

Time Intervals in Primary Angioplasty from Onset of Symptoms Until Restoration of Blood Flow

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Introduction and objective. A limitation to the widespread use of primary angioplasty is delayed reperfusion. Most current data are from clinical trials and there is little information about the use of primary angioplasty in clinical practice. The objective of this study was to analyze the duration of each stage leading to primary angioplasty in a hospital where it is the treatment of choice for acute myocardial infarction.

Patients and method. Prospective observational study of patients admitted to our hospital from April 2000 to August 2001 for acute myocardial infarction with an indication for reperfusion. The time intervals from onset of symptoms until the end of angioplasty were analyzed.

Results. Primary angioplasty was performed in 201 of 218 patients with an indication for reperfusion (92%). Median values (percentiles 25-75) were: Time 1 (onset of symptoms-hospital arrival): 91 (50-150) minutes. Time 2 (hospital arrival-call to interventional team): 20 (10-49) minutes. Time 3: (call to interventional team-team arrival): 15 (0-20) minutes. Time 4: (team arrival – patient arrival at the catheterization laboratory): 10 (5-15) minutes. Time 5 (patient arrival-opening of coronary artery): 20 (15-30) minutes. Time 6 (opening of coronary artery-TIMI III flow): 10 (0-25) minutes.

Conclusions. The most time-consuming stage in primary angioplasty was from the onset of symptoms until patient arrival at the hospital (Time 1). Inside the hospital, the most time-consuming stage was the diagnosis and decision to perform angioplasty (Time 2). The rates of primary angioplasty could be increased if delays in reperfusion were reduced with respect to those considered acceptable in current practice guidelines.

Key words: *Myocardial infarction. Reperfusion. Coronary angioplasty.*

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Intervalos de tiempo transcurridos en la realización de la angioplastia primaria: desde el inicio de los síntomas hasta la restauración del flujo

Introducción y objetivo. Una limitación para el empleo generalizado de la angioplastia primaria es el retraso al que puede asociarse. La mayoría de los datos actuales procede de ensayos clínicos y existen pocos conocimientos respecto a su aplicación en la práctica clínica habitual. El objetivo del estudio fue analizar los tiempos invertidos en cada etapa en la realización de una angioplastia primaria en un hospital donde es el tratamiento de reperusión de elección en el infarto agudo de miocardio.

Pacientes y método. Estudio prospectivo observacional de los pacientes con infarto agudo de miocardio ingresados en nuestro centro e indicación de tratamiento de reperusión entre abril de 2000 y agosto de 2001. Se analizan los tiempos parciales desde el inicio de los síntomas hasta la finalización de la angioplastia.

Resultados. Se realizó angioplastia primaria a 201 de los 218 pacientes con indicación de tratamiento de reperusión (92%). La medianas (percentiles 25-75) fueron: tiempo 1 (inicio de síntomas-llegada hospital): 91 min (rango, 50-150); tiempo 2 (llegada al hospital-llamada a equipo de hemodinámica): 20 min (rango, 10-49); tiempo 3 (llamada al equipo de hemodinámica-llegada equipo): 15 min (rango, 0-20); tiempo 4 (llegada equipo-llegada del paciente al laboratorio): 10 min (rango, 5-15); tiempo 5 (llegada paciente-apertura arteria responsable): 20 min (rango, 15-30); tiempo 6 (apertura arteria-flujo TIMI III): 10 min (rango, 0-25).

Conclusiones. El tiempo más prolongado en la realización de la angioplastia primaria transcurre desde el inicio de los síntomas hasta la llegada al hospital. Dentro del hospital son el diagnóstico y la decisión de realizar la angioplastia lo que motiva el mayor tiempo. Es posible generalizar la realización de la angioplastia primaria con tiempos claramente inferiores a los recomendados en las actuales guías de actuación.

Palabras clave: *Infarto. Reperusión. Angioplastia coronaria.*

INTRODUCTION

Recent studies have demonstrated that reperfusion treatment with primary angioplasty improves the short and long-term prognosis in patients with acute myocardial infarction (AMI) compared with thrombolytic treatment.¹⁻⁵

ABBREVIATIONS

AMI: acute myocardial infarction.
CLBBB: complete left bundle-branch block.
ECG: electrocardiogram.

The main limiting factors for the use of primary angioplasty are, on the one hand, the availability of infrastructure, material, and trained personnel and, on the other hand, ensuring that the intervention of the artery responsible for infarction is performed as soon as possible after infarction is diagnosed.

The delay in restoring coronary blood flow deserves special attention in primary angioplasty because, due to the complexity of the procedure, effective opening of the artery can be delayed so much that the advantages over thrombolysis are lost.⁶⁻⁹ Precise knowledge of the different partial times from the onset of symptoms to the conclusion of primary angioplasty can help to design measures for reducing these times, thus improving the results obtained with primary angioplasty.¹⁰

Most of the findings on primary angioplasty available come from randomized clinical trials or retrospective registries of large databases where it has been demonstrated that, in spite of the application of broad inclusion criteria, patients with a less favorable clinical profile and patients with longer delays are excluded.¹¹ The data published in these studies may not reflect reality as observed with the generalized use of primary angioplasty as reperfusion treatment in AMI

In the present study we proposed to measure the duration of each phase, from the onset of symptoms of infarction to the presence of a normal flow in the artery responsible for infarction in the routine clinical practice of a center where primary angioplasty has been performed as the treatment of choice in myocardial infarction since April 2000.

PATIENTS AND METHOD

Design and patients

Prospective observational study of a cohort of patients.

The patients in which primary angioplasty was indicated consecutively in our center from 1 April 2000 to 31 August 2001 were included. The patients referred from other centers for the performance of primary angioplasty were excluded.

Angioplasty was considered primary when it was performed without previously carrying out thrombolysis in patients who met the class I criterion for performance according to the practice guidelines in acute

myocardial infarction of the ACC/AHA (American College of Cardiology/American Heart Association):^{12,13}

– Chest pain of anginal characteristics or other symptoms compatible with myocardial ischemia lasting more than 30 min in spite of the administration of antianginal treatment.

– Elevation of the ST segment ≥ 0.1 mV in the electrocardiogram (ECG) of at least two contiguous leads or a new (or presumably new) complete left bundle-branch block (CLBBB) appearing within 12 h of the onset of symptoms or later if the symptoms of myocardial ischemia persist.

Since the beginning of the program of primary angioplasty as the treatment of choice in AMI (April 2000), all patients seen in the emergency room of our hospital with suspected AMI are evaluated by the cardiologist on duty, who establishes the indication for reperfusion treatment and immediately contacts the intervention team on call. Primary angioplasty is not performed as reperfusion treatment for AMI in our center only if the intervention team is occupied with another procedure that cannot be postponed, the patient refuses catheterization, coronary anatomy is unfavorable, or the cardiologist on call decides against it.

Analyses were based on the «intention to treat». All the patients for which the hemodynamics team was contacted to perform primary angioplasty were included in the study, even if the procedure was not carried out.

Variables

The characteristics of the presentation of infarction and the procedure performed were collected prospectively with the patients' demographic and baseline data. For the time analysis a series of time intervals were defined, which are described in Table 1. The different times were collected as follows:

– The time of onset of the symptoms was obtained directly from the patient or family members.

– The time of arrival at the hospital was the earliest time noted on the emergency room admission form as the time of arrival of the patient at the hospital or the first time noted on the nursing form of the hospital emergency room. If infarction began while the patient was hospitalized, the time of the arrival was considered to be the time of onset of symptoms.

– The time of acceptance by the intervention team noted was the time when telephone contact was made with the hemodynamics specialist in charge of performing the angioplasty.

– The time of arrival of the intervention team and time of arrival of the patient to the hemodynamics laboratory, presence of antegrade flow in the responsible coronary artery, and presence of TIMI III flow in

TABLE 1. Definition of the times analyzed and patients included in each time

Times	Intervals	Patients included
Simple		
Time 1	Onset of symptom-arrival at hospital	All
Time 2	Arrival at hospital-call to intervention team	All
Time 3	Call to intervention team-arrival of intervention team	All
Time 4	Arrival of intervention team-patient in hemodynamics laboratory	All
Time 5	Patient in hemodynamics laboratory-antegrade flow in artery responsible for AMI	All
Time 6	Coronary flow in responsible artery-TIMI III of responsible artery	Only patients treated successfully
Composites		
Time A	Call to intervention team-beginning PTCA (arrival of patient to hemodynamics laboratory)	All
Time B	Onset of symptoms-TIMI III of responsible artery	Only patients treated successfully
Time C	Call to intervention team-TIMI III of responsible artery	Only patients treated successfully
Time D	Arrival at hospital-coronary artery with antegrade flow	All

the responsible coronary artery were noted by nursing personnel during the procedure at the indication of the intervening physician. For the times until final TIMI III flow was obtained, only patients who underwent intervention and achieved a normal final flow were analyzed.

In time 2 (time from arrival at the hospital until the intervention team was called in), the cause of anomalous and extreme times (outliers) was analyzed.

Procedures that concluded with TIMI III flow in the artery responsible for infarction without major complications in the hemodynamics laboratory (death, deterioration of the initial Killip class, or cerebrovascular accident during the intervention) were considered successful.

Times were expressed in relation to the total time of the patients included in the study and separately depending on whether the intervention was performed during working hours or not. Working hours were understood to be the hours when the intervention team

was present in the hospital for scheduled interventions.

Statistical analysis

The variables corresponding to the baseline characteristics of the patients were expressed as follows: the qualitative variables were expressed as percentages and the quantitative variables as mean and standard deviation.

The variables that refer to the times and their dispersion were expressed as the median and 25th and 75th percentiles. The dispersion was shown graphically by box-plot diagrams, where the box represents the 25th-75th quartiles, the central line indicates the median, and the interval lines above and below the box indicate the maximum and minimum values of the distribution, respectively, after excluding anomalous and outlier values. The anomalous values, defined as those separated 1.5x from the 25th percentile on the left or from the 75th percentile on the right (P75-P25), are shown as white circles. The outlier values, defined as those separated 3x from the 25th percentile on the left or from the 75th percentile on the right (P75-P25), are shown as black circles.¹⁴

Analyses were made with the SPSS® statistical package, version 10.0.

RESULTS

Between 1 April 2000 and 31 August 2001, 218 patients presented an AMI that met criteria for reperfusion treatment in our hospital. Primary angioplasty was indicated in 201 of them (92%), in accordance with the inclusion criteria of this study.

The baseline characteristics of the patients are described in Table 2. The mean age was 65±11 years and three-fourths of the patients (74%) were men. Almost half of the infarctions (42.8%) were anterior (86 patients).

In 12 patients (6%) the indication was clinical manifestations compatible with acute myocardial infarction and the presence of CLBBB in the ECG. In 5 patients with CLBBB (42% of the patients with CLBBB), the intervention was not performed because no coronary lesion that explained the patient's clinical picture was found in coronary arteriography. A patient with CLBBB and cardiogenic shock died after coronary arteriography, before beginning the intervention.

After coronary arteriography, coronary angioplasty was performed on the artery responsible for AMI in 186 patients (92.5%), with 172 (92.5%) of the 186 therapeutic procedures performed being considered successful.

The different times observed are shown in Table 3. The longest time was from the onset of symptoms to arrival of the patient at the hospital (median 91 min). As for the times after the patient comes into contact

TABLE 2. Baseline characteristics of patients included in the study

n=201	n (%)
Age, mean±SD	65±11
Age ≥75 years	43 (21.4)
Female sex	52 (25.9)
Risk factors	
Smoking	99 (49.3)
Arterial hypertension	98 (48.8)
Diabetes mellitus	62 (30.8)
Hypercholesterolemia	72 (35.8)
History of cardiovascular disease	
Previous myocardial infarction	52 (25.9)
Previous coronary angioplasty	24 (11.9)
Previous coronary surgery	7 (3.5)
Previous CVA	10 (5.0)
Anterior infarction	86 (42.8)
Shock at time of admission	22 (10.9)
CLBBB in admission ECG	12 (6.0)
Coronary intervention	186 (92.5)
Use of stent*	173 (93)
Use of thrombectomy devices*	28 (15)
Successful interventionist procedure*	172 (92.5)

*In relation to the total of treated patients. CVA indicates cerebrovascular accident; CLBBB, complete left bundle-branch block.

with the hospital, the longest times, with median values of 20 min, were time 2 and time 5, in which AMI was diagnosed and the decision was made to carry out primary angioplasty (time 2), and anterograde flow was obtained in the artery responsible for AMI, from the arrival of the patient to the hemodynamics laboratory (time 5). The times studied are shown graphically in Figure 1.

The median time passed from the indication of primary angioplasty to arrival of the intervention team to the hemodynamics laboratory was 15 min. Outside

working hours the median time was 20 min, with 75% of the times below 25 min.

Considered as a group, the time from the onset of symptoms to reperfusion (time B) had a median value of 190 min, the median time from the establishment of the indication for reperfusion to its achievement (time C) being 55 min.

The largest dispersions were found in the time from admission to the indication of primary angioplasty (time 2) (Figure 2). A total of 16 patients presented extreme times and in 7 cases times were anomalous. Two patients had a time of more than 15 h from admission to establishment of the indication for primary angioplasty in spite of having been hospitalized with this indication. Review of the clinical histories of the patients allowed the causes of the longest delays to be identified. The main cause was diagnostic error (67% of the cases, 16 patients), generally a delay in performing the ECG on patients with clinical manifestations suggestive of infarction or incorrect interpretation of an ECG with evident signs of AMI. In 25% of cases (6 patients) longer delays were due to an ECG with baseline electrical disturbances (pacemaker rhythm, left bundle-branch block) that obscured the diagnosis of AMI, and in 8% (2 patients), additional studies or treatments had to be performed before primary angioplasty.

In the comparison of the times that each phase lasted in relation to whether or not treatment was performed during the work day (Table 3), there was a significant difference in times 3 and A (which reflect the time it took for the intervention team to reach the hospital) and time 4, indicating a significant but very small delay (2 min) in the arrival of the patient to the hemodynamics laboratory. The other composite times, B, C and D, showed no significant differences. From the beginning of the program no changes were

TABLE 3. Times from the onset of symptoms to the end of the procedure in the complete sample in relation to the arrival of the patient in working hours or not (in minutes)

	Median (25th-75th percentiles)			P
	Complete sample (n=201)	Work days hours (n=54)	Outside work day (n=147)	
Time 1 (symptoms-arrival at hospital)	91 (50-150)	70 (45-152)	95 (60-151)	NS
Time 2 (arrival at hospital-call)	20 (10-49)	15 (5-60)	14 (7-26)	NS
Time 3 (call-arrival of team)	15 (0-20)	0 (0-0)	19 (10-20)	<.005
Time 4 (team-patient in laboratory)	10 (5-15)	10 (5-20)	8 (5-20)	.002
Time 5 (patient in laboratory-open artery)	20 (15-30)	25 (18-30)	20 (15-30)	NS
Time 6 (open artery-TIMI III)	10 (0-25)	15 (3-30)	10 (0-20)	NS
Time A (call-patient in laboratory)	25 (15-30)	12 (5-20)	25 (19-30)	<.005
Time B (symptoms-TIMI III)	190 (135-298)	172 (132-299)	190 (140-290)	NS
Time C (call-TIMI III)	55 (40-80)	50 (35-73)	60 (45-80)	NS
Time D (arrival at hospital-open artery)	65 (45-101)	60 (41-105)	68 (50-98)	NS

Times 6, B and C refer to procedures in which a final TIMI III flow was obtained

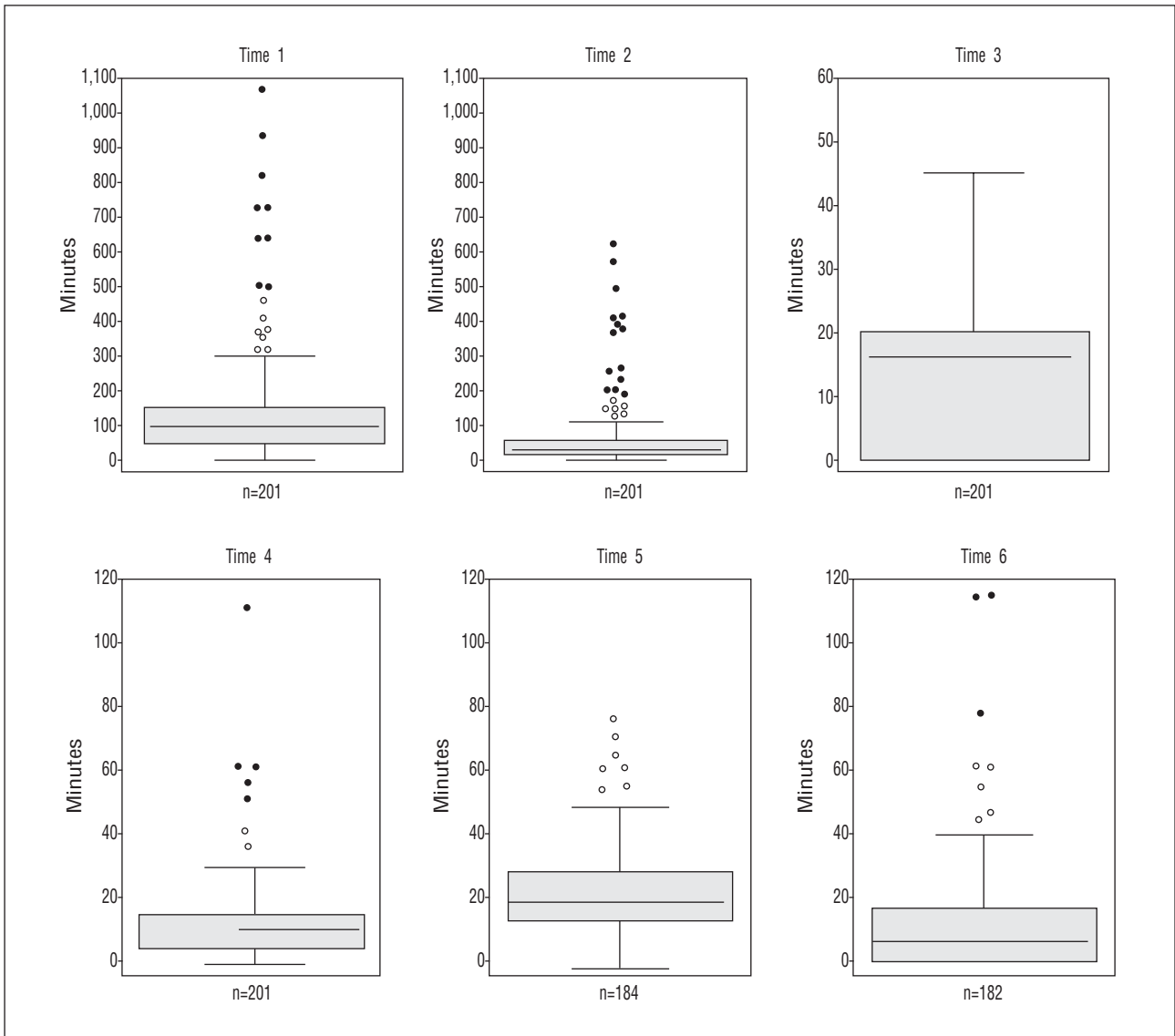


Fig. 1. Box-plot diagrams of the different simple times from the onset of symptoms until obtaining of TIMI III flow (see Table 1 for the definition of times). The box represents the 25th-75th quartiles; the central line, the median; the interval lines above and below the box, the maximum and minimum values of the distribution, respectively, excluding anomalous and outlier values. O indicates anomalous value, separated by 1.5x from the 75th percentile on the right (75th percentile-25th percentile); ●, outlier, separated by 3x from the 75th percentile on the right (75th percentile-25th percentile).

observed in the medians of the composite times (Figure 3).

DISCUSSION

In our experience with the use of the primary angioplasty as the treatment of choice for AMI, the artery responsible for the infarction was open with an hour of the patient's arrival at the hospital in 45% of the patients. The longest times were observed from the onset of symptoms to arrival of the patient to the hospital and, once in the hospital center, from arrival to the hospital to the decision to contact the intervention

team.

The effectiveness of reperfusion treatment depends on the delay from the onset of symptoms. The data of the main clinical trials on the use of thrombolysis¹⁵⁻¹⁹ and recent studies of the use of primary angioplasty^{9,20} have demonstrated a reduction in the benefit obtained, in terms of mortality and preservation of ventricular function,²¹ as reperfusion treatment is performed later after the onset of infarction.

Primary angioplasty, by its characteristics (it requires a laboratory and a trained intervention team and depends on the technique of the hemodynamics specialist to achieve reperfusion), can be associated with

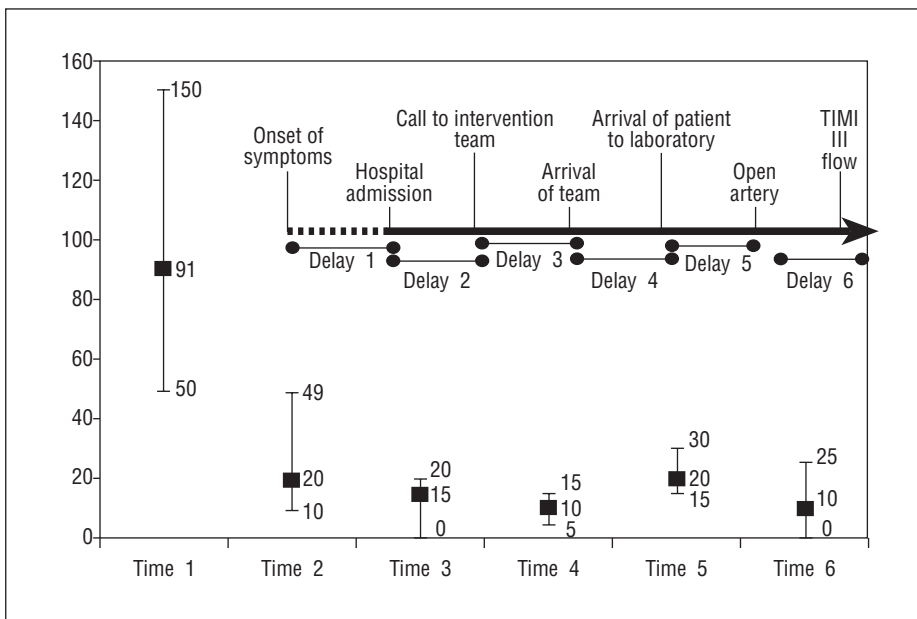


Fig. 2. Median and 25th-75th percentiles of different simple times from the onset of symptoms to obtaining TIMI III flow.

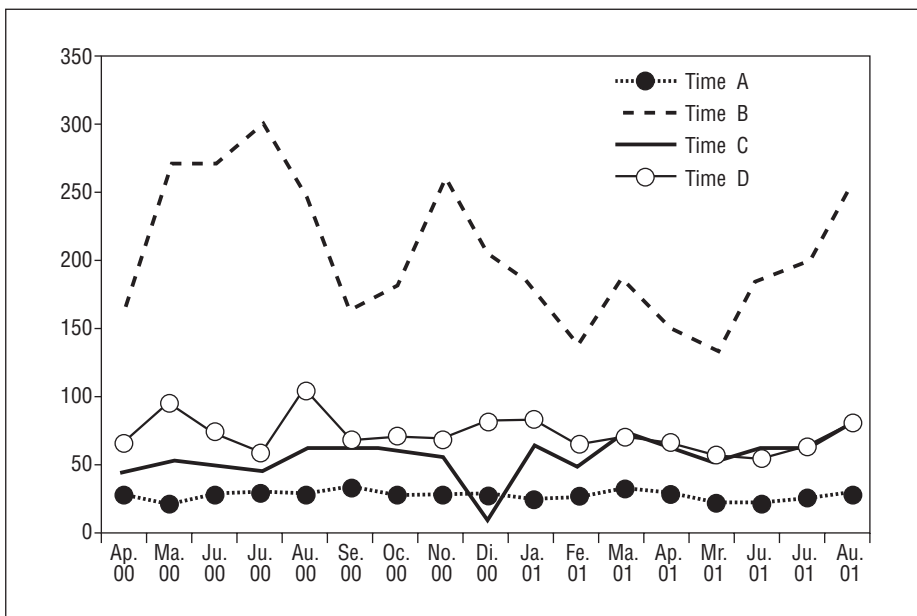


Fig. 3. Evolution of the median of the composite delays in the monthly course of the program.

longer delays than reperfusion based on the intravenous administration of a thrombolytic drug.⁸ With respect to the above, a possible cause of failure of previous studies to demonstrate the benefit of primary angioplasty in patients may be due to performing the technique in patients who received thrombolysis in the same trials.^{9,22}

The delays reported in the literature (most from controlled clinical trials) do not necessarily coincide with the findings of each particular center, in the same way that it is already known that the favorable conditions of clinical trials are not always found in clinical practice.¹¹

In our 17-month experience using primary angio-

plasty as the reperfusion treatment of choice in AMI, the coronary artery responsible for AMI was open within an hour of hospital admission in 45% of the patients. The figure of 45% of patients in our study in which the artery was opened in less than 60 min measured from the time of arrival of the patient at the hospital (time D) contrasts notably with that reported in previous registries. In the American NRMI-2 (National Registry of Myocardial Infarction), only 8% of patients had a time of less than an hour from admission to the beginning of angioplasty. The median time (time D, 65 min) was similar or clearly shorter than that reported in this and other previous studies (Table 4). The fact that this was a study of patients hospitali-

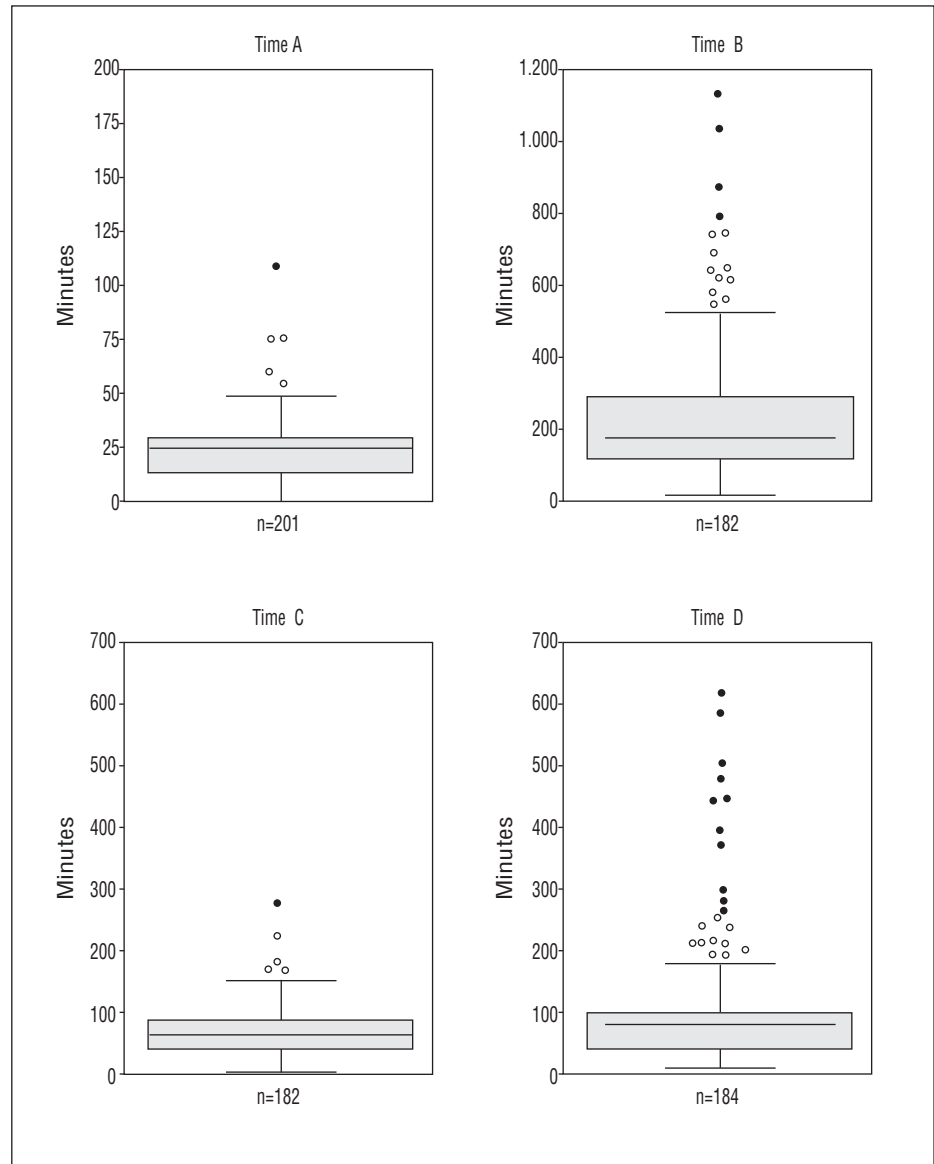


Fig. 4. Box-plot diagrams of carton of the different grouped times (see Table 1 for definitions of times). The box represents the 25th-75th quartiles; the central line, the median; the interval lines above and below the box, the maximum and minimum values of the distribution, respectively, excluding anomalous and outlier values. o: anomalous value, separated by 1.5x from the 75th percentile on the right (75th percentile-25th percentile); ●: outlier, separated by 3x from the 75th percentile on the right (75th percentile-25th percentile).

zed in a single center and that the indication for treatment and call to the hemodynamics team were generally made from the door of the hospital emergency service could have contributed to minimizing the short delay, which comes close to the delay sometimes observed between admission and the administration of a thrombolytic drug.

The longest time observed from the onset of symptoms to the performance of coronary angioplasty was the time that the patient took to reach the hospital. The extrahospital nature of this time makes its reduction difficult and, although some subpopulations are known to be associated with more prolonged delays,²³⁻²⁵ only information campaigns targeting the community and better access to the healthcare system can be used to try to reduce the time from the onset of symptoms and arrival at the hospital.

The second longest delay takes place in the hospital,

TABLE 4. Times observed in previous studies of primary angioplasty

Author, year, and bibliographic reference	Design	Time	Duration, min
Berger et al 1994 ³¹	Clinical trial	Randomization-balloon inflation	78 (mean)
Grines et al 1993 ³²	Clinical trial	Randomization-angiography	60 (mean)
De Boer et al 1994 ³³	Clinical trial	Admission-balloon inflation	64 (mean)
Cannon et al 2000 ²⁰	Observational	Admission-balloon inflation	116 (median)
GUSTO IIb 1999 ⁹	Clinical trial	Randomization-balloon inflation	76 (median)
Caputo et al 1997 ¹⁰	Observational	Admission-balloon inflation	97 (mean)
García et al 1999 ³	Clinical trial	Onset symptoms-balloon inflation	197 (median)

between the time of admission and contact with the hemodynamics team (time 2). This time is consumed by the contact of the patient with the hospital center, the diagnosis of infarction, and therapeutic decision-making. Although, it is one of the longest delays in our experience, it is a time not considered in clinical trials that express the hospital delay in carrying out primary angioplasty as the time from randomization of the patient to balloon inflation.

Although the median time of 20 min observed hardly seems reducible (since a clinical history and ECG must be made in most cases), we detected up to 25% of patients who spent more than 45 min from admission to contact with the intervention team. Examination of the anomalous and extreme cases revealed that the main causes of this longer delay were problems in the diagnosis of infarction, whether due to a nonspecific ECG of AMI or diagnostic errors committed in patients with symptoms and signs that define AMI.

The delay due to the primary angioplasty *per se*, understood as the time from calling in the hemodynamics team to establishment of a normal blood flow in the responsible artery, lasted a median time of 55 min (time C) in our experience. The location of our laboratory in a medium-sized city in Spain with good communications has meant that team displacements rarely take more than 20 min, and in 50% of cases are less than 15 min. This probably has meant that, although a greater delay is observed in the composite times A, B, C, and D, when primary angioplasty is performed outside the work day (Table 3), the difference was so small (a median of 10 min) that no significant difference was observed except in the times directly related to the time it took the intervention team to get to the hospital. These differences, because of their scant magnitude, had very little clinical relevance. The other delays (times 4, 5 and 6) depended on the mean experience of the intervention team and complexity of the lesions involved. Since no reference values exist in the literature, at present it is not possible to establish target objectives, but intervals of 10-15 min are difficult to reduce. Obtaining greater rates of TIMI III flow by facilitated angioplasty before the intervention could be a strategy, if a clinical benefit is demonstrated, thus shortening the time until normal flow is attained in the artery responsible for AMI.

Considering the overall times (Table 3 and Figure 4), reperfusion was achieved in 50% of patients within 3 h of the onset of symptoms (time B) and in 20% of patients in less than 2 h. This 2-h limit has been associated with an important reduction in mortality in earlier studies,^{20,21} although it was reached in only some patients in these studies,²⁰ due to the delay of more than 1 h in that most patients have in arriving at the hospital.

The time from the indication of reperfusion (when

the hemodynamics team is called in) and obtaining a final TIMI III flow (time C) is probably the time that best defines the delay of primary angioplasty in achieving reperfusion in patients after the diagnosis of AMI is made. In our experience, this time had a median value of 55 min, which was similar or less than the mean reperfusion time associated with the use of intravenous thrombolysis in various national registries.²⁶⁻³⁰ Figures for the time of onset of thrombolytic treatment were sometimes greater (door-to-needle time, not including the time required for thrombolysis to act).^{27,28}

Although the objective of a care protocol in the treatment of AMI should attempt to reduce to minimize the mean time to reperfusion, the 45-50 min limit from the decision to perform primary angioplasty to the achievement of TIMI III flow is probably close to the minimum for performing the technique. It may be more productive to center the efforts of an angioplasty program not on cutting a few minutes (once optimal mean times are reached), but in trying to eliminate the clearly discordant delays that some patients experience.

Limitations

In the present study times are not described in relation to the moment of balloon inflation. This omission somewhat limits comparisons with the times reported in previous studies, especially the classic *door-to-balloon time*. This omission was deliberate. Consigning the time of balloon inflation as equivalent to «needle time» of the thrombolysis may continue to be valid in conventional intervention procedures. However, the current use of thrombectomy before balloon angioplasty (up to 15% in our series), direct stent implantation, and the existence of cases with TIMI III flow after the first injection condition the real value of the time of inflation of the angioplasty balloon as a reference for beginning reperfusion treatment. The times referred until an open artery or TIMI III flow is observed in the responsible artery, given the high rate of success achieved in the interventions, could be a more valid reference for time in which action is taken in each case of primary angioplasty.

CONCLUSIONS

In a program of reperfusion treatment of AMI based almost exclusively on primary angioplasty, it is possible to restore blood flow in the artery responsible for AMI in a median time of 190 min from the onset of symptoms. The longest time is from the onset of symptoms to arrival of the patient to the hospital. In our series, in the hospital phase the median time from admission to the indication of reperfusion is 20 min, and from admission to opening of the artery, 65 min.

Measures aimed at improving knowledge of the

symptoms of AMI in the community and facilitating access and to healthcare services and patients transportation, together with improvements in diagnostic tools and more fluid decision-making in the hospital could be useful in reducing the delay to reperfusion in primary angioplasty.

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