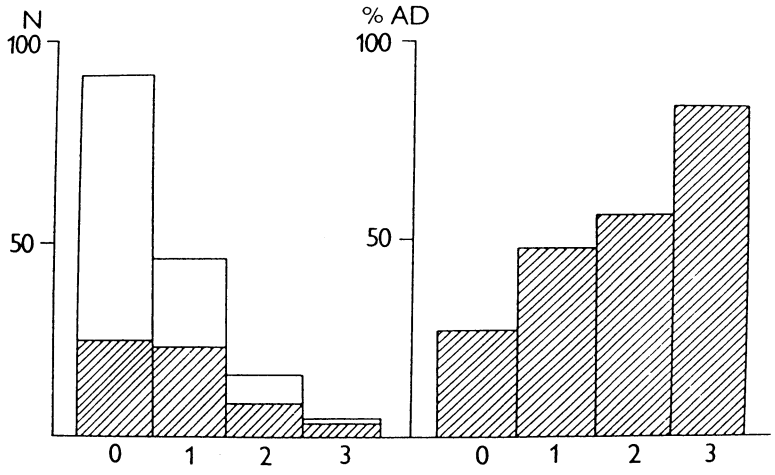

Fig. 2. *Distribution of 162 patients (left, empty columns) according to the number (0-3) of the positive standard risk factors (ejection fraction < 40 %; positive late potentials; presence of ventricular extrasystoles > 10/h). Number of patients (left, hatched columns) and their relative occurrence (right, hatched columns) in subgroups with additive autonomic dysfunction (baroreflex sensitivity < 3 ms/mm Hg and/or SDNN index < 30 ms) in each group. Correlation coefficient between the number of risk factors and the relative occurrence of autonomic dysfunction (%) was 0.98 ($p<0.05$).*

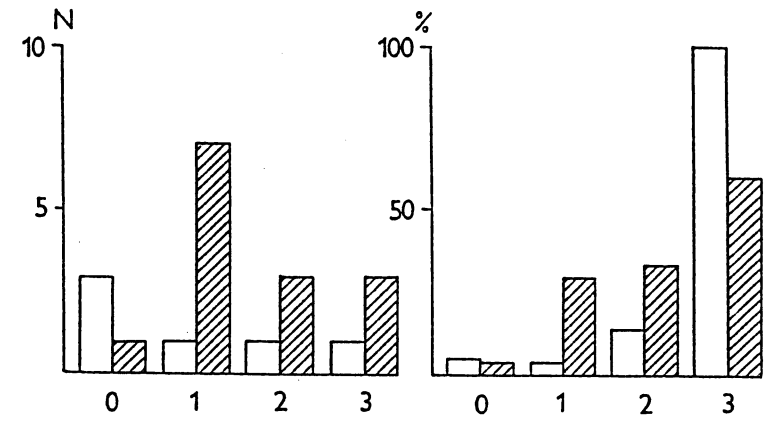

Fig. 3. *Number of deceased patients (left) and relative mortality (right) according to the number (0-3) of the positive standard risk factors (ejection fraction < 40 %; positive late potentials; presence of ventricular extrasystoles > 10/h) without autonomic dysfunction (baroreflex sensitivity ≥ 3 ms/mm Hg and/or SDNN index ≥ 30 ms) – empty columns; and with autonomic dysfunction – hatched columns.*

The mortality in the same individual groups of patients is shown in Figure 3. On the left, the absolute numbers of deceased patients without AD and with AD are given. The relative mortality in these groups of patients with respect to AD is shown in Figure 3 (right). In a group of 92 patients without standard risk factors there was no difference in the mortality between patients with AD (4 %) and without AD (4.5 %). In 6 patients with three standard risk factors, the average mortality for both subgroups (with and without AD) was high, namely 66.6 %. Five of these patients had AD. Sixty-four patients belonged to a subgroup with one or two standard risk factors, 32 had AD and 32 did not have AD. The mortality was 6.25 % in patients without AD and 31.2 % in those with AD ($p<0.025$). It is concluded that the mortality in patients after myocardial infarction with a moderate risk determined by standard risk factors was increased five times within two years in the additive presence of AD.

Discussion

Ischemic injury of the myocardium is frequently complicated by ventricular arrhythmias, the obvious cause of sudden cardiac death. An increased sympathetic and/or a decreased parasympathetic nervous activity increases the risk for CD. Parasympathetic activity, which exerts a protective effect against the appearance of ventricular tachyarrhythmias, is often altered in patients after myocardial infarction.

It is therefore of particular interest to assess tonic and reflex autonomic activity, e.g. by heart rate variability and BRS, respectively. Determination of BRS and heart rate variability based on nonspectral analysis of 24-hour ECG recordings, defined the patients at risk of cardiac death very reliably. Each method explores different aspects of the autonomic control of the heart – HRV analysis reflects the vagal tone, whereas BRS reflects the readiness of vagal reflexes. In the last few years, BRS has been evaluated as an independent and additional factor of prognostic value. The ATRAMI multicenter prospective study involving nearly 1300 patients clearly proved that low values of BRS (< 3 ms/mm Hg, measured as the rate-pressure response to intravenous phenylephrine) carried a significant multivariate risk of cardiac mortality, independent of standard markers (La Rovere *et al.* 1998).

Our study presents a modified approach of the non-invasive identification of patients with an increased risk of death after MI. The method of BRS determination by spectral analysis in patients after myocard infarction (Fišer *et al.* 1997, Honzíková *et al.* 1997c, Semrád *et al.* 1998, 1999) is easily usable in clinical practice. It differs from the method used in the ATRAMI study based on the administration of a vasoactive drug. We compute BRS by the spectral analysis of the variability of blood pressure and pulse intervals, recorded non-invasively for three minutes. We thus avoid further risk from vasoactive drug administration for the patient. We found the critical value of BRS determined by spectral analysis 3 ms/mm Hg (Honzíková *et al.* 1997b), i.e. an identical value to that found by the phenylephrine method. Furthermore, the spectral method was also compared with the classical methods. The correlation between BRS determined by the phenylephrine method and by spectral analysis was found to be very high in some studies in healthy subjects (Robe *et al.* 1987) and also in post-MI patients (Maestri *et al.* 1998).

The main aim of our study was to test whether the examination of the test identifying autonomic dysfunction in post-MI patients could improve the stratification procedure. It has clearly been shown for the first time that the risk of autonomic dysfunction for increased cardiac mortality depends on the complexity of ischemic injury to the heart. If the injury is not marked with more than one standard risk factor, it does not play any role whether AD is additionally present or not. On the other hand, the mortality in patients with three standard risk factors is very high and the role of AD itself in these patients is spurious: in our study, only one patient out of 162 patients had three standard risk factors without AD. For adequate statistical evaluation, it would be necessary to have a group of about 30 patients. Our experience shows that only a multicentric study could answer the question whether autonomic dysfunction influences mortality in patients with three standard risk factors.

It may be argued that the patients should have been studied after pharmacological washout. We attempted to assess whether non-invasive determination of BRS and other non-invasive indices of the risk for sudden cardiac death are of the practical significance. We therefore preferred to examine patients under standard therapy (the medication was referred to in Methods). Naturally, the effect of a therapy on risk factors is being

studied intensively. For example, the positive influence of thrombolytic therapy on the BRS after MI has been shown (Odemuyiwa *et al.* 1993, Honzíková *et al.* 1997c). The effect of beta-blockers on sympatho-vagal balance seems to be complicated. The parallelism between vagal tone and respiratory sinus arrhythmia, and the increased respiratory sinus arrhythmia during beta-blockade could reflect a vagotonic effect of this class of drugs (Wargon *et al.* 1998). La Rovere *et al.* (1992) reported that beta-blockade augmented BRS only in 40 % of patients after MI. A considerable variation between subjects (Chen *et al.* 1999) appeared in the effect of beta-blockers on BRS in hypertensive patients (beta-blockade increased BRS in 24 patients and decreased BRS in 11 cases). Increased heart rate variability and BRS were reported in normal subjects (Pitzalis *et al.* 1998b). The explanation of these results might be due to the heart rate oscillations, which mainly reflect parasympathetic activity (Grasso *et al.* 1997). An impairment of BRS can also be genetically conditioned since it has been demonstrated that ACE inhibition increases BRS in some strains of rats only (Lantelme *et al.* 1998). In our study, the patients were treated by a combined therapy.

The most important result seems to be the fact that the two-years mortality in patients after myocardial infarction with a moderate risk determined by standard clinical examinations is increased five times when autonomic dysfunction is present. That means that autonomic dysfunction in patients with moderate risk is a life compromising factor. On the basis of our study we suppose that introduction of the determination of autonomic dysfunction into clinical practice would significantly improve estimation of the risk of cardiac death in this group of patients. We conclude that the introduction of the measurement of autonomic dysfunction in routine risk stratification may assist in the decision whether to use additional therapeutic intervention. This index is of special importance in patients with mild risk and its measurement would thus improve the care of these patients.

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