Ambulatory Blood Pressure Monitoring After Acute Myocardial Infarction: Development of a New Prognostic Index

ORIGINAL SCIENTIFIC CONTRIBUTION

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Development of a New Prognostic Index

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Abstract

Aim: To assess the usefulness of ambulatory blood pressure monitoring (ABPM) in the prognostic stratification of patients with a recent myocardial infarction.
Method: The study population included 75 patients consecutively admitted at our institution for acute ST-segment elevation myocardial infarction (STEMI). All patients underwent ABPM 3 weeks after discharge and were subsequently followed for 12 months.
Results: The age (Y), mean 24-hour diastolic blood pressure (mDBP) and mean 24-hour beat-to-beat interval (mBBI) values were found to be independent predictors of the combined endpoint of cardiac death and symptomatic left ventricular dysfunction during the follow-up period. A prognostic index was then developed from such variables, according to the formula (mDBP + mBBI/10) – Y. This index, when considered as a categorical variable, in its 'low' figures (cut-off <88), showed a significant prognostic value ($p < 0.0001$). The predictive value of the index for the combined endpoint was higher than left ventricular ejection fraction (50% versus 36%).

The negative predictive value of low systolic blood pressure (BP) during the acute phase of myocardial infarction (AMI) is well known.[1] However, the predictive value of BP measurements in the early weeks after the acute event is still unknown. Previous studies have either included patients who do not correspond to the present clinical scenario of mechanical and pharmacological reperfusion, or had unreliable methodologies.[2-5] To the best of our knowledge, no study has employed ambulatory blood pressure monitoring (ABPM) to define the trend of BP values soon after an AMI and correlated their variations to subsequent cardiovascular events.

This study aimed to evaluate the usefulness of ABPM in the prognostic stratification of patients with a recent AMI. We tested the hypothesis that data derived from ABPM might provide us with a new prognostic index. We also compared the predictive value of this index with the predictive value of left ventricular ejection fraction (LVEF).

Methods

The study population included 75 patients (58 males, 17 females, mean age 62.3 ± 11 years [1 SD]) of 100 patients consecutively admitted and discharged, alive, from our institution during a 12-month period after an acute ST-segment elevation myocardial infarction (STEMI).

The exclusion criteria were permanent arrhythmia, a constant paced rhythm and inability of the patient to follow the study protocol, or relevant comorbidities. The aims and method of the study were explained to and accepted by the eligible patients.

Diagnosis of acute STEMI was made on the basis of at least two of the following criteria:

- an ST-segment elevation ≥1mm in at least two contiguous leads
- chest pain lasting more than 30 minutes
- peak creatine phosphokinase (CPK) values exceeding more than twice the upper limit of normal.[6]

The baseline characteristics of the patients are shown in table I. The study was merely observational, and no specific pharmacological interventions were considered. Medical therapies administered during follow-up are shown in table II.

ABPM was performed 3 weeks after discharge on an outpatient basis with a Spacelabs 90207 system. The Spacelab device

Table I. General features of the study population

Parameter	Value
Age (y)	62.3 ± 11.1
Gender (females) [%]	22.6
Body mass index (kg/m^2)	28.7 ± 3.8
Clinical systolic blood pressure (mm Hg)	121.3 ± 12.8
Clinical diastolic blood pressure (mm Hg)	73.4 ± 7.4
Heart rate (beats/min)	65.2 ± 10.1
Current smoking (%)	60.0
Hypertension (%)	54.2
Diabetes (%)	20.0
Serum total cholesterol (mg/dL)	183.6 ± 40.5
Serum creatinine (mg/dL)	1.1 ± 0.5
CPK peak (IU/L)	1481.2 ± 1504.2
Anterior myocardial infarction (%)	45.7
Non-anterior myocardial infarction (%)	54.3
Left ventricular ejection fraction (%)	0.53 ± 0.11
Thrombolysis (%)	25.7
Primary percutaneous transluminal coronary angioplasty (%)	24.2
Other therapy (%)	50.1

measures BP employing oscillometer methodology, and BP values recorded with such a tool do not significantly differ from intra-arterial measurements.[7] Systolic and diastolic BP measurements, as well as heart rate (HR) measurements, were performed each 15 minutes for 24 hours with a proper arm cuff. All ABPM reports considered for the study had more than 21 hours of monitoring, with at least 1 valid measurement per hour. BP readings were automatically elaborated with dedicated software. A mean of 23 hours of recording was obtained with a mean of 82 measurements per ABPM participant.

The following variables derived from the ABPM were considered: mean 24 hours systolic (mSBP) and diastolic BP (mDBP), mean 24-hour pulse pressure (PP), mean 24-hour beat to beat interval (mBBI), corresponding to the mean 24-hour HR; the following clinical and laboratory data were also collected in all cases: age (Y), peak CPK, pre-discharge serum creatinine (Cr), Killip class on admission.

The proposed prognostic index (PI) was developed using only independent outcome predictors.

The LVEF was assessed during hospitalisation with an Acuson 128XP/10 echocardiograph, according to the Simpson method.[8] The enrolled patients were followed-up through an outpatient visits at 3 weeks, and 6 and 12 months after discharge.

Cardiac death and symptomatic left ventricular dysfunction, defined as acute pulmonary oedema, or the development of signs and symptoms consistent with heart failure and requiring hospitalisation, were considered a combined endpoint. Repeated STEMI, new episodes of angina and revascularisation interventions, have not been included in the endpoint unless followed by symptomatic left ventricular dysfunction or death.

Statistical Analysis

Mean (± SD) values were calculated for continuous variables, while frequencies were measured for categorical variables. Differences between groups were analysed by unpaired Student's t-test for continuous variables, and by χ^2 or Fisher's exact test for categorical variable as appropriate.

The cumulative risk of the combined endpoint (cardiac death, admission for heart failure or acute pulmonary oedema) was estimated by means of the Kaplan-Meier method. Survival curve subgroups were then formally compared using the log-rank test.

Logistic regression analysis was used to determine the relationship of baseline characteristics with the occurrence of the combined endpoint during follow-up. The following variables, determined from the baseline evaluation, were considered potential predictors of the combined endpoints: mSBP, mDBP, PP and mean HR during ABPM, echocardiographic LVEF, peak CPK values, age, Killip class >2. These variables were analysed in a stepwise fashion to develop a model of the study endpoint (occurrence of cardiac death, heart failure or acute pulmonary oedema during follow-up). Data analysis was performed using the SPSS statistical software package (SPSS 8.0, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

During the 12-month follow-up period, 10 events were observed (in 13% of the patients): three cases (4%) of acute pulmonary oedema and seven cases of cardiac death (9%) [six of refractory heart failure and one of sudden death]. Peak CPK and Killip

Table II. Pharmacological treatment during follow-up

	3 weeks (%)	6 months (%)	12 months (%)
α-blockers	4.1	2.1	2.1
ACE inhibitors	72.2	61.3	54.6
Angiotensin II receptor blockers	1.3	4.1	4.1
β-blockers	80.1	66.6	56.8
Calcium channel blockers (dihydropiridines)	10.4	5.3	5.3
Calcium channel blockers (non-dihydropiridines)	10.6	18.6	20.4
Digitalis	2.6	2.6	2.6
Diuretics	21.3	14.6	16.3
Nitrates	62.3	44.3	37.3

Table III. Main characteristics in patients with and without events during the follow-up

	Events during follow-up	No events during follow-up	p-Values
Age	70.6 ± 5.8y	59.8 ± 11.4y	0.0001
Females	44.4%	19.8%	0.09
Diabetes	11.1%	18.6%	0.59
Killip class >2	11.1%	4.5%	0.41
Mean 24h systolic blood pressure	103.9 ± 16.5mm Hg	122.6 ± 10.8mm Hg	0.0001
Mean 24h diastolic blood pressure	59.9 ± 8.5mm Hg	69.9 ± 6.5mm Hg	0.0001
Mean 24h RR interval	812 ± 98 msec	1119 ± 101 msec	0.0001
Pulse pressure	42.1 ± 12.8mm Hg	50.1 ± 10.4mm Hg	0.031
Prognostic index	73.4 ± 19.4	107.1 ± 16.1	0.0001
Left ventricular ejection fraction	0.43 ± 0.07%	0.59 ± 0.11%	0.0001
Serum creatinine	1.7 ± 0.9 mg/dL	0.9 ± 0.3 mg/dL	0.0001
Creatine phosphokinase peak	2387.4 ± 2287.2 U/L	1599.3 ± 1034.4 U/L	0.07

class >2 did not show any predictive value in the univariate analysis, and were excluded from the subsequent multivariate analysis (table III).

In the multivariate analysis mDBP, mBBI, Y and LVEF were found to be independent predictors of the study endpoint (table IV). The PI was than built with such variables, according to the formula (mDBP + mBBI/10) – Y.

The LVEF was not included in the PI, as such an index was meant to be independent from this parameter; all events occurred in patients with 'low' PI values (<88). Among the 10 patients with events, seven had a history of hypertension, six of hypercolesterolaemia, one of diabetes and three were smokers.

The Kaplan-Meier curves for the two groups, divided according to the 'low' (<88) or 'high' (>88) index readings, were quickly showed to be diverging (figure 1), and the statistical significance was $p < 0.0001$.

After 1 year, the positive predictive value of the index, considering the threshold value as 88, resulted as 50%. The negative predictive value was 100%.

Among the 22 cases with LVEF, <50%, only eight had events, with a positive predictive value of 36%. The negative predictive value of the index, with LVEF values ≥50%, was 96%.

Discussion

The identification of patients with a high risk of mortality and major cardiovascular events represents an extremely important issue in cardiology, particularly for those patients who have recently experienced a STEMI and are asymptomatic.

Several non-invasive methods have been proposed, taking into account the various physiopathological aspects of ischaemic cardiomyopathy, such as exercise stress, and/or echostress testing[9] for residual ischaemia,[10] late potentials[11] and QT dispersion[12] for electric instability; heart rate variability[13] and baroceptive sensitivity[14] for adrenergic hyperactivity; and LVEF for left ventricular dysfunction.[15] Several indexes have also been proposed, clinical and/or instrumental, invasive and non-invasive, in the short and long-term.[16-19]

The search for a new method, and the development of a new index in order to evaluate the risk for patients with recent STEMI, would be superfluous if it did not yield a tool that was simpler but equally as effective as the more traditional methods used for evaluating risk. At present, LVEF is the most widely used PI in patients after acute STEMI, and echocardiography is the most widely used method of assessment. Nevertheless, the LVEF only evaluates one component of the risk, namely the systolic function of the left ventricle. This is a haemodynamically relevant parameter, but only one of several aspects in the complexity of events that follow acute STEMI. The PI we propose is composed of more than one variable, mDBP is added to mBBI and patient age is subtracted from their total.

This PI, as well as the LVEF, has a positive predictive value for cardiac death and ventricular dysfunction at their 'low' values. The 'lower' is the mDBP, the 'shorter' is the mBBI, and the older the patient, the more negative the prognosis will be. The cut-off value of 88 used in our study is obviously arbitrary and testifies that lower figures imply a poor prognosis.

Table IV. Independent predictors of the combined endpoint by logistic regression analysis

	Odds ratio	95% confidence interval	p-Value
Age	1.21	1.04–1.33	0.03
Mean 24h diastolic blood pressure	0.81	0.72–0.95	0.04
Mean 24h RR interval	1.19	1.08–1.29	0.03
Left ventricular ejection fraction	0.61	0.53–0.74	0.03

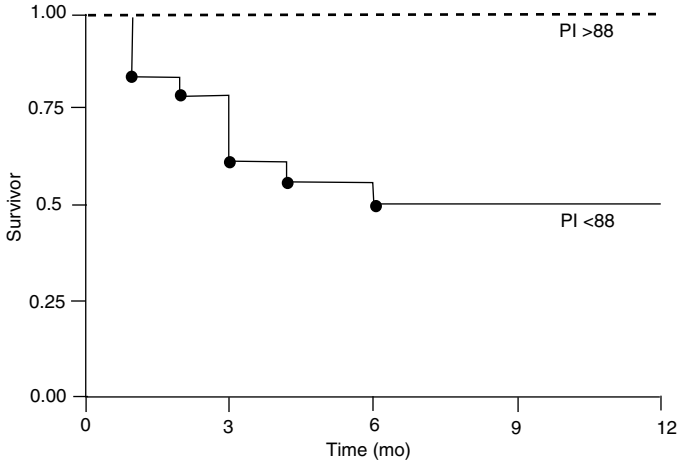

Fig. 1. Kaplan-Meier estimates of event-free survival according to the new prognostic index.

If we examine the single components of the PI in all cases, we discover that 9 out of the 10 events (six deaths and three acute pulmonary oedema) had a mDBP <65mm Hg, and all had a mDBP <70mm Hg.

Many large studies point to a link between 'low' mDBP values and cardiovascular death. The Framingham data[20] analysis has shown that in patients with a previous STEMI there is a statistically significant 'U' curve between diastolic BP and new ischaemic events, and that such a curve seems to be independent from pharmacological treatment.

The Multiple Risk Factor Intervention Trial (MRFIT),[21] involving more than 5000 patients with a previous STEMI and who were followed for up to 16 years, confirmed that low values of diastolic blood pressure (DBP) can correlate to an increase in cardiovascular death rate. A clear 'U' trend in the link between DBP and death curve is present in the first years of follow-up. A nonlinear trend between DBP and death risk was also noted in investigations involving general cohort study groups, not only in pathological sub-groups.[22]

In the Ohasama study,[22] patients belonging both to the lower (DBP <67mm Hg), and to the higher quintile (>83mm Hg), respectively, presented with the highest number of adverse events.

All these studies,[20-22] which used the sphygmomanometer method of 'random' BP, or the oscillometer method of 'basal' BP, seem to confirm our data, showing an increase in mortality at 'low' DBP values.

In our study, however, there were no cases of death or ventricular dysfunction in the rising portion of the curve. The short follow-up period used in our study could explain the difference between our results and those of the previously quoted studies. The 'higher' BP values constitute a significant risk of repeated infarction and heart failure in the long-term, but in recent myocardial infarction 'low' DBP was more likely to predict adverse events.

The causal link between low DBP and cardiovascular events may lie in the physiology of coronary circulation, whose flow takes place mostly in the diastole. Low DBP causes a reduction in the myocardial perfusion gradient, which in turn is established by the intra-coronary pressure which is opposed by extra-coronary resistances and the ventricle filling pressure. Moreover, the coronary flow is self-regulating, in order to be constant at certain BP levels, below which it rapidly decreases.[23]

The reason as to why patients with a recent STEMI and higher risk of cardiovascular death have an ambulatory low DBP is unclear. However, it is possible that low DBP values are caused by left ventricular dysfunction, which in turn is determined by the STEMI itself. Obviously it is necessary to exclude the possibility that it is a result of a pharmacological overdose resulting from an over 'aggressive' attitude toward the lowering of BP in order to reduce the risk.

In conclusion, in patients with recent myocardial infarction, low mean DBP values (<65mm Hg) have to be viewed with suspicion, forgetting, just for a moment, the dogma linearly connecting BP and risk.[24,25] An elevated HR (short mBBI) has been largely described as an independent predictor of morbidity and cardiovascular death, particularly in ischaemic cardiomyopathy.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) 2 and GISSI 3 studies,[26,27] involving about 20 000 inpatients admitted to hospital for AMI, have proved that HR (estimated from three consecutive RR intervals of ECG performed at admission and discharge), is linearly associated with cardiovascular death in hospital, and at 6 months after myocardial infarction. The multivariate analysis demonstrated in these studies, that HR, measured with a simple method, is an independent predictor of cardiovascular death.[28]

In our study, HR was determined as the mean of the values collected every 15 minutes with the ABPM over a 24-hour period, therefore, providing a value which was closer to the real HR in that moment compared to that given in the GISSI studies.

It is well known that elevated HR values may be an indicator of haemodynamic instability and/or may represent an unfavourable increase of the sympathetic activity. Moreover, an elevation in the number of beats per minute has a strong negative effect on a patient with ischaemic heart disease, increasing their myocardial oxygen consumption and at the same time reducing the availability of the diastolic time for the coronary flow. In fact, the shortening of the cardiac cycle reduces the duration of its single

intervals. In 9 out of 10 events in our study, the mean HR has been >65 beats per minute (mBBI <923 msec).

The formula for the calculation of a PI ([mDBP + mmBBI/10] – Y) takes into account the mBBI, but not the mean HR. This was deemed necessary since the mean HR and mDBP have an opposite predictive significance in their numeric values, which is unfavourable for low mDBP values and high mean HR values. Moreover, in order to calculate the PI, mBBI was divided by 10, because its values are expressed in msec and mostly in hundreds, while mDBP (mm Hg) and age in years (Y) are expressed in tens.

With regard to age, 8 of 10 patients were more than 65 years old, and seven were more than 70 years old.

In order to relate age to mortality and events we should consider Terenzio's words: "senectus ipsa est morbus".[29]

In the PI we propose several physiopathologic elements: myocardial perfusion gradient, coronary flow diastolic time, myocardial oxygen consumption, possible adrenergic hyperactivity and many changes due to age.

The PI constitutes a new entity and the results from our study suggest that it is superior to the LVEF in predicting cardiac death and events caused by left ventricular dysfunction after STEMI in 1-year follow-up.

Limitations of the Study

All study designs have some limitations, the following are the limitations of this study:

- the ABPM, even if easy to perform and devoid of adverse events, needs a period of at least 24 hours. In addition, the parameters collection are intermittent, and limited to a maximum of 96 during the 24 hour period.
- this method is not reliable in cases of permanent supraventricular tachyarrhythmias or frequent paroxymal arrhythmias.
- if patients with pacemakers do not have a permanent sinus rhythm and/or atrial tracking function (VAT), the PI is not usefully determinable;
- the population group of the study was limited, and our data will need to be confirmed by further studies.

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