The prognostic value of myocardial viability recognized by low dose dipyridamole echocardiography in patients with chronic ischaemic left ventricular dysfunction

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Aims The aim of this study was to assess the prognostic value of myocardial viability recognized as a contractile response to vasodilator stimulation in patients with left ventricular dysfunction in a large scale, prospective, multicentre, observational study.

Methods and Results Three hundred and seven patients (mean age 60 ± 10 years) with angiographically proven coronary artery disease, previous (>3 months) myocardial infarction and severe left ventricular dysfunction (ejection fraction <35%; mean ejection fraction: 28 ± 7%) were enrolled in the study. Each patient underwent low dose dipyridamole echo (0.28 mg . kg⁻¹ in 4 min). Myocardial viability was identified as an improvement of ≥0.20 in the wall motion score index. By selection, all patients were followed up for a median of 36 months. One-hundred and twenty-four were revascularized either by coronary artery bypass grafting (n=83) or coronary angioplasty (n=41). The only end-point analysed was cardiac death. In the revascularized group, cardiac death occurred in one of the 41 patients with and in 16 of the 83 patients without a viable myocardium (2.4% vs 19.3%, P<0.01). Using a Cox proportional hazards model, the presence of myocardial viability was shown to exert a protective effect on survival (chi-square 4.6, hazard ratio 0.1, 95% CI 0.01–0.8, P<0.03). The survival rate in medically treated patients was lower than in revascularized patients irrespective of the presence of a viable myocardium (79.7% vs 86.2, P=ns).

Conclusion In severe left ventricular ischaemic dysfunction, myocardial viability, as assessed by low dose dipyridamole echo, is associated with improved survival in revascularized patients.

Key Words: Dipyridamole stress echocardiography, myocardial viability, prognosis, revascularization.

See page 803 for the Editorial comment on this article

Introduction

The echocardiographic hallmark of myocardial viability by pharmacological stress echocardiography is
represented by a transient recovery in contractile function, which is present in viable, but not in necrotic tissue. Several studies have documented the ability of pharmacological stress echocardiography, either by an inotropic or by a vasodilator stimulus, to predict functional recovery in patients with left ventricular dysfunction and chronic coronary artery disease after a revascularization procedure[1–12]. Low dose dipyridamole stress echocardiography has been shown to be an effective tool in the detection of myocardial viability[13,14]. In fact, it has been demonstrated that viable segments have a recruitable coronary reserve which, in its turn, is mirrored by inotropic reserve[15]. The diagnostic accuracy of low dose dipyridamole in the detection of myocardial viability is comparable to that elicited by low dose dobutamine stress echocardiography[16,17].

Although it is clinical practice for myocardial viability to be identified by low dose pharmacological stress echo its prognostic meaning remains unclear to date. With the increasing prevalence of ischaemic heart failure, a potentially large population might benefit from intervention based on the results of testing for myocardial viability. At present, however, we are not always sure how to look for it, when to look for it, and its meaning, in terms of prognostic stratification and impact on patient management. The aim of this study was to assess the prognostic value of low dose dipyridamole echo in patients with chronic ischaemic heart disease and global severe left ventricular dysfunction in a prospective, large scale, observational, multicentre, study design. The VIDA (Viability Identification with Dipyridamole Administration) study enrolled 307 patients from 11 centres, all with established experience in stress echo and quality-controlled in stress echo reading.

### Methods

**Patients selection**

The study population consisted of 307 consecutive patients enrolled from 1 January 1995 to 30 June 1997 in each of the participating centres and selected on the basis of the following criteria: (1) angiographically-proven coronary artery disease (>75% reduction of at least one major coronary vessel visually assessed at coronary angiography performed any time prior to study enrolment); (2) chronic ischaemic disease (no acute myocardial infarction in the preceding 3 months, in order to avoid a significant component of stunned myocardium); (3) a global severe left ventricular dysfunction (ejection fraction <35% by the single plane area–length method with 2D echocardiography); and (4) a transthoracic echocardiogram of adequate quality to assess resting regional wall motion (the echocardiogram was considered adequate if >13 out of the maximum total of 16 segments could be visualized). Follow-up information was available in all patients. Demographic characteristics of the study patients are presented in Table 1.

Of the total population of 307 patients, 124 were revascularized and 183 were medically treated. The decision to revascularize was made by the referring physician during the usual work-up of the patients, taking into consideration several variables, including clinical presentation, coronary anatomy, left ventricular function, evidence of ischaemia and documentation of viability by independent techniques such as rest–redistribution Thallium or PET. Stress echo data were collected and analysed by stress echocardiographists who were not involved in patient treatment, either

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<td>WMSI at rest</td>
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<td>WMSI at peak dipyridamole</td>
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<td>Delta WMSI&gt;0.20 (%)</td>
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<td>Coronary anatomy</td>
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<td>three-vessel disease (%)</td>
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WMSI=wall motion score index.

**Table 1**

**Patient characteristics**
surgically or medically. Since the project was investiga-
tive and used a novel protocol for the detection of
myocardial viability, the data were not considered for
clinical decision making.

Resting and stress echo

After an electrocardiogram had been recorded at rest
and intravenous access was secured, all patients under-
went, in the same session at study entry, resting echo and
stress echo during a low dose dipyridamole infusion
(0.28 mg . kg$^{-1}$ over 4 min).

Regional wall motion was assessed according to the
recommendations of the American Society of Echo-
cardiography, using a 16-segment model of the left
ventricle$^{[18]}$. In all studies, segmental wall motion was
semiquantitatively graded as follows: normal=1; mark-
edly hypokinetic, marked reduction of endocardial
motion and thickening=2; akinetic, virtual absence of
inward motion and thickening=3; and dyskinetic, para-
doxical wall motion away from the centre of the left
ventricle in systole=4. It was agreed a priori to ignore
‘mild’ or ‘questionable’ hypokinesia, which was graded
as normal. A wall motion score index was derived by
dividing the sum of individual segment scores by the
number of interpretable segments$^{[18]}$.

A wall motion score index was derived for the rest and
peak stress echocardiograms in all patients, as pre-
viously described for the baseline echocardiographic
examination. A segment was considered to be viable
when it improved by one grade or more at peak stress
(for instance, a hypokinetic segment becoming normal,
or an akinetic segment becoming hypokinetic). In order
to quantify the amount of myocardium showing a
contractile reserve elicited by low dose dipyridamole,
myocardial viability was assessed also according to a
continuous parameter defined as the delta wall motion
score index expressing the difference between the rest
wall motion score index and the low dose wall motion
score index. This parameter provides information, not
only on the presence but also on the extent of contractile
viability, and was used a novel protocol for the detection of
myocardial viability[20]. Patients

Quality control of stress echocardiographic
readings

Quality control of the diagnostic performance in the
different centres was of critical importance to acquire
meaningful information for the data bank. In the en-
rolled centres, the quality control was performed based
upon two criteria, each one having to be met to fulfil the
quality control requirements$^{[19,20]}$.

For the first criterion, 20 stress echo studies were
videotaped in the coordinating centre (Institute of
Clinical Physiology in Pisa). In all 20 studies, the reading
of two experienced independent observers was concord-
ant as to presence and site of dyssynergy, and the stress
results were in full agreement with the presence and site
of coronary stenoses during coronary angiography. The
unanimous reading of the two observers was arbitrarily
assumed to be the ‘gold standard’ against which the
reading of each participating centre was evaluated. The
reader from each centre interpreted the videotape in a
blinded fashion, with no access either to clinical and
angiographic data or to the interpretation given by other
observers. It was assumed a priori that the minimum
threshold of concordance, to pass this part of the quality
control, had to be 90%.

The second criterion consisted of random sampling of
20 consecutive studies from each contributing centre.
These 20 studies were examined in a blinded fashion by an
experienced cardiologist–echocardiographist from the
coordinating centre—whose reading was arbitrarily
assumed to be the ‘gold standard’. It was assumed a
priori that 80% was the minimum threshold of concord-
ance to pass quality control. The lower concordance
cut-off, in comparison with the first reading, was
because this second set of tapes was not selected on the
basis of superior quality but randomly sampled from
each centre in a consecutive fashion.

All the 11 enrolled centres met the minimum
requirements of quality control.

Follow-up data

Follow-up data were obtained from at least one of four
sources: review of the patient’s hospital records, per-
sonal communication with the patient’s physician and
review of the patient’s chart, a telephone interview with
the patient conducted by trained personnel, or patient
visits to staff physicians at regular intervals in the
outpatient clinic. The only event considered was cardiac-
related death. For patients who died in hospital or at
home, the cause of death was elucidated from the
medical record, the family and the local physician who
signed the death certificate. The definition of cardiac-
related death required documentation of significant
arrhythmias or cardiac arrest, or both, or death attribu-
table to congestive heart failure or myocardial infarction
in the absence of any other precipitating factors. In the
case of death out of hospital, for which no autopsy was
performed, sudden unexpected death was attributed to
a cardiac cause. Therefore the outcome events were
all causes of cardiac death for survival. Myocardial
revascularization was performed either by coronary
artery bypass grafting or percutaneous transluminal
angioplasty. Follow-up data were obtained in all patients.

**Statistical analysis**

Results are expressed as mean value ± SD. The individual effect of certain variables on event-free survival was evaluated with the use of the Cox regression model (SPSS Software, 1997). The analysis was performed according to the unmodified forward selection stepwise procedure. In this case, the variables were entered in the model on the basis of a computed significance probability; accordingly, the variable that has the most significant relationship to dependent outcome is selected first for inclusion in the model, and a solution to the functional form of the equation is computed. At the second and subsequent steps, the set of variables remaining at each point is evaluated, and the most significant is included if it improves the prediction of the outcome (dependent variable), but in this case this probability is conditional on the presence of the variable already selected. The algorithm ceases to select variables when there is no further significant improvement in the prediction of the whole model.

Variables selected for examination were: age, gender, history of angina, history of heart failure, history of myocardial infarction, hypertension, hypercholesterolaemia, diabetes mellitus, smoking habit, ejection fraction, revascularization procedures, wall motion score index at rest, rest–low dose stress wall motion score index variation (delta low dose dipyridamole wall motion score index). Continuous variables were compared by the chi-square statistic; a Fisher’s exact test was used when appropriate. Kaplan–Meier life table estimates of spontaneously occurring event-free survival were used to summarize the follow-up experience in these patients and to clarify presentation. Differences of survival curves were tested with the log-rank statistic.

Receiver–operating characteristics analysis was used to determine the ‘optimal’ cut-off value for the prediction of late events, with respect to the wall motion score index at rest and the number of viable segments. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity.

A $P$ value below 0.05 was considered statistically significant.

**Results**

*Feasibility and tolerability of dipyridamole stress echocardiography*

No patient had major complications during the test. The test was completed in all patients. In four patients, low dose dipyridamole was associated with an ischaemic response (worsening of regional wall motion).

![Figure 1 Kaplan–Meier survival curves (with the endpoint as death, only) in patients undergoing coronary revascularization. Myocardial viability could be distinguished by the number of segments which had improved, using as a cut-off value the difference between the resting wall motion score index and the low dose dipyridamole wall motion score index (delta WMSI) set at 0·20. A small amount of viable myocardium is associated with a greater incidence of cardiac death ($P<0.01$).](image)

**Rest and low dose findings**

The resting wall motion score index was 2·25 ± 0·36. Following dipyridamole, the wall motion score index was 2·12 ± 0·39 ($P<0.01$ vs rest wall motion score index). Seventy-seven patients (25% of the total population) had a delta low dose wall motion score index higher than or equal to 0·20, with an inotropic response to low dose dipyridamole in at least four segments on resting dysfunction. In the revascularized group (n=124) viability was present in 41 (33%) patients.

**Follow-up data: cardiac-related death**

Patients were followed-up for a median of 36 months (range:1–39). During the follow-up, there were 54 cardiac deaths. In the revascularized group, cardiac death occurred in one of the 41 patients with and in 16 of the 83 patients without a viable myocardium (2·4% vs 19·3%, $P<0.01$). Kaplan–Meier survival estimates showed a better outcome for patients with, compared to patients without, a viable myocardium who underwent coronary revascularization (97·6% vs 77·4%, $P=0·01$). In Fig. 1, the cumulative survival rates in patients with a high grade of myocardial viability (delta wall motion score index $\geq$ 0·20) vs those with a low grade or no viability (delta wall motion score index < 0·20) are shown. At the univariate analysis, in the revascularized group, myocardial viability was the only significant variable. In the stepwise analysis, the only independent predictor was the presence of myocardial viability exerting a protective effect on survival (chi-square 4·6, hazard ratio 0·1; 95% CI 0·01–0·8, $P<0·03$) (Table 2). The sensitivity and specificity of the test for the prediction of death at the cut-off value of 0·20 was 94% and 38%.
left ventricular dysfunction and extensive viability treated with revascularization are more likely to survive than medically treated patients\cite{21-28}. A protective effect has been documented when myocardial viability is recognized with either nuclear medicine\cite{21-26} or stress echo techniques\cite{27,28}. The main finding of the present study, i.e. the striking protective effect of myocardial viability on survival of revascularized patients, is in keeping with the available evidence. Some peculiarities of the present study should, however, be considered: (1) the sample size of 307 patients, which is one of the largest populations studied to date; (2) the strict enrolment criteria, allowing only patients with documented coronary artery disease to be included, rather than patients with unknown coronary anatomy or idiopathic cardiomyopathy, as in other series\cite{22}; (3) the inclusion of patients studied >3 months after a myocardial infarction, thus excluding patients with a significant stunning phenomena linked to recent myocardial infarction; (4) the use of an ischaemic stressor alternative to dobutamine, such as dipyridamole, allowing myocardial viability to be studied through a pharmacological tool totally unrelated to beta-adrenoreceptor myocyte density rather than to adenosine accumulation\cite{14}; (5) finally, the study design — prospective multicentre, with peripheral readings from quality control centres — allowed the ‘effectiveness’ of the prospective value of low dose stress echocardiography to be assessed.

Improved survival in revascularized patients: the pathophysiological rationale

Our patients, with severe resting dysfunction submitted to revascularization, had a clearly better survival when a significant amount of viable myocardium could be detected before revascularization by low dose pharmacological stress echo. In our study, low dose functional recovery translates into a survival benefit for revascularized patients — all of whom had depressed left ventricular function at study entry. The relationship between the risk of cardiac death and the reduction in ventricular function shows a hyperbolic trend\cite{29}; our patient population was located in the steep segment of the curve, where it is possible that an improvement in regional function obtained with a revascularization procedure is likely to translate into a dramatic improvement of prognosis. The high surgical risk in this population is outweighed by a long-term improvement of survival when a large amount of dysfunctional but viable myocardium is present. The absence of viable myocardium downstream of a critical coronary artery stenosis substantially weakens the indication for revascularization and directs clinical decisions towards medical therapy or — when possible — cardiac transplantation.

Discussion

In patients with severe left ventricular dysfunction undergoing coronary revascularization, the presence and extent of myocardial viability identified by low dose dipyridamole is associated with a higher probability of survival. The extent of myocardial viability is related to better survival when a high number of segments transiently improve their function with low dose stress echocardiography. In the present population, no other clinical variable and/or resting echo parameter was able to predict the outcome. When coronary revascularization was undertaken in the absence, or with a small area of viable myocardium, the procedure was linked to a higher incidence of cardiac death.

Comparison with previous studies

The rapidly growing literature on the prognostic value of myocardial viability suggests that patients with global

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<th>Table 2</th>
<th>Stepwise predictors of cardiac death in revascularized patients</th>
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<tr>
<td>Chi-square</td>
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<td>Δ WMSI &gt; 0·20</td>
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WMSI = wall motion score index; HR = hazard ratio.

Figure 2 Kaplan–Meier survival curves (with the endpoint as death, only) in medically treated patients. Myocardial viability could be distinguished by the number of segments which had improved, using as a cut-off value the difference between the resting wall motion score index and the low dose dipyridamole wall motion score index (Δ WMSI) set at 0·20. The presence of viable myocardium is not related to better survival (P=ns).

183 medically treated patients

Time (months)

Cumulative survival (%) 0 10 20 30 40 50 60 70 80 90 100

Δ WMSI > 0·20 (74·8%) 74·8% 70·8% 66·8% 62·8% 58·8% 54·8% 50·8% 46·8% 42·8% 38·8% 34·8%

Δ WMSI < 0·20 (64·2%) 64·2% 60·2% 56·2% 52·2% 48·2% 44·2% 40·2% 36·2% 32·2% 28·2% 24·2%

183 medically treated patients

Comparison with previous studies

The rapidly growing literature on the prognostic value of myocardial viability suggests that patients with global

Study limitations

The patient population underwent coronary revascularization on the basis of standard clinical criteria and
independent of the stress echo result. Patients were not allocated to a treatment in a randomized fashion but according to the clinical judgement of the referring physician; nonetheless there were no significant differences among the study groups relative to global ventricular function, medical treatment and coronary anatomy. The study design was observational, and did not interfere with patient management. The information on myocardial viability recognized by low dose stress echocardiography was not considered in the decision to revascularize, since at the time of data acquisition, physicians ignored the meaning of this parameter in terms of potential benefit at long-term follow-up. There is now an emerging body of literature that suggests that patients who are revascularized have a better prognosis, but the evidence was not as firm and universally accepted at the time of data collection as today.

The decision to revascularize a patient is complex and multifactorial, taking into account many different variables, including clinical presentation, coronary anatomy, left ventricular function, evidence of ischaemia, and documentation of viability by several different independent techniques. In addition, local access to invasive procedures can vary widely. Even when all these variables were kept constant — in the very same centre — there was vast room for opinion, intuition and bias. We used a vasodilator stressor for the detection of myocardial viability, dipyridamole, a less conventional stressor for the detection of myocardial viability than dobutamine, but with some advantages over it: first, the infra-low dose used in the present study is hardly an ischaemic dosage; in fact only four patients out of 307 developed myocardial ischaemia; second, the infra-low dose is not influenced by beta-blocking treatment (23% in our patient population)130, widely employed today in patients with global ventricular dysfunction and coronary artery disease.

We used a cut-off value for the detection of myocardial viability, translating a continuous variable into a dichotomous one: a 0-20 value corresponds on average to four segments showing viability, which is equivalent to 25% of the ventricle.

Clinical implications

Patients with chronic coronary artery disease and severe left ventricular dysfunction represent a common, and increasingly frequent, problem in modern cardiological practice. The documentation of an extensive inotropic response by low dose dipyridamole stress echo in these patients carries important diagnostic, prognostic and therapeutic indications. From the diagnostic viewpoint, the inotropic response identifies myocardial viability and a high likelihood of recovery upon revascularization. From the prognostic viewpoint, an important inotropic response is associated with a substantially better survival with revascularization therapy, and with a trend to better survival with medical therapy. From the therapeutic viewpoint, the greater the amount of viable myocardium detected, the tighter the indication to revascularize these patients. More viability means lower acute risk and better long-term survival following revascularization. On the basis of the present results and consistent with nuclear medicine findings, the prognostic protection conferred by viability is only detected when it exceeds a critical threshold of at least four segments with resting dysfunction24,31.

In striking contrast with the beneficial value shown in revascularized patients, a dipyridamole-induced contractile response lacked prognostic prediction in patients who were not revascularized. This result might appear to conflict with the potentially substantial protective effect of myocardial viability, as already demonstrated in patients evaluated early after an acute myocardial infarction20,21. Nonetheless the meaning of myocardial viability in medically treated patients with severe chronic left ventricular dysfunction and coronary artery disease is controversial and the large body of evidence present in the literature has not provided sound and consistent results up to now.22. The real prognostic meaning of myocardial viability in medically treated patients with coronary artery disease remains uncertain to date, with some studies representing a detrimental, others a neutral, and still others a beneficial effect on survival23,25-26,32-36. In a preliminary report of the VIDA study — subproject Dobutamine stress echo study37, 204 medically treated patients with chronic ischaemic left ventricular dysfunction, had a better survival in the presence of a large area of viable myocardium (A wall motion score index ≥0.18) compared to those with a small area or no myocardial viability (A wall motion score index <0.18) (70-8% vs 53-9%, P<0.02). It is also possible that, due to the non-randomized nature of the study, some form of referral bias was unavoidable leading to the exclusion from revascularization of ‘sicker’ patients with viable myocardium.

The consequences of these clinical implications are far-reaching. Low dose dipyridamole stress echo should allow removal of some patients (those with severe left ventricular dysfunction and evidence of myocardial viability) from the cardiac transplant list, reorienting some of them towards the more accessible and less expensive coronary revascularization. Therefore, in the clinical framework of ischaemic cardiomyopathy, myocardial viability has to be taken into consideration along with the conventional clinical variables such as coronary anatomy, ejection fraction and inducible ischaemia to orient the treatment of the patients with left ventricular dysfunction. The presence of myocardial viability can guide the clinical cardiologist, but only when a considerable amount of it is detectable. In fact, similar to ischaemia, a viable response can be titrated: it is not a binary, dichotomous answer but a continuous response that should be titrated in different shades of gray.

References

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