Experience of the Institute of Cardiology in the assessment of patients with acute chest pain by Nuclear Cardiology techniques

Experiencia del Instituto de Cardiología en la evaluación del paciente con dolor torácico agudo mediante técnicas de Cardiología Nuclear

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ABSTRACT

The World Health Organization acknowledges that cardiovascular disease is the leading cause of death in adults worldwide, and one third of all causes of death. Chest pain accounts for 6% of all visits to emergency departments. Proper diagnosis of those cases with normal or nondiagnostic electrocardiogram is therefore essential, allowing adequate risk stratification and appropriate treatment. The usefulness of different imaging techniques to study these patients in the acute setting is assessed, with emphasis on Nuclear Cardiology techniques. The experience of the Institute of Cardiology and Cardiovascular Surgery in Havana, Cuba, with regard to the use of these techniques in patients with acute chest pain, is reported.

RESUMEN

La Organización Mundial de la Salud reconoce que la enfermedad cardiovascular es la primera causa de mortalidad en adultos a nivel mundial, y constituye un tercio de todas las causas de muerte. El dolor torácico representa un 6 % de los motivos de visita a los servicios de emergencia. El diagnóstico adecuado de aquellos casos con electrocardiograma normal o no diagnóstico es por tanto esencial, pues permite una adecuada estratificación de riesgo y un tratamiento apropiado. Se examina la utilidad de diferentes técnicas de imagen para estudiar a estos pacientes en el contexto agudo, con énfasis en las técnicas de Cardiología Nuclear. Se presenta la experiencia del Instituto de Cardiología y Cirugía Cardiovascular de La Habana, Cuba, con la utilización de estas técnicas en el paciente con dolor torácico agudo.

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INTRODUCTION

The World Health Organization (WHO) acknowledges that cardiovascular disease is the leading cause of death in adults, both men and women, worldwide, and that it accounts for one third of all causes of death[1]. It is

interesting to note that the WHO estimates that 80% of these deaths occur in developing countries, with limited resources to address the problem[1].

In Cuba, heart diseases were the leading cause of death until 2011. In 2012 they were exceeded by malignant tumors. However, figures are still very similar[2]. It is considered that heart disease and cerebrovascular disease together, both as manifestations of atherosclerotic disease, are the leading cause of death in the country; something that reflects the world situation.

Chest pain accounts, approximately, for 6% of the causes for visits to emergency departments (ED)[3]. Acute coronary syndromes (ACS) comprise a group of diseases, among which are the ACS with and without ST segment elevation, and unstable angina[4]. These ACS cause acute chest pain and are part of the causes of pain in patients who come to the ER. Obviously, patients with typical angina pain, electrocardiographic findings of ischemia or ST segment elevation and positive cardiac enzymes are admitted to hospital and correctly treated as an ACS. However, these clinical symptoms account for only 10% of patients presenting to the ED with chest pain[5].

After the patient comes into the ER, several hours may pass before the enzymes are positive in those with an acute coronary event. In addition, the electrocardiogram (ECG) may also be normal in patients with acute myocardial infarction and unstable angina. Hence, an early identification and a correct approach with patients who come to the ED with a possible ACS represent a major problem faced by the doctors who receive them, because it can be difficult to establish a diagnosis, which leads to the fact that 50% of cases are wrongly considered to be of cardiac origin, and that 5% of them are improperly discharged considering that the cause is non-cardiac[6]. This can lead to increased health care costs for unnecessary admissions and, more worryingly, to an increase of cardiac events in patients who were wrongly discharged.

Available imaging techniques in cardiology for the diagnosis of patients with acute chest pain

In addition to the information obtained from the medical history, the ECG and the cardiac enzymes that are available for diagnosing the cause of acute chest pain, which in typical cases are perfectly sufficient, different imaging techniques in cardiology have been used in patients presenting to the ED with chest pain, among them: echocardiography, nuclear magnetic resonance (NMR), cardiac computed tomography (CCT) and single-photon emission computed tomography (SPECT) with cardiac gated acquisitions.

Two-dimensional echocardiography shows modest sensitivity (88%) and specificity (78%) for risk stratification in patients with acute chest pain and normal or nondiagnostic ECG[7]. It allows the assessment of the global ventricular function and regional contractility disorders, as well as the presence of ventricular aneurysms, pseudoaneurysms, pericardial effusion and valvular dysfunction. Recently, contrast echocardiography has proved to be more useful[8].

Kwong *et al*[9], using NMR techniques, obtained a sensitivity of 84% and a specificity of 85% for detecting ACS, but this is not a practical option in the ED yet, since it is an expensive study, which is not widely available.

Moreover, the CCT has begun to be used in recent years for the assessment of acute chest pain[10], which has raised the term triple rule-out, since the same study may rule out three causes of chest pain: coronary, pulmonary embolism or acute aortic disease. Specifically in the case of obstructive coronary disease, because of its high sensitivity and especially due to its high negative predictive value (NPV), the CCT has a very low rate of false-negative studies, which is useful in situations where it is critical to exclude an important coronary artery disease, as in the case of ACS[11].

An example of this is the ROMICAT study (Rule Out Myocardial Infarction using Computer Assisted Tomography), which included 368 patients with low or intermediate risk of adverse cardiac events who presented to the ED with acute chest pain[10]. This study demonstrated that the presence of normal coronary arteries in the angiography using CCT obviated the need for additional tests and allowed a safe discharge without increasing short-term adverse events. However, in the subgroup of 150 patients who underwent a perfusion SPECT, sensitivity and NPV were virtually identical to those who underwent CCT, but there was a significant increase in specificity values (96 vs. 54-87 %) and positive predictive value (80 vs. 17-35%)[10].

A recent meta-analysis of 1 349 patients concluded that the CCT is an instrument of high level of predic-

tion (sensitivity of 95% and specificity of 87%) for excluding ACS in patients presenting to the ED with acute chest pain, and low to intermediate probability of ACS[12]. However, in the case of the CCT, it is necessary to consider the use of a potentially nephrotoxic contrast and the dose of radiation for the patient.

Besides the angiography by CCT, this technique also allows an assessment of the presence of calcium in the coronary arteries. It has been suggested that the coronary artery calcium score (CAC score) is a fast and efficient tool for the screening of patients with acute chest pain[13], with a sensitivity of 98-100% and a high NPV for identifying patients with acute myocardial infarction, and very low rates of adverse cardiac events have been detected in patients with CAC score = 0[13].

UTILITY OF NUCLEAR CARDIOLOGY TECHNIQUES IN THE ASSESSMENT OF PATIENTS WITH ACUTE CHEST PAIN

With regard to acute chest pain, it is important to consider the long lasting dispute between anatomical approach versus functional approach in risk stratification and treatment of coronary artery disease. The functional significance of a coronary stenosis is not always apparent, particularly in the case of stenoses that reduce the lumen diameter by 50 to 90%. For example, Gaemperli *et al*[14] demonstrated an excellent correlation between invasive coronary angiography and the angiography using CCT, but both techniques showed a poor association with the presence of ischemia in perfusion SPECT, because a stenosis ≥50 % does not necessarily cause ischemia.

However, in several trials involving over 100 000 patients, the presence of ischemia as a physiological measure that is assessed in the perfusion SPECT was an important predictor of cardiac events, with independent and incremental value in relation to clinical variables and even anatomical variables[15]. It follows that the physiological measurement of ischemia is a very important aspect to consider in assessing the risk of future cardiac events. Therefore, to take into account only the presence of a coronary stenosis will

be a suboptimal termination variable for the assessment of patients in the acute setting, when the main problem is the prognosis, and determining whether revascularization is necessary or not.

This justifies the use of an alternative functional approach with nuclear techniques; specifically perfusion SPECT at rest. However, this is not new, the studies with thallium-201 began more than 30 years ago[16], but due to the characteristics of those gamma cameras (planar, with less image resolution) and the radioisotope thallium-201, with higher radiation dose to the patient, these studies were not put into practice.

Subsequently, with the development of tomographic cameras (SPECT) and radiopharmaceuticals using technetium-99 metastable (Tc-99m), such as methoxy isobutyl isonitrile (MIBI) or tetrofosmin, these studies began to useful again and, in fact, can provide information on both myocardial perfusion and ventricular function with the same test. Since these compounds are taken up by the myocardium in proportion to blood flow, without significant redistribution, it allows patients to be injected during the pain and that the images are acquired hours later, it does not interfere with the usual measures taken in the ED. The images, once acquired and processed, are a reflection of the area at risk at the time of the tracer injection.

The perfusion SPECT at rest, in the acute chest pain setting, predicts the occurrence of cardiac complications, with sensitivities between 90 and 100%, and a NPV of 99%[17]. This high NPV allows the identification of those patients who require a less intensive treatment, or those who may be discharged, while its high sensitivity allows the identification of those who should be admitted to hospital, with a proven cost-effectiveness ratio[18].

In a randomized study (Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain [ERASE]), which was a milestone for the assessment of perfusion SPECT in the acute setting, a total of 2 172 patients were included and standard treatment was compared with standard treatment plus a perfusion SPECT at rest with Tc-99m MIBI. It showed a reduction of 14% of hospital admissions if SPECT was performed; which provided evidence to recommend it for acute chest pain in the ED as a class I indication[18].

Experience of the Institute of Cardiology

The experience of the working group of the Institute of Cardiology and Cardiovascular Surgery in Havana, Cuba, in the use of perfusion SPECT in patients with acute chest pain and normal or nondiagnostic ECG is shown below.

In order to assess the feasibility of performing, in developing nations, the SPECT at rest in the acute chest pain setting to rule out an ACS in patients with low to intermediate probability of coronary heart disease, the International Atomic Energy Agency (IAEA) conducted a multicenter study entitled Diagnostic performance of gated-SPECT MPI at rest in patients presenting to the emergency room with chest pain and a normal or nondiagnostic ECG[19], in which the Institute of Cardiology and Cardiovascular Surgery participated in Cuba.

This study included 356 patients from 10 centers belonging to eight countries who were injected a technetium radiotracer during the episode of acute chest pain, or within six hours after the end of it. As a primary response variable, it was considered the composite of death, nonfatal myocardial infarction, recurrent angina and coronary revascularization at 30 days of inclusion in the study. Sixty-nine patients (19.4%) had a positive perfusion SPECT (perfusion defects) and 52 (14.6%) had a cardiac event during follow-up. The abnormal SPECT at rest was the only variable that independently predicted the primary variable (odds ratio [OR]: 8.19; confidence interval [CI] of 95%: 4.10 to 16.40; p = 0.0001). The SPECT at rest showed a NPV of 92.7% for the primary variable and 99.3% for death or infarction[19].

As part of this research, a study was conducted at the Institute of Cardiology and Cardiovascular Surgery with the secondary purpose of identifying whether there was agreement between the results of the perfusion SPECT and the presence of coronary calcium in the CCT, in patients with acute chest pain[20]. Fifty-five patients with acute chest pain and normal or nondiagnostic ECG were studied, and followed up for one year. Of these, 16 (29%) had an abnormal perfusion SPECT at rest, and in 11 patients (20%) it was equivocal (summed rest score [SRS] of perfusion ≤3).

The results of this study agree with the findings of other studies, ranging from 46%[21] to 9%[22] with ab-

normal perfusion SPECT.

Classifying an equivocal perfusion result as normal or abnormal can be controversial. Indeed, it is difficult to regard it as normal in the course of an acute chest pain and consequently not admitting the patient to hospital (in our case, for example, in two patients with equivocal SPECT, there was need for percutaneous coronary intervention (PCI) during the first month after the initial episode). Therefore, in our experience, in cases with equivocal results with a SRS equal to 3, especially if the tracer injection was performed during the episode of pain, it is advisable to admit the patient and continue the study before discharge.

A weak agreement between perfusion SPECT and the CAC score (Kappa coefficient of agreement: 0.25) was observed. In 12 patients (23%), an invasive coronary angiography was performed as a result of a positive SPECT, which led to a PCI in nine cases (75%). A positive SPECT (with abnormal or equivocal result) was associated with the occurrence of complications at follow-up (χ^2 = 19.961, p <0.0001). The relative risk (RR) for presenting these complications during the first year, in the case of a patient who came to ED with acute chest pain and a normal or nondiagnostic ECG, with an abnormal perfusion SPECT, was 7.5 (95% CI: 2.8 to 19.2; p <0.05), but in the case of a positive CAC score, the RR was 1.77 (95% CI: 0.69 to 4.56; p = NS)[20].

This study concluded that patients with acute chest pain and normal or nondiagnostic ECG, and with a normal perfusion SPECT at rest, have a very low probability of cardiac complications during the first year, while the CAC score is not useful for risk stratification.

Therefore, it stresses again the controversy between anatomical information vs. functional information, since the anatomical condition of the coronary arteries is not proportionally associated with myocardial ischemia; because ischemia is the result of a combination of elements that not only include the anatomy, namely the obstruction of the coronary lumen, but also the characteristics of the atherosclerotic plaque and the perfused myocardial region. In this sense, the work of Priest[23] can be helpful, because even though the authors propose a two-stage strategy (first a CCT, and a stress SPECT only in those patients with indeterminate results, as a less expensive option) they also recognize that a negative CCT was associated with a higher complication rate than in the case of SPECT.

In the experience of our working group, the protocol of SPECT at rest is undoubtedly more useful in the case of patients with no history of myocardial infarction, since it is just a protocol of perfusion at rest; and if the patient had a history of infarction, there may be a perfusion defect in the area of infarction, which would make it difficult to determine if there is a reinfarction there.

Among the causes of false positive SPECT are the attenuation defects in the anterior and inferior segments, due to breast attenuation (in women) and diaphragmatic attenuation, respectively. To make a differential diagnosis with an ischemic defect, it may be useful an assessment of the segmental wall motion and its systolic thickening, which may be altered in an acute ischemic episode, and would be normal if there is an attenuation defect, or, still better, apply an attenuation correction during the image processing.

Another possibility is the SPECT with a stress-rest protocol. It may be used, according to the preferences and protocols established in each hospital, in patients presenting with acute chest pain who have an ECG that is nondiagnostic of ischemia and negative cardiac enzymes after 24 hours of their arrival at the ED. Nabi *et al*[24], in a prospective observational study that included 1 576 patients who were assessed over a period of six months, found out that complication rates were higher in patients with abnormal SPECT (40%) vs. normal SPECT (1.6%), p < 0.0001; and concluded that the addition of SPECT results increased significantly risk prediction, above clinical variables.

In our department, we have incorporated the protocol of perfusion SPECT at rest in patients presenting to the ED with acute chest pain and normal or nondiagnostic ECG as part of regular work protocols, as long as the tracer injection is performed during the episode of acute chest pain or within six hours after the end of it. This protocol can easily be used in those hospitals with a Nuclear Medicine department and an ED for receiving patients. **Figure 1** shows the case of a patient who came to the ED with an acute chest pain that had ceased four hours before the injection of the radiotracer. In the perfusion at rest image, an uptake defect is noticed in the anterior, apical and anteroseptal segments. **Figure 2** shows the left anterior descending artery with a proximal stenosis of 90%, and the outcome after PCI.

It is important to consider some aspects that must be taken into account when interpreting the results of a perfusion SPECT in the setting of acute chest pain:

- Due to the limits of resolution of the SPECT technique, small ischemic areas (<5% of the left ventricle) may not be detected.
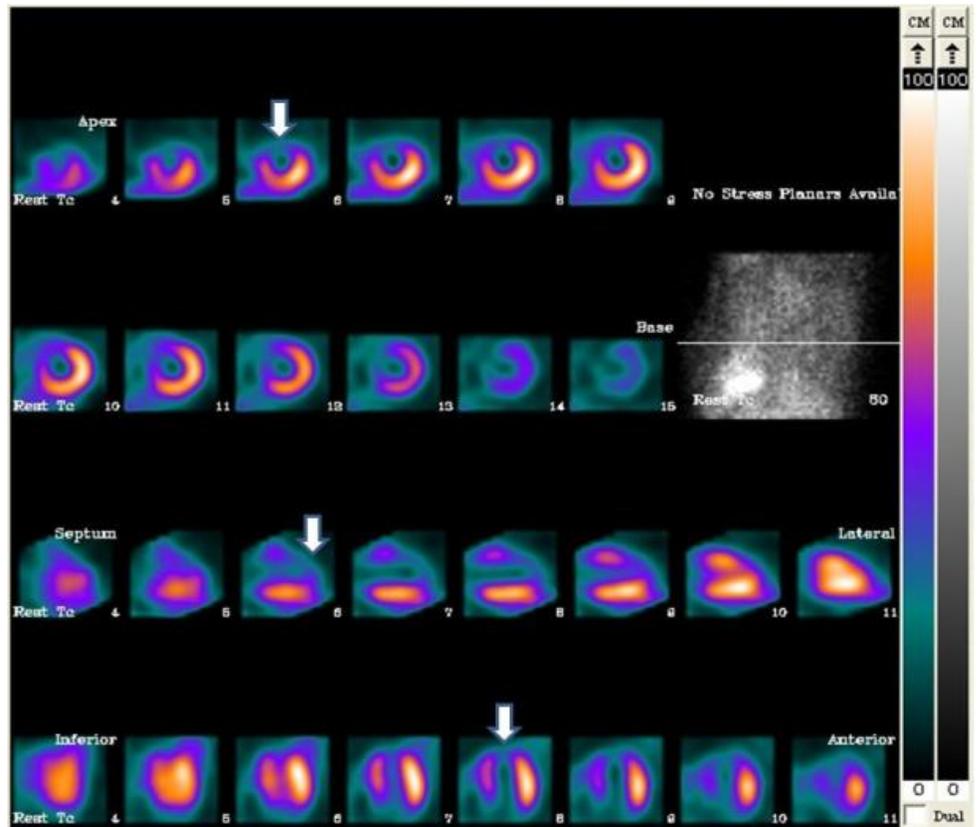- For the best possible sensitivity with SPECT, pa-

Figure 1. Male patient who came to the ED with an acute chest pain that had ceased four hours before the injection of the radiotracer. In the perfusion at rest image the uptake defect can be noticed in the anterior, apical and anteroseptal segments (arrows).
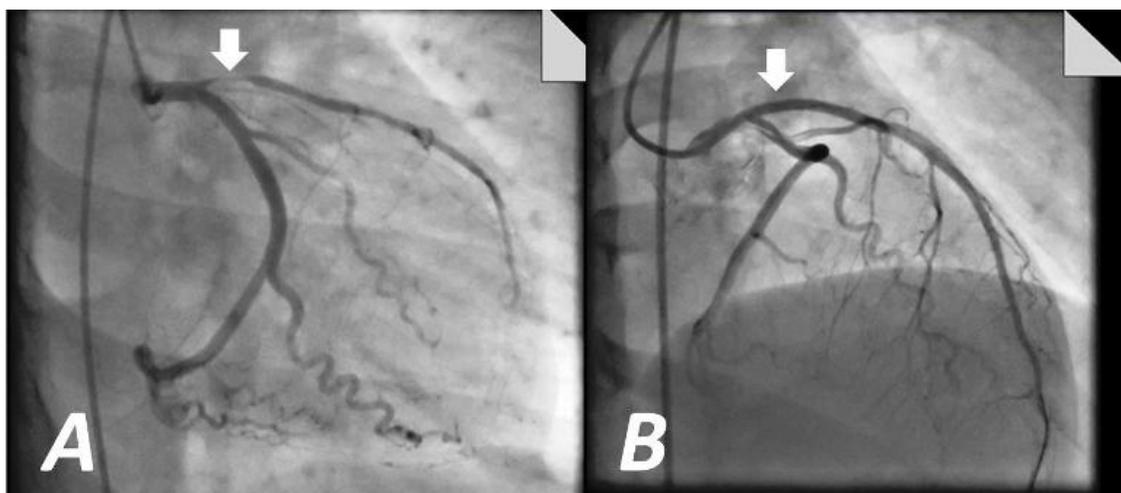
Figure 2. Image of an invasive coronary angiography. **A.** Left anterior descending artery with a proximal stenosis of 90% (arrow). **B.** Result after percutaneous coronary intervention (arrow).

tients should be injected with the radiopharmaceutical of choice during the episode of pain or near the end of it. However, both, our study and the multicenter study sponsored by the IAEA included patients who were injected up to six hours after the end of pain and the results were adequate. Logically, a shorter delay in the injection timing with regard to the pain leads to increased sensitivity of the perfusion SPECT.

- Another alternative that may be useful in these cases is to combine the results of the SPECT with serial markers of necrosis.

Generally, Nuclear Medicine departments do not offer a 24-hour service, restricting the availability of this protocol to the working hours. However, Schaeffer *et al*[22] showed that if the patient arrives in the early morning, an injection of the radiotracer in the early hours, with acquisition after 6:00 am, when Nuclear Medicine technologists reach the hospital, may be a valid alternative.

CONCLUSIONS

In patients presenting to the emergency room with acute chest pain and having a normal or nondiagnostic electrocardiogram, a normal perfusion SPECT at rest is associated with a very low probability of cardiac complications during the first year. Therefore, the SPECT at rest is a useful protocol in the screening of ACS in cases that do not have a typical diagnosis.

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