

# Prognostic Value of Infarct Size Measured by Gated SPECT Scintigraphy

## Valor pronóstico del tamaño del infarto de miocardio cuantificado mediante SPECT gatillada

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### ABSTRACT

**Background:** Despite the improved sensitivity and specificity of SPECT myocardial perfusion imaging to detect myocardial involvement after acute myocardial infarction (AMI), there is little information about the usefulness of early infarct size (IS) measurement by this method for risk stratification and prognosis.

**Objectives:** The goal of this study was to evaluate the usefulness of quantifying IS by gated SPECT scintigraphy to predict cardiovascular events in patients with a first AMI.

**Methods:** Patients with a first ST-segment elevation AMI were included from 2009 to 2014. Infarct size was estimated using the Cedars QPS software. The incidence of events (heart failure, ventricular arrhythmias, mortality and a composite of the three events) was evaluated at one year.

**Results:** One-hundred and forty nine patients were included in the study; mean age was  $59 \pm 11$  years and 81.9% were men. Diabetes was present in 16.1% of cases, 9.4% had a history of myocardial revascularization, 84.6% were admitted in Killip and Kimball class A, 43% of AMIs were located in the anterior wall and 69.8% of the patients underwent reperfusion. Left ventricular ejection fraction estimated by gated SPECT scintigraphy was  $51\% \pm 14\%$ . Follow-up was completed in 95.9% of cases. An IS cutoff point of 22% (ROC curve) was established to predict the composite endpoint at follow-up (sensitivity 92%, specificity 81%, AUC: 0.94%), dividing the sample into two groups: Group I (IS <22%) and Group II (IS  $\geq$ 22%). The prevalence of the composite endpoint was greater in Group II (2.1% Group I vs. 50% Group II;  $p < 0.001$ ). Infarct size  $\geq 22\%$  was the only variable identified as predictor of events during follow-up (OR 1.978; 95% CI 1.887-1.996;  $p < 0.001$ ).

**Conclusion:** Early quantification of IS by gated SPECT scintigraphy is an independent risk predictor at one year that allows risk stratification in patients with a first AMI.

**Keywords:** Myocardial Infarction/physiopathology - Cardiac Gated Single-photon Emission Computer Assisted Tomography - Prognosis

### RESUMEN

**Introducción:** Si bien la SPECT de perfusión miocárdica ha mejorado la sensibilidad y la especificidad en la detección del compromiso miocárdico luego de un infarto agudo de miocardio (IAM), aún es escasa la información sobre la determinación precoz del tamaño del infarto (TI) con este método para la estratificación del riesgo y su valor pronóstico.

**Objetivos:** Evaluar la utilidad de la cuantificación del TI estimado por SPECT gatillada en la predicción de complicaciones cardiovasculares en pacientes con un primer IAM.

**Material y métodos:** Se analizaron los pacientes con IAM con elevación del ST desde 2009 a 2014, excluyéndose aquellos con IAM previo. El cálculo del TI se realizó con el software Cedars QPS. Se evaluaron eventos al año: insuficiencia cardíaca, arritmias ventriculares, muerte y la combinación de los tres eventos.

**Resultados:** Se incluyeron 149 pacientes, con edad media de  $59 \pm 11$  años, el 81,9% de sexo masculino. El 16,1% eran diabéticos y el 9,4% presentaban revascularización previa. El 84,6% ingresaron en Killip y Kimball A, el 43% de los IAM fueron de territorio anterior y el 69,8% de los pacientes fueron reperfundidos. La fracción de eyección del ventrículo izquierdo por SPECT gatillada fue del  $51\% \pm 14\%$ . Se realizó seguimiento clínico en el 95,9% de los casos. El punto de corte del TI (curva ROC) para predecir eventos combinados al seguimiento se estableció en 22% (sensibilidad: 92%, especificidad: 81%, ABC: 0,94), con el cual la muestra se dividió en dos grupos: Grupo I (TI <22%) y Grupo II (TI  $\geq$ 22%). La prevalencia de eventos combinados fue mayor en el Grupo II (2,1% Grupo I vs. 50% Grupo II;  $p < 0,001$ ). El TI  $\geq 22\%$  se identificó como la única variable predictora de eventos al seguimiento (OR 1,978; IC 95% 1,887-1,996;  $p < 0,001$ ).

**Conclusión:** La cuantificación precoz del TI mediante SPECT es un predictor independiente de riesgo al año que permite establecer una estratificación del riesgo en pacientes con un primer IAM.

**Palabras clave:** Infarto del miocardio/fisiopatología - Tomografía computarizada por emisión de fotón único sincronizada cardíaca - Pronóstico

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## Abbreviations

<sup>99m</sup> Tc	Technetium-99m
CK	Creatine phosphokinase
SD	Systolic dysfunction
ECG	Electrocardiogram
LVEF	Left ventricular ejection fraction

AMI	Acute myocardial infarction
HF	Heart failure
MRI	Magnetic resonance imaging
SPECT	Single photon emission computed tomography
IS	Infarct size

## INTRODUCTION

Heart failure (HF) is the clinical expression of systolic dysfunction (SD) as a consequence of acute myocardial infarction (AMI) and its presence produces a three-fold increase in mortality compared to uncomplicated AMI. (1) The presence of HF in AMI is associated with infarct size (IS) and mechanical complications. (2) The magnitude of SD is the sum of necrotic myocardium plus ischemic but viable myocardium. Early reperfusion is the best treatment to prevent the development of HF and reduces mortality by limiting the area at risk and the final necrotic tissue.

Traditionally, the area of myocardial necrosis has been estimated using complementary tests as serial determination of myocardial injury biomarkers, electrocardiogram (ECG) and echocardiography. The new imaging techniques, as single photon emission computed tomography (SPECT) scintigraphy and magnetic resonance imaging (MRI), have improved the sensitivity and specificity to detect myocardial impairment. Although late gadolinium enhancement MRI is the gold standard to estimate IS, particularly in subendocardial infarctions, (3-5) SPECT myocardial perfusion imaging is also useful to estimate the extent of necrosis, and cardiac phantom studies have demonstrated the usefulness of this technique in determining IS. (6) A software developed in the last years (Cedars QPS software) has contributed to the estimation of IS by gated SPECT myocardial perfusion imaging. The method was validated in a cohort of AMI patients, resulting in a significant correlation between both methods. (7)

Although there are different studies (8-15) evaluating the predictive value of quantifying IS for risk stratification after AMI and its prognostic value at 1-year follow-up, there is still little information about early IS assessment using myocardial perfusion SPECT scintigraphy. The aim of this study was to evaluate the prognostic value of early IS evaluation by gated SPECT scintigraphy with technetium-99m (<sup>99m</sup>Tc) sestamibi in patients with a first ST-segment elevation AMI.

## METHODS

### Patients

The study cohort included patients prospectively and consecutively admitted to the coronary care unit with ST-segment elevation AMI between October 2009 and October 2014. The diagnosis of AMI was based on the presence of persistent ST-segment elevation  $\geq 1$  mm in limb leads and  $\geq 2$  mm in at least two contiguous precordial leads in the ECG. Patients with previous AMI (n=12) were excluded to avoid overestimating the perfusion defect.

### Gated SPECT myocardial perfusion imaging

Gated SPECT myocardial perfusion images were acquired at rest using a dual head digital gamma camera (VENTRI, General Electric) with high-resolution collimator. <sup>99m</sup>Tc sestamibi was given intravenously and images of myocardial uptake of the tracer were obtained after one hour along a circular orbit following a "step and shoot" acquisition protocol, starting in the right anterior oblique position at 45° and ending in the left posterior oblique position at 45°. The study was stored in a 64 x 64 matrix. A Butterworth filter was used for tomographic reconstruction.

All the studies were performed during hospitalization and after the reperfusion strategy had been administered, considering in all cases that the patient was clinically stable and that the parameters of myocardial injury (conventional cardiac enzymes) had returned to normal levels. Every study was interpreted by board-certified cardiologists trained in nuclear cardiology who were blind to the clinical information of the patient.

Infarct size was estimated using the automatic, computer-based QPS software (Cedars-Sinai Medical Center) that is widely used and has been previously validated. (16) The software includes the count of the circumferential profiles between the endocardial and epicardial surfaces, establishing a standard 5 point-score automatic measurement for each of the twenty myocardial segments. The automatic score summation is compared with the limits of a normalized database from a population of patients without AMI.

### Follow-up

Clinical follow-up at one year after AMI was performed by medical visit or telephone contact to establish the presence of cardiovascular complications during follow-up: sustained ventricular arrhythmia requiring hospitalization, HF and cardiovascular mortality.

### Statistical analysis

All the statistical calculations were performed using SPSS 19.0 statistical package. Results were expressed as mean, median or range. Variables were analyzed with the chi square test or Student's t test, as applicable. A p value  $< 0.05$  was considered statistically significant. An analysis of the area under the ROC curve was used to determine the IS cutoff value associated with the presence of events. A logistic regression analysis was performed to establish the variables associated with cardiovascular complications during follow-up.

### Ethical considerations

The study protocol was approved by the Institutional Teaching and Research Committee. An informed consent form was considered unnecessary as this was a retrospective analysis of data.

## RESULTS

The cohort consisted of 149 patients; 81.9% were men

and mean age was  $59.6 \pm 11$  years. The most common site of AMI was the anterior wall (43%). Demographic variables are summarized in Table 1.

At the moment of presentation, 84.6% of patients were in Killip and Kimball class A and only 2.6% in Killip and Kimball class C-D. Median time from symptom onset to hospitalization was 4 hours and maximum CPK level was 778 IU/L.

Reperfusion was achieved in 69.8% of cases and 85.6% corresponded to primary percutaneous coronary intervention. The most frequent culprit vessel was the left anterior descending artery (46.8%), followed by the right coronary artery (37.8%) and the left circumflex artery (15.3%). In 57.3% of the patients there were no significant coronary artery stenoses in other coronary vessels.

#### Gated SPECT myocardial perfusion imaging

All the patients underwent early gated SPECT myocardial perfusion imaging [median at day 5 (range: 3-9)]. The mean IS obtained at rest was 14.6% (range 1% to 57%), measured as the percentage of the left ventricular mass involved. In 68.5% of patients IS was <20%, in 26.8% between 20% and 40% and in 4.7% >40%. Left ventricular ejection fraction (LVEF) was evaluated by echocardiography and gated SPECT scintigraphy in all the patients during hospitalization, and no significant differences were found between both methods ( $50.6\% \pm 11.3\%$  vs.  $51.5\% \pm 14\%$ ;  $p = ns$ ).

#### Follow-up and complication predictors

Clinical follow-up was completed in 96.9% of cases, during a median interval of 11 months. The prevalence of ventricular arrhythmias was 7%, of heart failure 11.2%, of cardiovascular mortality 1.4% and of combined events 17.5%.

The diagnostic yield of IS to predict combined events during follow-up was evaluated with the ROC curve and a cutoff point of 22% was obtained [area under the ROC curve 0.94; 95% CI 0.914-0.985 ( $p < 0.001$ ); sensitivity 92%; specificity 81%] (Figure 1). Based on these results, the population was divided into two groups: Group I: IS <22% (69.1%) and Group II: IS  $\geq 22\%$  (30.9%). Table 2 shows the rate of cardiovascular events during follow-up in the two groups of patients.

**Table 1.** Population characteristics

Male gender, % (n)	81.9 (122)
Age, years (range)	$59.6 \pm 11$ (26-85)
Hypertension, % (n)	52.3 (78)
Diabetes mellitus, % (n)	16.1 (24)
Dyslipidemia, % (n)	36.9 (55)
Smoking habits, % (n)	61.1 (91)
Previous angina, % (n)	11.4 (17)
Previous revascularization, % (n)	9.3 (14)

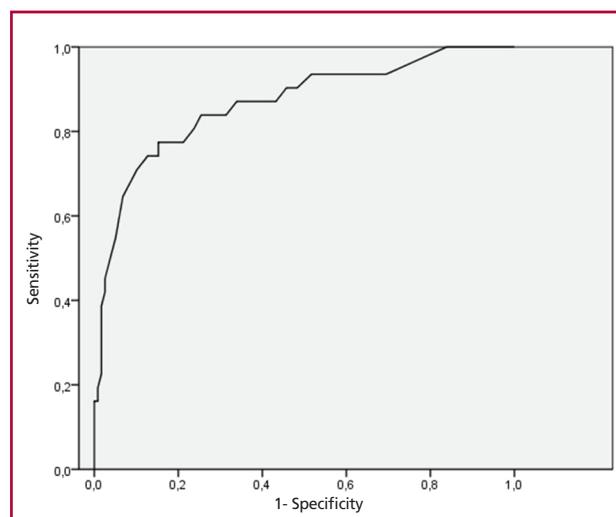
Univariate analysis was performed using the variables of clinical relevance to predict presence of combined events, as shown in Table 3. Based on these results, all the variables with a  $p$  value  $\leq 0.1$  in univariate analysis and prevalence  $> 2\%$  entered a logistic regression analysis. This analysis determined that  $IS \geq 22\%$  (OR 1.978; 95% CI 1.887-1.996;  $p < 0.001$ ) was the only independent predictor of combined cardiovascular events during follow-up. (Table 4).

The Kaplan-Meier method was used to perform a survival study and both groups were compared using the log-rank test. Cardiovascular event-free survival at one-year follow-up was significantly higher in Group I ( $p < 0.001$ ) (Figure 2).

#### DISCUSSION

Heart failure complications following AMI are related with the extent of myocardial necrosis. The possibility of developing cardiac arrhythmias increases and mortality is clearly higher compared with uncomplicated AMI. Early IS estimation may be useful for early risk stratification and to establish the outcome at one year.

Infarct size measured by SPECT myocardial perfusion imaging with  $^{99m}\text{Tc}$  sestamibi is a variable easily obtained, particularly with newly developed softwares, which can estimate it both accurately and automatically. Masci et al. analyzed IS in 260 patients with AMI and SD using MRI (17) and in the multivariate analysis found that IS was the only independent predictor of ventricular remodeling and recovery of LVEF during follow-up. A recent study analyzing a series of patients with AMI and LVEF dysfunction, demonstrated that IS was the only predictor of functional recovery 6 months after AMI. (18) These findings show the importance of estimating IS in the acute phase of myocardial infarction, as it is a long-term prognostic factor, which would not be underestimated in the early stages as might occur with LVEF. In our study, we have found that unlike IS, LVEF estimated



**Fig. 1.** ROC curve to detect infarct size cut off point

	Ventricular arrhythmias %	Heart failure %	Mortality %	Combined events %
Group I	2.1	5.8	0	2.1
Group II	17.4	34.8	4.3	50
p	0.001	<0.001	0.039	<0.001

**Table 2.** Cardiovascular events during follow-up

	Absence of events (n=118)	Combined events (n=25)	p
Male sex, %	83.1	76	0.4
Age, years	58.8 ± 10	63 ± 12	0.08
Diabetes, %	16.1	16	0.9
Anterior AMI, %	40.7	64	0.03
Killip and Kimball class C-D, %	1.7	4	0.4
No reperfusion, %	28.8	36	0.4
LVEF <40%, %	8.5	36	<0.001
AMI ≥22%, %	19.5	92	<0.001

**Table 3.** Univariate analysis

AMI: Acute myocardial infarction. LVEF: Left ventricular ejection fraction.

**Table 4.** Multivariate analysis

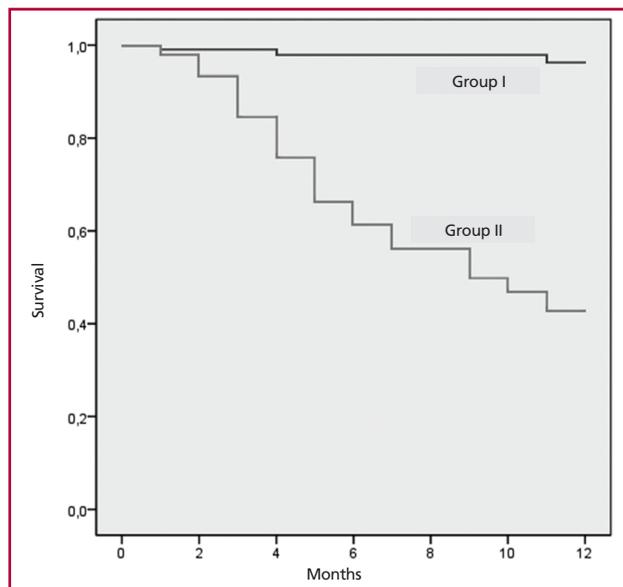
Stress-echo	OR	95% CI	p
Age	1.028	0.972-1.069	0.42
Anterior AMI	1.568	0.432-4.974	0.53
LVEF <40	1.638	0.99-1.361	0.13
AMI ≥22%	1.978	1.887-1.996	<0.001

AMI: Acute myocardial infarction. LVEF: Left ventricular ejection fraction.

by echocardiography or gated SPECT scintigraphy during hospitalization is not an independent predictor of combined events during follow-up (see Table 4). This could be due to myocardial stunning producing systolic dysfunction during the acute phase with subsequent recovery or improvement, while the extent of necrosis would persist unchanged across time.

Miller et al. analyzed IS with <sup>99m</sup>Tc sestamibiSPECT imaging in 409 patients and observed the different IS in their population, with a median of 12% at discharge. (19) During follow-up, they reported higher mortality in the group of patients with IS >12% compared with patients with lower necrosis. Mean IS in our population was about 14%, similar to the one reported in their registry. In our study, the cut off point for IS with adequate sensitivity and specificity determined by the ROC curve was significantly higher (22%). In our experience, gated SPECT scintigraphy was performed in most cases at day 5, when the biomarkers of myocardial injury had returned to normal levels.

Different multicenter studies have shown reproducibility and good correlation between IS and mortality; therefore, this parameter is used as an alternative endpoint to mortality when new therapeutic strategies are evaluated. Sample size can be reduced



**Fig. 2.** Analysis of combined event-free survival at one-year follow-up using Kaplan-Meier curves of patients in Group I (infarct size <22%) and Group II (infarct size ≥22%)

when this alternative endpoint is used. However, this variable is not always taken into account in daily clinical practice to estimate risk stratification after AMI.

In a meta-analysis of 10 randomized trials including 2,376 patients with AMI and primary percutaneous coronary intervention, Stone et al. observed a clear correlation between IS and mortality at one year, when the extent of the necrotic area was analyzed by quartiles. (20) That study determined that an IS >20% could identify patients with the highest risk of combined events at one year,

Today, the extent of myocardial necrosis can be quantified with different software. In our study, we

used the QPS software, which provides automatic and rapid information from a simple SPECT myocardial perfusion imaging study performed at hospital admission during the acute phase of AMI. In our experience, IS resulted an independent predictor of combined events at one year, including ventricular arrhythmias, heart failure and all-cause mortality, and was independent of age, sex, diabetes, Killip and Kimball class, anterior location of AMI, absence of reperfusion and LVEF. Unlike the IS calculated by SPECT imaging, LVEF could depend on left ventricular loading conditions and on the patient's hemodynamic status and/or stunned myocardium after reperfusion.

By establishing a cut off point, we could identify two groups of patients with different risk. In patients with AMI involving <22% of the left ventricle, event-free survival was significantly higher than in patients with larger infarcts. This cut off point differs from the 12% value reported by Miller et al. (19) which emerges as the median IS in their population and is similar to the median 10% IS of our population. In our case, the cutoff point was calculated using the ROC curve, resulting in a better balance between sensitivity and specificity.

### Limitations

The small sample size and the descriptive nature of this study are limitations in the interpretation of results. Also, as this study was performed in a single center, the results cannot be extrapolated to the general population. In addition, although not a goal of the study, IS calculated by gated SPECT myocardial perfusion imaging was not compared with other diagnostic tests. The cutoff point chosen for ejection fraction could conceal its importance as independent predictor. Further studies are necessary to validate IS as an independent predictor of events.

Finally, we should mention that measuring IS for risk stratification implies patient exposure to gamma radiation.

### CONCLUSIONS

Early quantification of IS by gated SPECT myocardial perfusion imaging with <sup>99m</sup>Tc sestamibi is an independent predictor of risk at one year that can establish risk stratification in patients with a first MI.

### Conflicts of interest

None declared

(See authors' conflict of interest forms in the web/ Supplementary Material).

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