

Usefulness of Parametric Imaging-Based Quantitative Myocardial Contrast Echocardiography in Predicting the Functional Recovery of Akinetic Segments Following Primary Angioplasty in Acute Myocardial Infarction Patients

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Introduction and objectives. Myocardial contrast echocardiography (MCE) is useful for predicting the functional recovery of akinetic segments in patients undergoing primary angioplasty after acute myocardial infarction (AMI). Recently, parametric imaging-based quantitative MCE has been developed for measuring perfusion. Our aims were: *a*) to measure perfusion in akinetic myocardial segments in patients undergoing primary angioplasty using parametric imaging-based quantitative MCE, and *b*) to assess the usefulness of these measurements in predicting functional recovery of these segments.

Patients and method. The study group comprised 49 consecutive patients undergoing primary angioplasty. Both MCE and standard echocardiography were performed between 2 and 5 days after AMI. Six months later, additional standard echocardiography and coronary angiography were performed. Perfusion was quantified independently off-line from parametric images.

Results. The patients' mean age was 62.3 ± 14.5 years (39 men; 79.2%). Some 170 akinetic segments were detected. Of these, 105 (62.1%) recovered function. The quantitative MCE parameter that best predicted functional recovery was myocardial blood flow velocity (β): the area under the receiver operating characteristic (ROC) curve was 0.96 (95% CI, 0.92-0.99). For a cut-off point of 31 dB/s, the sensitivity was 87.62%, the specificity was 95.31%, the positive predictive value was 96.8%, and the negative predictive value was 82.43%. These results were better than those obtained using qualitative methods for assessing myocardial perfusion.

Conclusions. Perfusion measurement by parametric imaging-based quantitative MCE is useful for predicting the functional recovery of akinetic segments in patients undergoing primary angioplasty after AMI. The technique provides superior information to older qualitative methods.

Key words: *Echocardiography. Perfusion. Myocardial infarction.*

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Utilidad de la ecocardiografía de contraste miocárdico con cuantificación basada en imagen paramétrica para la predicción de la recuperación funcional de segmentos acinéticos en pacientes con infarto agudo de miocardio sometidos a angioplastia primaria

Introducción y objetivos. La ecocardiografía de contraste miocárdico (ECM) es útil para predecir la recuperación funcional de los segmentos acinéticos en pacientes que reciben una angioplastia coronaria transluminal percutánea primaria. Se ha desarrollado recientemente la imagen paramétrica para la cuantificación de la perfusión. Los objetivos son: *a*) valorar de forma cuantitativa la perfusión de los segmentos acinéticos en pacientes que reciben angioplastia primaria, y *b*) evaluar la utilidad de la cuantificación con imagen paramétrica para predecir la recuperación funcional de los segmentos acinéticos.

Pacientes y método. Se analizó a 49 pacientes con infarto agudo de miocardio (IAM) que recibieron angioplastia primaria. Se realizó ecocardiograma estándar y ECM entre los 2 y 5 días posteriores al IAM. Se realizaron ecocardiograma estándar y cateterismo a los 6 meses. La evaluación cualitativa y cuantitativa fue realizada *off-line* por 2 investigadores independientes.

Resultados. La edad media fue de $62,3 \pm 14,5$ años (39 varones). En el estudio basal se detectaron 170 segmentos acinéticos. La recuperación funcional fue observada en 105 segmentos. El mejor parámetro cuantitativo para predecir la recuperación funcional fue la velocidad del flujo sanguíneo (β): el área bajo la curva ROC fue 0,96 (intervalo de confianza del 95%, 0,92-0,99). Para un punto de corte de 31dB/s, la sensibilidad fue del 87,62%, la especificidad del 95,31%, el valor predictivo positivo del 96,8% y el valor predictivo negativo del 82,43%. Estos resultados son mejores que los obtenidos con el método cualitativo.

Conclusiones. La cuantificación de la perfusión con imagen paramétrica es una herramienta útil para predecir la recuperación funcional de los segmentos acinéticos en pacientes que reciben angioplastia coronaria transluminal percutánea primaria y es mejor que la valoración cualitativa.

Palabras clave: *Ecocardiografía. Perfusion. Infarto de miocardio.*

ABBREVIATIONS

AMI: acute myocardial infarction.
 MCE: myocardial contrast echocardiography.
 TIMI: thrombolysis in myocardial infarction.

INTRODUCTION

Reperfusion therapy with primary angioplasty has contributed to reduced morbidity and mortality in patients with acute myocardial infarction (AMI).¹ The speed and extent of microvascular flow restoration are related to eventual functional recovery of affected segments. Viable areas are identified by detecting microcirculation integrity.²⁻⁴ However, restoration of contractile function depends on the proportion of myocardium saved and, therefore, on the percentage of microvascular flow.

Myocardial contrast echocardiography (MCE) is a technique currently under development that has shown its usefulness in identifying viable tissue.^{5,6} Prediction of functional recovery using MCE has been evaluated in several studies⁷⁻⁹ but to our knowledge, measurement of perfusion has been qualitative or semi-quantitative.

The development of techniques that use bubble behavior to measure parameters such as volume, myocardial blood flow and myocardial filling time has led to advances in detecting microvascular dysfunction.¹⁰

New, recently-developed software (Q-lab, Philips, Andover, USA) provides color-coded parametric imaging of the myocardium. This produces a 4-color map: 1 color represents myocardial blood volume (a); a second, myocardial blood flow velocity; a third, myocardial blood flow ($\alpha \times \beta$); and the fourth maps data quality at each point in the region of interest (Figure 1).

The objectives of our study were:

1. To quantify myocardial perfusion of akinetic segments in patients with AMI undergoing primary angioplasty.
2. To determine the usefulness of parametric imaging-based measurement to predict functional recovery of akinetic segments.

PATIENTS AND METHODS

Study Design

We recruited 49 consecutive patients diagnosed with AMI and undergoing primary angioplasty who presented none of the exclusion criteria and were scheduled for coronary angiography at 6-month follow-up. Following our standard protocol for this group, patients underwent a perfusion study using 2-dimensional contrast echocardiography at 2-5 days post-infarction. At 6 months, they underwent another coronary angiography and standard echocardiography.

Population

We performed a prospective analysis of 49 patients admitted with a diagnosis of AMI and undergoing primary angioplasty.

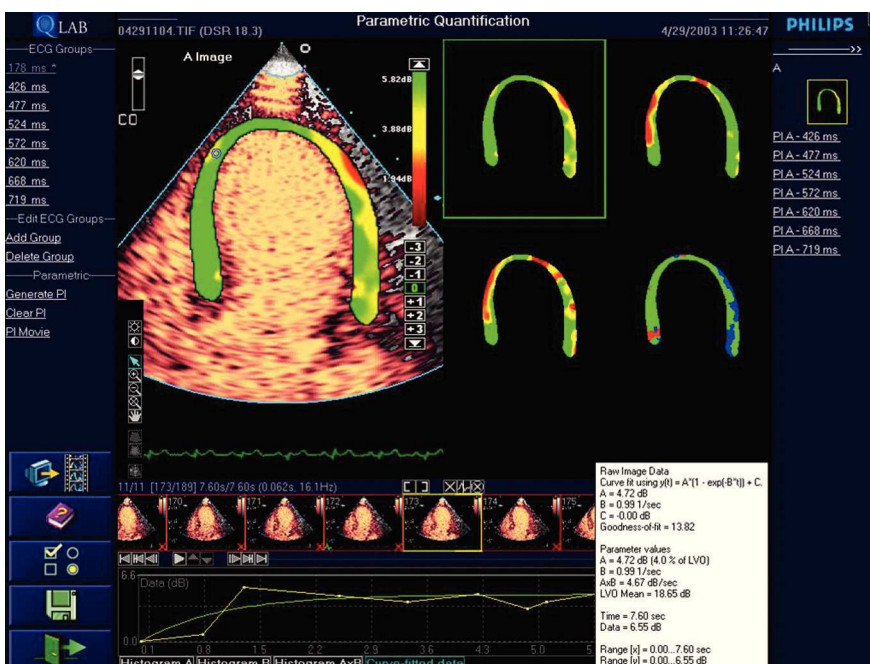


Figure 1. Parametric image of myocardium. The parametric image provides 4 color maps: one represents myocardial blood volume (top left); another blood flow velocity (top right); another myocardial blood flow (bottom left); and the fourth is a map of data quality at each point (bottom right).

Diagnosis of AMI was based on 2 of the following criteria:

- Characteristic precordial pain >30 min.
- ST-segment elevation of 2 mm in at least 2 adjacent leads.
- MB isoenzyme of creatin kinase (CK-MB) elevation to twice reference levels.

Exclusion criteria included: presence of previous infarction, poor acoustic window, hemodynamic instability, and patient refusal to be included in the protocol.

Coronary Angiography

After diagnosis of AMI, all patients underwent urgent coronary angiography following our hospital protocol. Decisions on revascularization procedures, stenting, and administration of antiplatelet agents were the responsibility of the medical team attending.

After primary angioplasty, flow in the infarction-related vessel was determined with the Thrombolysis in Myocardial Infarction Trial (TIMI) classification. Procedures were considered successful when TIMI grade 3 flow and residual stenosis <50% were present.

Coronary angiography was performed to monitor the procedure at 6 months post-infarction. Restenosis was considered to have occurred when a luminal reduction of $\geq 70\%$ was found.

Echocardiographic Study

Echocardiography was performed with a Philips 5500 version C.1 unit with S3 sound. Images obtained were stored on disc.

Standard Echocardiography

All patients underwent baseline echocardiography with harmonic imaging, which determined regional wall motion in the apical 2- and 4-chamber views according to the American Society of Echocardiography recommendations.¹¹ Interpretations were defined as: 1 = normokinesia, 2 = hypokinesia, 3 = akinesia, and 4 = dyskinesia.

Evaluation of regional wall motion was done by 2 independent researchers. The opinion of a third researcher was called upon to resolve disagreements.

Intramyocardial Contrast Echocardiography

All patients underwent real time myocardial contrast echocardiography 48 hours after the onset of symptoms. The 48 hour delay was employed because prior to this hyperemia can cause hemodynamic changes.^{12,13}

We used Sonovue[®] contrast agent, a suspension of micro-bubbles whose active product is sulphur hexafluoride, an innocuous gas eliminated through the respiratory system. The product is presented in the form of particles that activate when added to a saline solution and shaken vigorously for 30 seconds. Administration of the contrast agent was by continuous infusion using a specially designed perfusion pump that continually shakes the product to ensure its efficacy. The dose administered varied from 0.8 to 1.2 mL/m (depending on body surface) until the myocardial segments were suitably opaque. No adverse effects occurred in connection with use of the contrast agent.

All patients were informed of the protocol and gave their consent prior to inclusion in the study.

Perfusion Echocardiography

Perfusion was measured in real time using the Power modulation method that has previously been demonstrated to be a valid means of detecting myocardial perfusion.^{14,15}

The imaging protocol includes 20 consecutive cycles after the activation of an impulse of 5-10 high mechanical index cycles. Imaging starts after the flash, when the myocardial bubbles have been destroyed, in order to measure the myocardium filling with micro-bubbles.

Quantitative Evaluation of Perfusion

Off-line quantitative analysis of perfusion was performed by 2 independent researchers, experienced in contrast echocardiography using Q-Lab software.

Measurement (Figure 1) involved a series of steps: first, the area of the myocardium was selected in the apical 2- and 4-chamber views (using a manual trace). Second, an automatic selection was made of all of frames corresponding to the same cycle (end-systole) for 20 beats. From this selection, the Q-Lab software provided 3 parametric images corresponding to color maps that represent the various parameters studied, and a fourth image for quality control. In the first 3 maps, the A parameters (*plateau*), β (velocity of myocardial filling by the micro-bubbles) and $A \times \beta$, are represented by a scale of colors at each point on the myocardium. The colors show the degree of perfusion: green = normal, yellow = reduced, and red = absence of perfusion. The fourth image gives information about data quality at each point. The great advantage of this measurement procedure is that it avoids measuring zones where quality is inadequate.

Qualitative Evaluation of Perfusion

Qualitative analysis of perfusion in akinetic segments was performed by 2 independent observers with

a third called to settle any disagreement. Measurements were classified as normal or abnormal. Abnormal was defined as when the segment presented absence of perfusion or patchy (heterogeneous) perfusion; normal was defined as when perfusion was complete (homogeneous).

Follow-up

All patients underwent coronary angiography and standard echocardiography at 6 months post-revascularization.

Interobserver and Intraobserver Analysis

We randomly selected 20 studies for analysis on different days by the same observer to determine intraobserver variability. These studies were also analyzed by an independent observer to determine interobserver agreement. Both investigators were blinded to the results of analysis prior to the studies.

Statistical Analysis

Statistical analysis was performed with SPSS 11.0. Quantitative variables were analyzed as mean \pm standard deviation and qualitative variables as percentages.

To study the association between 2 quantitative variables we used the intraclass correlation coefficient. Reproducibility was considered almost perfect if the coefficient was between 0.81 and 1.0. We constructed ROC curves to determine the optimal cutoff point using the prevalence of the sample of patients in the study with equal weight given to false positives and false negatives. The cutoff point chosen was that which in each case maximized the percentage of correct classifications. Statistical significance was defined as $P < .05$.

RESULTS

Baseline Characteristics

We excluded 9 of the 58 patients enrolled due to poor acoustic window (3), acute coronary syndrome during follow-up (2) and significant restenosis of the culprit artery (4), leaving 49 in the study group.

Mean age was 62.3 ± 14.5 years and 39 (79.6%) patients were men. Mean time to catheterization was 5.6 ± 2 hours following onset of symptoms. Post-infarction ejection fraction was 46 ± 2 . Post-AMI regional wall-motion score index was 2.6 ± 1.2 . Patients' baseline characteristics are shown in Table 1.

Quantitative Analysis of Akinetic Segments

Baseline analysis of regional wall motion detected

170 akinetic segments of which 105 (62.1%) had recovered function at 6-month follow-up. At 6 months, ejection fraction was 48 ± 9 and regional wall-motion index was 2.1 ± 0.9 . Results of parametric imaging-based quantitative evaluation of akinetic segments appear in Table 2. Comparison of 2 groups (with and without functional recovery of akinetic segments) shows a statistically significant difference.

Qualitative Analysis of Akinetic Segments

Results of qualitative analysis were: sensitivity 81%, specificity 79.7%, positive predictive value 86.7% and negative predictive value 71.8% (Table 3).

Intraobserver and Interobserver Variability

Analysis of A, β , and $A \times \beta$ indicated good interobserver reproducibility. Intraclass coefficient correlations were 0.82, 0.9, and 0.85 for A, β , and $A \times \beta$, res-

TABLE 1. Baseline Characteristics*

Variable	Absolute Value (Percentage), Mean \pm SD
Age, years	62.3 \pm 14.5
Men	39 (79.6)
Sinus rhythm/atrial fibrillation	5 (20.2)/44 (79.8)
Previous PTCA	1 (2)
Previous revascularization surgery	0
Pre-AMI angina	15 (30.6)
Risk factors	
Hypertension	21 (42.9)
Diabetes	8 (16.3)
Hyperlipidemia	20 (40.8)
Smoking	25 (51)
Biochemical parameters	
CK peak	1550 \pm 1415
Troponin peak	49.6 \pm 66
Angiographic parameters	
TIMI flow <3 prior to primary PTCA	40 (79.5)
TIMI flow <3 following primary PTCA	2 (4.1)
Presence of collateral circulation	13 (26.5)
Vessel responsible	
Left anterior descending artery	22 (44.9)
Right coronary artery	18 (36.7)
Circumflex	9 (18.4)
Use of anti-IIb-IIIa agents	16 (32.7)
Use of stent	44 (89.8)
Echocardiographic parameters	
LVEF	46 \pm 2
LVEDV	88 \pm 4
LVESV volume	44 \pm 3
RWMSI	

*PTCA indicates percutaneous transluminal coronary angioplasty; CK, creatinase; LVEF, left ventricular ejection fraction; RWMSI, regional wall-motion index; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

pectively. Intraobserver reproducibility was also good: 0.9, 0.9, and 0.8 for A, β , and $A \times \beta$, respectively.

Relationship Between Quantitative Analysis of Myocardial Perfusion and Functional Recovery of Akinetic Segments

We constructed ROC curves to determine the validity of the different parameters in predicting functional recovery of akinetic segments (Figure 2). Table 3 shows that measuring β was the best parameter to predict recovery of regional wall motion. The area under the ROC curve for β was 0.96 (confidence interval [CI] 95%, 0.92-0.99) for a cutoff point of 31 s^{-1} , sensibility was 87.6%, specificity 95.3%, positive predictive value 96.8%, and negative predictive value 82.4%.

DISCUSSION

The objective of primary angioplasty is to restore flow in the infarction-related artery, limit the area of necrosis and preserve contractile function.

How much myocardium is saved heavily depends on blood flow in the area at risk. In fact, permeability of the myocardial artery is not synonymous with normal microcirculation flow and different degrees of microvascular dysfunction may exist, such as no-reflow or limited reflow. In fact, microvascular dysfunction in the area at risk is an independent predictor of remodeling and worse long-term clinical evolution.¹⁶

Standard echocardiography comes first in the functional study of affected segments as it enables us to evaluate wall motion and thickness. Improved detection of boundaries thanks to harmonic imaging and, sometimes, the addition of a contrast agent, usually

leads to correct evaluation of global and regional left ventricular function. However, standard echocardiography cannot be used to identify the pathophysiological mechanism of segments that remain akinetic. Moreover, in the presence of myocardial stunning, functional recovery can require days or weeks.¹⁷ Distinguishing between stunning and necrosis is relevant to management of patients with severe systolic dysfunction or cardiogenic shock following revascularization.

Myocardial contrast echocardiography has proved a useful technique in the study of coronary microcirculation in patients with AMI and is a valuable tool to predict functional recovery of akinetic segments.^{18,19}

Given that the contrast agent is a pure, intravascular tracer, techniques for measuring blood volume, blood flow and recirculation velocity have been developed. The application of these permits a more objective and more easily reproducible evaluation of degree of perfusion. Finally, parametric imaging has become a new method of obtaining quantitative images of microcirculation flow.²⁰

Our results on the value of MCE to predict functional recovery of akinetic segments in patients with AMI coincide with those reported elsewhere.^{7,8-20} However, to our knowledge this is the first study of perfusion with quantification of myocardial flow in this group of patients.

The value of our study design is that:

1. Real-time imaging has demonstrated itself a valid means of detecting perfusion and is technically simple, meaning it can be employed by less well-trained personnel.

2. The use of an infusion pump specially designed for the contrast agent used *a)* assures optimal performance of the agent which, as it is permanently shaken, maintains its echogenic properties over the period of

TABLE 2. Parametric Imaging-Based Quantitative Parameters of Myocardial Perfusion*

	1. Functional Recovery	2. Without Functional Recovery	3. Total	P (1 vs 2)
A	481±3	354.5±176	433±175	<.001
β	51.6±3	22±6	40.33±25.1	<.001
$A \times \beta$	24 636±15 281	7779.7±4100	106 650±18 230	<.001

*A indicates myocardial blood volume; β , myocardial blood flow velocity; $A \times \beta$: myocardial blood flow

TABLE 3. Parameters Representing Diagnostic Benefits of the Variables Evaluated*

	ABC, 95% CI	Cutoff	Sensitivity,%	Specificity,%	PPV,%	NPV,%
A	0.8 (0.7-0.8)	308 dB	89.5	50	74.6	74.4
β	0.96 (0.9-0.99)	31 s^{-1}	87.6	95.3	96.8	82.4
$A \times \beta$	0.9 (0.9-1.0)	10 574 dB/s	92.4	81.3	88.9	86.7
MCE.Q			81	79.7	86.7	71.8

*A indicates myocardial blood volume; ABC, area under the (ROC) curve; $A \times \beta$, myocardial blood flow; β , myocardial blood flow; CI, confidence interval; MCE.Q, myocardial contrast echocardiography. Qualitative analysis; NPV, negative predictive value; PPV, positive predictive value.

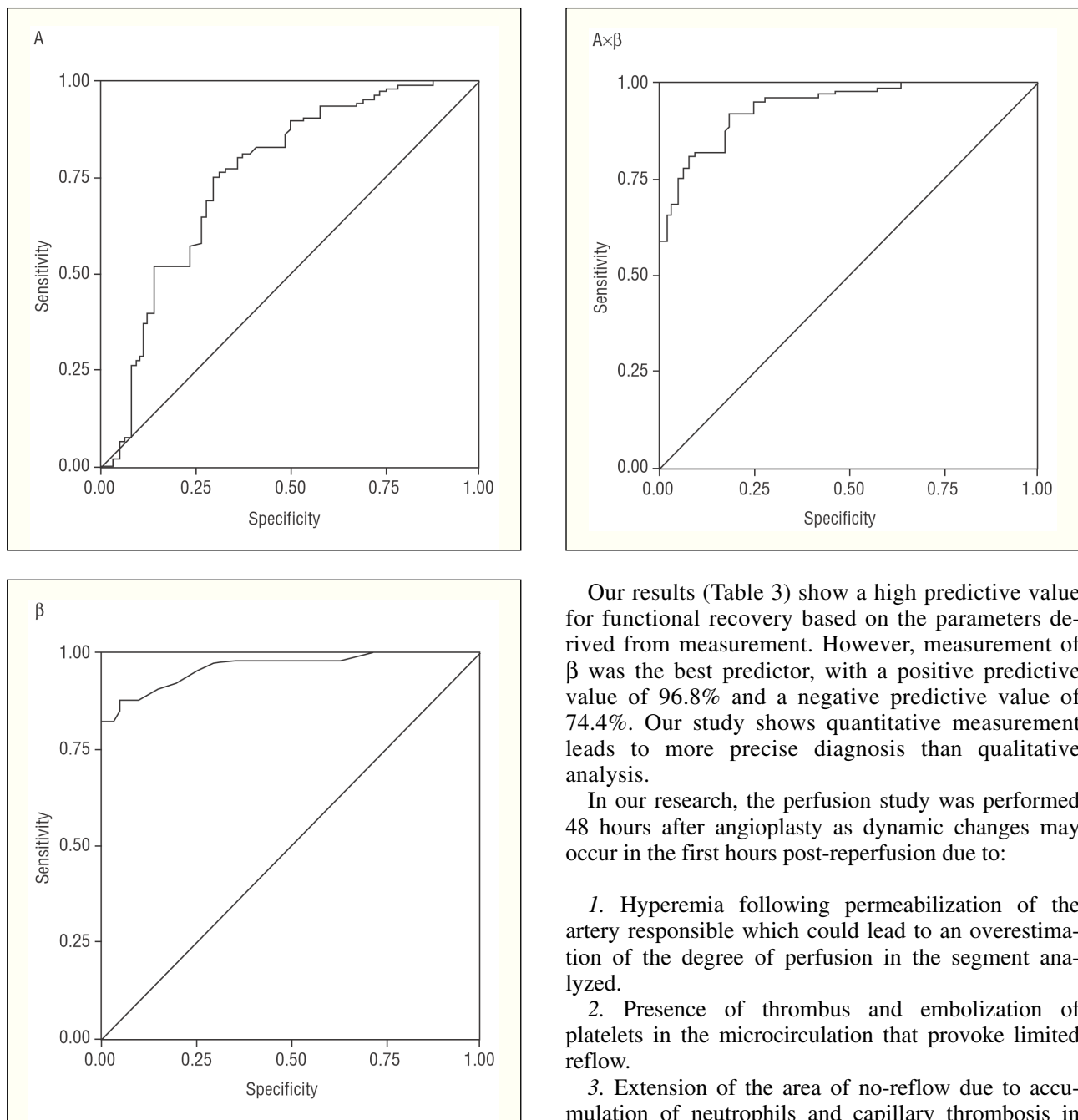


Figure 2. ROC curves of the different quantitative parameters obtained with parametric imaging (A, β , and $A \times \beta$) in the prediction of functional recovery of akinetic segments at 6 months.

the study, and *b*) maintains a constant perfusion index, which is especially relevant in quantifying degree of perfusion.²¹

3. A quantitative method provides a more reproducible evaluation.

4. Parametric imaging-based quantification (Q-Lab software) detects possible zones of error or artifact where quantitative measurement is inappropriate.

Our results (Table 3) show a high predictive value for functional recovery based on the parameters derived from measurement. However, measurement of β was the best predictor, with a positive predictive value of 96.8% and a negative predictive value of 74.4%. Our study shows quantitative measurement leads to more precise diagnosis than qualitative analysis.

In our research, the perfusion study was performed 48 hours after angioplasty as dynamic changes may occur in the first hours post-reperfusion due to:

1. Hyperemia following permeabilization of the artery responsible which could lead to an overestimation of the degree of perfusion in the segment analyzed.
2. Presence of thrombus and embolization of platelets in the microcirculation that provoke limited reflow.
3. Extension of the area of no-reflow due to accumulation of neutrophils and capillary thrombosis in the course of reperfusion.
4. Intramyocardial bleeding due to microvascular damage.²²

Sakuma et al²³ showed the optimal time for a perfusion study following AMI is 1 day post-recanalization.²³ Balcells et al⁸ found that perfusion measured 3-5 days post-angioplasty gave results almost identical to those found in the chronic phase.

After follow-up coronary angiography performed 6 months following discharge, we excluded 4 patients who presented restenosis reducing the final sample to 49 patients without significant lesion in the vessel responsible. Consequently, we can affirm that the

lack of functional recovery of segments that remained akinetic was not related to a new, significant epicardial lesion.

Clinical Implications

Myocardial contrast echocardiography is a simple, feasible, low cost technique that can be used in the first days post-AMI. This is especially important in patients with severely depressed systolic function as confirmation of necrosis in akinetic segments could lead to the use of certain therapies, such as automatic defibrillator implantation, prior to discharge. This would not even be considered in patients with a high probability of functional recovery.

CONCLUSIONS

Measurement of myocardial perfusion by contrast echocardiography and parametric imaging permits us to predict functional recovery of akinetic segments after myocardial infarction. The technique is more sensitive and specific than the traditional, quantitative evaluation of myocardial perfusion.

Limitations

After completion of our study and at the time of writing, the use of Sonoveu[®] has been contraindicated in patients with recent acute coronary syndrome or unstable ischemic heart disease, including evolving myocardial infarction, typical at-rest angina in the previous 7 days, significant worsening of cardiac symptoms in the previous 7 days, recent coronary intervention, or other factors suggesting clinical instability (e.g. recent deterioration of electrocardiographic, laboratory or clinical findings), functional class III/IV acute heart failure or severe arrhythmias. However, we believe our results can be extrapolated to the use of other second generation contrast agents.

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