EDITORIAL

ASSESSMENT OF CHEST PAIN IN THE EMERGENCY ROOM. THE ROLE OF NUCLEAR CARDIOLOGY

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Key words: Emergency chest pain. SPECT and Gated-SPECT myocordial perfusión.

A patient admitted to the Emergency Room with chest pain syndrome has always been a challenge for the cardiologist. About one third of the patients sent home come back with an acute myocardial infarction (AMI)[1,2] and in about one third of those admitted to the Coronary Unit the AMI diagnosis cannot be confirmed.[3,4] Frequently, the conservative behavior of observation and/or diagnostic wait is opted for, which increases the number of patients being admitted at the Intensive Care Coronary Unit (ICCU) and overpopulates this critical, costly and fast mobility area. This scenery also serves the risk of "professional liability" lawsuits.[5]

In the 1985-90 period, a 25% reduction of AMI morbidity and mortality was achieved,[6] thanks to a better knowledge of the etiopathogenesis, the continuous development of new technologies that provide a fast and reliable diagnosis, and very specially to the immediate use of new revascularization techniques. Finally, education of the medical staff and the public in general, with respect to primary and secondary means of ischemic coronary heart disease (CHD) prevention, have also contributed considerably.[6]

Some of the various problems and/or dilemmas that chest pain syndrome represent are described. **Questioning and careful physical examination** are the most important means by which a physician tries to distinguish an ischemic from a non-ischemic chest pain, being the latter the most frequent reason for the acute "thoracic" pain in emergency rooms.[7-9] Clinical assessment is still essential in the diagnostic process.[8] Specific characteristics of chest pain, typical in angina pectoris, are a great help for diagnosing. Yet, an atypical pain type does not preclude an AMI diagnosis, given the differences in personality, resistance to pain, stoicism, culture/education, diabetic neuropathy, etc. which can modify the usual angor characteristics.[10,11] Patients admitted with angina symptoms, subsets or equivalent, must be studied. These symptoms may be, for example, postprandial pain, nocturnal pain (soon after retiring, assuming recumbent position, demand ischemia, many hours after retiring, supply ischemia), dyspnea, rhythm alterations, syncope, or other frequently observed symptoms in diabetic or elderly patients. It is widely accepted that morbidity and mortality in patients with silent ischemia is as high as in individuals with painful ischemia.[11]

Physical examination findings that may be associate to ischemic heart disease, and therefore may direct us to a diagnosis, are: third or fourth heart sound (gallop), new mitral regurgitating murmur, septal rupture murmurs, lung rales and marked hypotension. These data also point out the seriousness and extension of an infarction and/or myocardial ischemia. However, absence of such symptoms does not rule out acute coronary insufficiency.[10,11]

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Equally necessary is to find out the existence of risk factors for coronary artery disease, such as family history, sex, age, hyperlipidemia, smoking, hypertension, and diabetes mellitus. These may determine, together with the patient's condition, the type of examination methods required to complete a diagnosis of coronary artery disease and stratify the risk. But there is no general agreement on their usefulness distinguishing patients with an acute infarction.[10-11]

Diagnostic decisions are based on an electrocardiogram (ECG) at rest, which, even at the time of pain, has low sensitivity for CAD diagnosis (35-65%) and low specificity (69%).[12]

Unfortunately, during the initial stages of this ailment, changes that point toward acute myocardial infarction (AMI) are found in under 50% of cases.[12,13] To find a patient with a clinical condition of AMI and a normal ECG is not unusual;[4,7] thus, the need to perform serial ECGs or keep the patient under constant electrocardiographic monitoring. In a prospective study of 1000 patients at moderate risk for CHD, automated serial 12 lead ECGs were monitored every 20 seconds and printed at least every 20 minutes during a mean period of 128 minutes in the Emergency room while awaiting hospital admission. The sensitivity of ST-segment elevation was increased by 16.2% from 45.6% to 61.8% ($p < 0.001$) with no decrease in specificity.[14]

The idea that chest pain with a normal ECG has a non-cardiac origin must be discarded and patient examination must be continued.[13]

Cardiac enzymes. In the early stages, an isolated determination of CPK enzyme and its MB fraction, in absence of electrocardiographic findings indicating an AMI, is of limited use for diagnosis since it is after 3-4 hours from the acute event onset that it increases considerably, and as a single isolated test it has a sensitivity of 35% to detect AMI.[15-17] In a prospective study in our Institute, the sensitivity of CPK-MB was of 50% and the specificity of 100% for AMI.[18] Serial enzymes determinations (using immunochemical analysis) with simultaneous ECGs increase sensitivity to over 88%. When the enzymatic method of enzyme process is used, test results take over 20-25 minutes, and about 1 hour if the immunochemical method is used.[15,16] To obtain faster laboratory results for a timely and reliable AMI diagnosis, in line with the present therapeutic approach of early revascularization, other fractions of CPK-MB have been isolated (4 isoforms). Myoglobin and troponin T[16,17] yield a higher sensitivity in a shorter period, but are not cost efficient. Myoglobin is the earliest tracer (2-3 hours) for myocardial ischemia detection, with a high sensitivity (100%), but has the problem of specificity since it is also produced in the skeletal muscle and can be increased in muscle skeletal disorders and in renal damage. Troponin proteins are located on the thin filament of the contractile apparatus of the myocite and consist of the three troponin subunits: C, T, and I. They become positive between 1 to 16 hours after the onset of myocardial injury, and elevations persist for 5 to 14 days. In the 0-4 hours period, it reaches a sensitivity of 33-50% with a specificity of 86-95%. This makes them ideal for late AMI but useless for the diagnosis of early AMI (< 6 hours) or infarct extension (> 72 hours and < 2 weeks). Both qualitative (bedside) and quantitative assays are now available for cardiac-specific epitopes, cTnT and cTnI.[17] Hamm et al.[19] performed a prospective study using qualitative, point-of-care testing for cTnT and cTnI in 773 patients with acute chest pain for less than 12 hours without ST segment elevation on their initial ECG. Testing was performed shortly after and repeated 4 to 6 hours later. Patients were followed for 30 days for the end points of cardiac death, and nonfatal recurrent (after 24 hours) AMI. The 773 patients had a final diagnosis of AMI in 24% and unstable angina in 43%; 33% had no evidence of coronary disease. Of 47 patients with AMI, 94% had a positive cTnT (cutoff, 0.18 mg/mL) and 100% a positive cTnI during emergency room testing. There were 34 cardiac events at 30 days, cTnI had a sensitivity of 94% and cTnT of 79.4% for death and recurrent AMI. The negative predictive value of cTnI was 99.7% and of cTnT was 98.9%. This study suggests that two qualitative measurements of cTnI after at least 6 hours of chest pain onset can discriminate cardiac events at 30 days follow-up. Although this potentially a very useful finding for the emergency room diagnosis of cardiac chest pain, multicenter studies are needed before its generalized implementation.

The bidimensional echocardiogram[20] at rest, or with dobutamine, plays an important role in myo-

cardial acute ischemia diagnosis. It has a sensitivity of 88% and specificity of 78%.

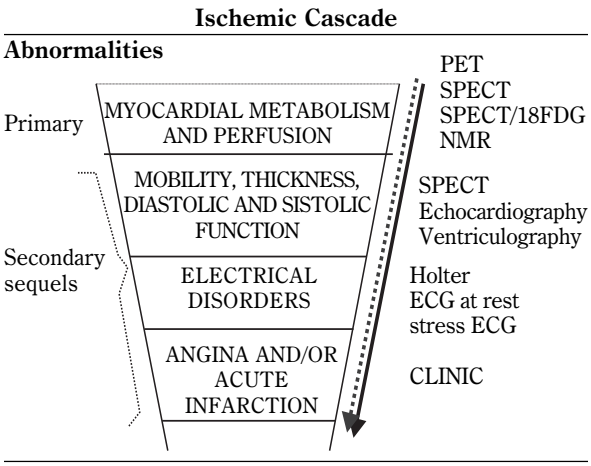
The role of Nuclear Cardiology. Approaching a patient with chest pain syndrome demands strategies to facilitate a fast and reliable diagnosis by non repetitive methods with high sensitivity and specificity, in detecting the early stages of acute ischemic heart disease.[21,22] Nuclear cardiology, by means of Positrons Emission Tomography (PET),[23] Single Photon Emission Computerized Tomography (SPECT), Gated-SPECT, and SPECT with 18-fluorodeoxi-glucose (SPECT/18-FDG) can detect initial alterations, produced by ischemia, such as metabolic disorders appearing as regional perfusion decreases.[22]

The chain of events that take place during an ischemic cascade[21] *(Figure 1)* shows that the decrease myocardial blood perfusion causes, *primarily,* metabolic alterations that produce changes at the cellular membrane's level. This translates into ion transport alterations and changes in intrinsic cellular properties. The use of radiotracers is therefore recommended, since for these to be captured by the myocardial tissue, cellular membranes and metabolism integrity, and regional myocardial blood flow perfusion are necessary.[22] *Consequences* of regional myocardial blood flow decrease, such as alterations of global and segmentary contractility, and cardiac muscle shortness may be assessed by means of radioisotopic ventriculography, electrocardiographic. Synchronized-SPECT (Gated-SPECT), as well as a by different echocardiographic techniques. In later stages electrocardiographic conduction and rhythm alterations are found, which can be detected by the ECG at rest, under stress and/or Holter. In the final stage, angina pain, the most common condition in the patient with coronary arterial disease, is found. Initial changes due to blood flow decreases can only be detected by perfusion nuclear cardiology studies. Therefore, protocols to study the different stages and the clinical development of an acute coronary syndrome have been established.[3,4,24]

Physical properties and usefulness of radiotracers

Radiotracer distribution in the myocardial cells is proportional to the myocardial blood flow. Its ability to enter cells depends on cellular function and an intact sodium-potassium ATPase system. *Thallium*-201 (TI-201) tracer has an energy of 69-83 keV with a mean life of 74 hours, and the amount required is 2-3 mCi. The images obtained immediately after the TI-201 injection reflect the **regional distribution** or perfusion of myocardial blood flow. Once it is within the cell, its accumulation is a dynamic process with the isotope in a continuous exchange, entering and leaving cells through cellular membranes (**distribution phase**).[23,25] Images obtained 2 to 24 h later (**redistribution phase**), by keeping a direct ratio with cellular oxidative metabolism, indicate the existence of myocardial viability, therefore, providing different physiopathologic data. The TI-201's early distribution is the clue of the protocol designed at the emergency room during chest pain, since excellent images are obtained 20 min after its administration at the arrival of the patient (see thereafter). **The perfusion defect is directly proportional to infarct size**. TI-201 has the relative disadvantage of its early redistribution required to obtain the images immediately after the injection. Another disadvantage[23] is its lower energy level, which produces images that are said to be "less sharp" (but not necessarily in this emergency circumstances). Also, a disadvantage is its lack of availability throughout the 24 h, since its production needs a cyclotron. At present its cost is lower than the isonitriles.

Isonitriles[26,27] are radiotracers with an energy of 140 keV and a mean life of 6 hours. Larger doses can be safely given to obtain defined and images quality. Due to their great intracellular charge, isonitriles are "grabbed" into the mitochondria hindering an important redistribution. As for Thallium their **capture is directly dependant on regional myocardial blood flow**. With Tc-99 Sestamibi a large hepatic and gastrointestinal concentration is obtained. Thus, after injected, the waiting period for image taking is 40-60 min, because it needs to be eliminated. Just like thallium, it provides information on ischemic tissue, necrosis zones, myocardial tissue "at risk" during an AMI, viability, and also identifies and quantifies the "salvage" myocardium resulting from a revascularization procedure.[26] *Tetrofosmin*[27] is a difosmin-cation that very quickly accumulates in the myocardium. It belongs to the group that binds to Tc-99m, with features similar to sestamibi; nevertheless, it has



PET: Positron Emission Tomography
SPECT: Single Photon Emission Computarized Tomography
ECG: Electrocardiogram
18 FDG: 18-Fluoro-deoxi-glucose
NMR: Nuclear Magnetic Resonance

FIG. 1.

the advantage of a faster depuration at the hepatobiliary level, which allows earlier imaging. Excellent Gated-SPECT images are obtained when isonitriles or tetrofosmin are used.

Pyrophosphates are used since 1974 based on the principle that calcium deposits in crystalline and sub-crystalline forms in damaged or necrotic myocardial cells (irreversibly). Its capture during AMI depends on the residual flow degree of the compromised artery. Activity starts 10-12 hours from the symptoms onset, reaching its maximum 24-72 hours, and decreasing until undetected in 10-15 days. Its activity increases with thrombolytic use or early perfusion.[29]

Antimyosin antibodies belong to the radiotracers group bound to monoclonal antibodies. A large immunoglobulin antimyosin Fab fragment binds to myofibrils exposed by the disrupted membranes of necrotic myocytes. Antimyosin is marked with Indium-111. Accumulation zones of the product ("hot spot") correspond to necrotic zones. Antimyosin is highly specific for myocardial necrosis diagnosis, its uptake degree has prognostic implications. Since, it is different from agents bound to technetium and thallium and it does not give information in regard to other aspects, such as residual ischemia, viability and mobility.

We have developed protocols[28,30-32] for specific circumstances to assess chest pain in an emergency room *(Figure 2)*. *Emergency Protocol I:* will be used in cases that due to their complexity (clinical, diagnostic, risk, etc.) require an emergency assessment, including even those received 12 hours after chest pain onset. *1st. Stage*: *Thallium-201 at rest.* 2-3mCi of TI-201 are administered and perfusion images are immediately taken and results obtained in 20 minutes. If needed, *a 2nd. stress stage* is performed with Tc-99m-Sestamibi or Tetrofosmin. Study duration: 60 minutes. To complete, ratify, or rectify diagnosis findings, the patient is subjected to drug stimulation with dipyridamole or adenosine. At the end of the pharmacological stress, 25 mCi of Tc-99m-sestamibi or Tetrofosmin are injected, and after a waiting period of about 40 minutes (for the purpose of reducing hepatic, visceral and biliary contamination of cardiac images), perfusion images are taken for 15 minutes. Results are obtained 60 minutes after the start of this second stage. This is how, in less than one hour and twenty minutes from patient's arrival to the emergency room, objective diagnostic information for the therapeutic approach can be obtained or else send the patient back home. Guidance for the immediate and mediate prognosis is obtained, which allows for individual patient risk rating.[24,31]

Relative Urgent Protocol II. Tc-99m sestamibi or tetrofosmin will be used in cases considered of relative emergency. *1st. stage:* Protocol at rest with Tc-99m sestamibi or tetrofosmin. Duration: 60 min. A dose of 8-10 mCi of Tc-99m sestamibi is injected. After one hour (to avoid or diminish cardiac contamination) the myocardial perfusion images are obtained during a 15 minutes period. *2nd. Stage:* with pharmacological stress using adenosine or dipyridamole and Tc-99 sestamibi or tetrofosmin. Add 60 minutes *(Figure 2)*.

Has been emphasize the convenience of injecting the radionuclide during or as close as possible to the onset of symptoms (pain) to achieve maximal results.[32] There is no general agreement as to its value or of an increased sensitivity in obtaining a positive perfusion image. Therefore, are not to be considered this perfusion findings as equivalent to an "effort or pharmacological stress study".

The value of our findings were the same,[33] irrespective of using at rest, TI-201 (Emergency protocol I) or Tc-99m sestamibi or Tetrofosmin

(Relative Urgent protocol II). Decision making is similar in both protocols according to results.

Three different perfusion results can be obtained: normal, doubtful, or with perfusion defect. In the latter condition, the patient is admitted in the ICCU to define the diagnostic and/or therapeutic approach, because, according to our findings,[33a] **an abnormal perfusion defect at rest** demonstrated a positive predictive value (PPV) of 88% (CI 95%, 67-96%) and an 87% specificity (CI 95%, 66-96%). Otherwise, when the myocardial perfusion imaging at **rest was normal or non-conclusive**, the patient had to subjected to the second stress stage perfusion, since 58% of our cases had normal resting myocardial perfusion and half of them became positive under pharmacological stress test. **The sensitivity at rest was of 61%** (IC 95%, 39-74%) and therefore could not validate the existence or absence of a perfusion defect, establishing the need to ratify findings and/or supplement the diagnosis by going on to the second stress stage of the protocol. *Under stress, a positive perfusion defect has a sensitivity of 97%* (CI 95%, 83-99%). Otherwise, a **negative or normal perfusion finding after stress demonstrated a remarkable negative predictive value** (NPV) of 95% (CI 95%, 73-99%) that rules out the presence of an acute coronary syndrome in those patients with chest pain and normal or doubtful ischemic ECG. Therefore, no admittance to the CCU nor catheterization is needed.

It should be emphasized that normal rest results obtained with TI-201 and/or Tc-99m sestamibi study, still require a stress test. The findings concur that the rest perfusion images obtained with TI-201 or sestamibi are extremely useful in case of an abnormal perfusion, 88% PPV, but not if the resting image is normal (sensitivity 61%); hence, the need to perform immediately thereafter a stress test to ratify or rectify the diagnosis, with the consequent loss of time and sometimes of an adequate emergency diagnosis and urgent therapeutic decision.[33]

Based on these experience, we have initiated our *Emergency Stress Protocol III* consisting of an immediate stress test with adenosine or dipyridamole at the patient's arrival at the emergency room, indistinctly with TI-201 or Sestamibi. The

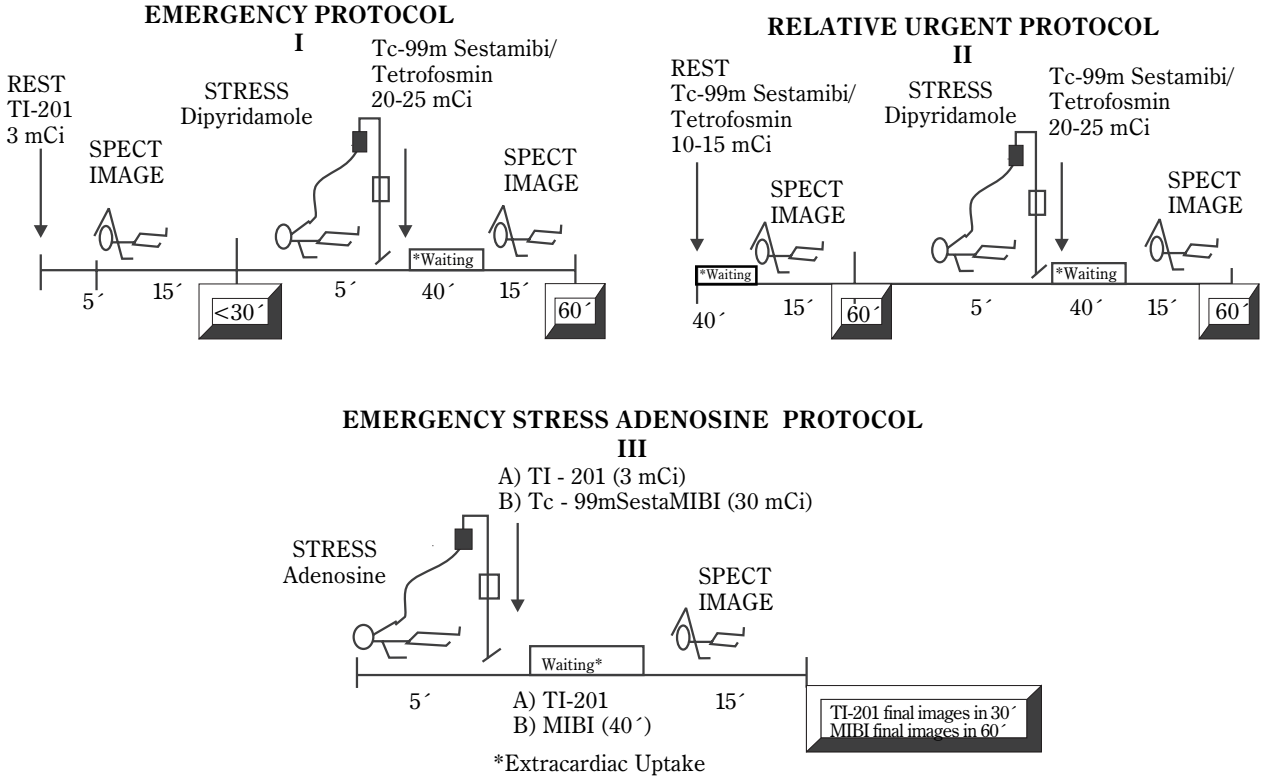


FIG. 2.

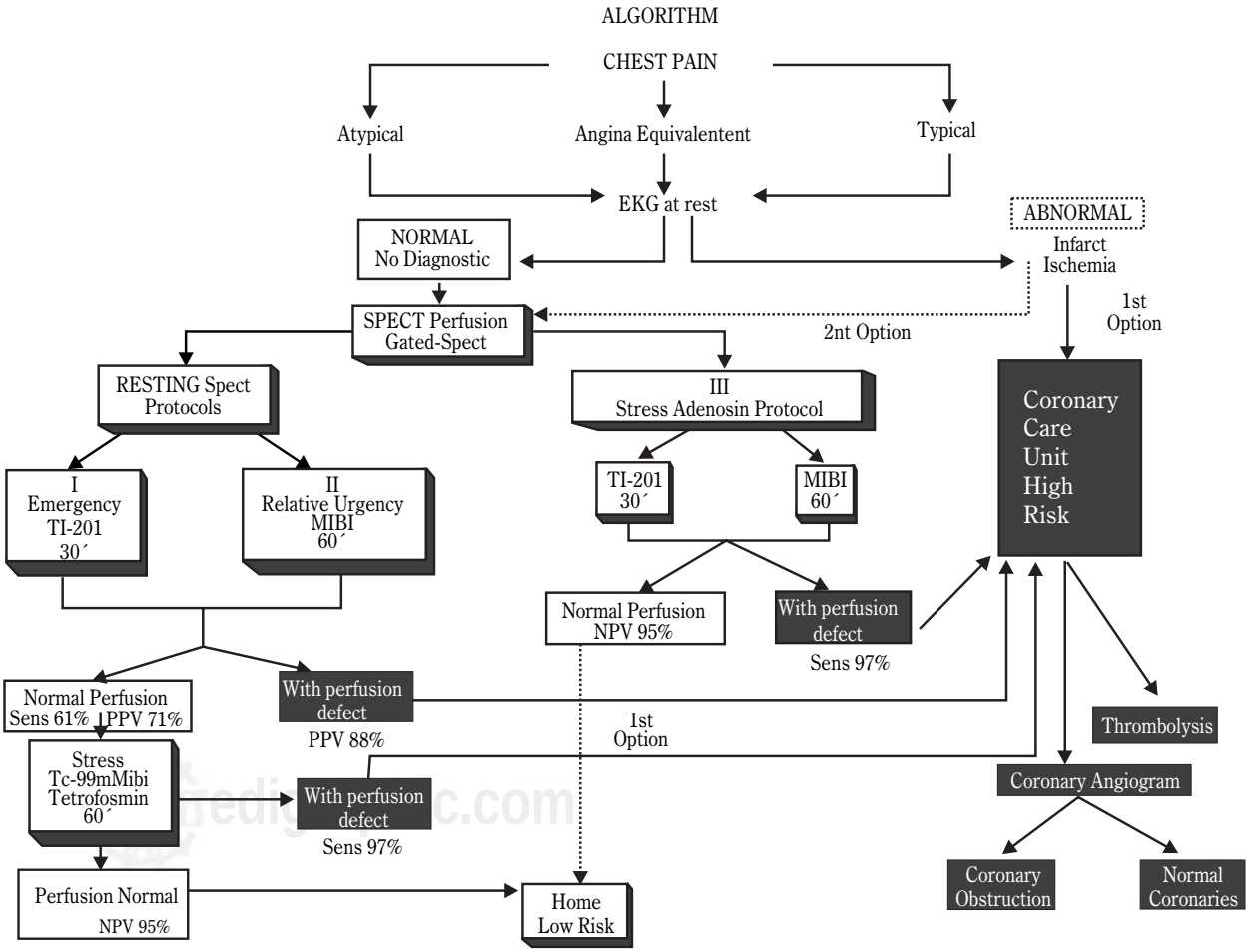
decision is to perform a stress SPECT imaging as the first diagnostic study. Our first 50 cases have demonstrated no complications, an excellent correlation with catheterization findings, and an important diagnostic and therapeutic time and cost saving *(*Algorithm *Table I)*.

While the results of a SPECT scintigraphy may obviate the need for coronary angiography, the two methods are complementary. Coronary angiography provides an anatomic "road map" and perfusion scintigraphy demonstrates the functional consequences of circulatory compromise on a cellular and global cardiac basis.

Several papers in the world literature show studies on assessment of chest pain in emergency rooms, by means of nuclear medicine,[28] among them, Wackers,[31] Bilodeau,[32] Varetto,[34] Hilton,[35] Stowers,[36] Heller,[37] Kontos,[38] Radensky,[39] Abbott,[40] who with different protocols, employing Thallium-201 or TC-99m Sestamibi or Tetrofosmin, at patient admission to the emergency room with chest pain syndrome, have evidenced that myocardial perfusion examinations have a high sensitivity and specificity, facilitating early diagnosis of coronary arterial disease. This allows to determine the range of risk, offer useful prognosis information to help the physician on a correct clinical decision, regarding hospitalization and adequate treatment of patients suspected with acute coronary syndromes, and the dismissal of low risk patients when those syndromes are ruled out, therefore avoiding larger costs due to hospitalization.[41]

Extension of the immediate diagnosis horizon (Table II). Emergency room should expand their diagnostic view, not only to solve immediate problems but also for those of mediate im-

Table I



portance. In other words, to establish the myocardial ischemic diagnosis is not enough; the need arises to have complete information about the risk consequences of an acute coronary obstructive process, in order to make diagnostic and therapeutic decisions in the short and long term, and to define prognosis more clearly.[42,43] Besides, the various techniques used on the AMI patient admitted in the emergency room would allow to: demonstrate and quantify in an objective, direct and reliable manner, myocardium at risk, evaluate the degree and extension, identify with a high percentage of success the artery responsible for the AMI, assess through the Gated-SPECT functional repercussions, systolic thickening, ejection fraction, diastolic dysfunction, abnormal regional wall motion as well as results of the specific therapies used, (percentage of myocardium saved).

CONCLUSIONS

- The evaluation of patients with chest pain in the emergency room must begin with the clinical findings and 12-lead electrocardiogram to classify patients into different risk strata.
- In the examination of chest pain syndrome upon admittance to the emergency room, scin-

Table II
Broad Spectrum View in the Emergency Room of Nuclear Cardiology: diagnosis, assessment and correlations

1. **LV Myocardium in risk**[*]
   Severity: depends on extension, size and depth (non transmural and transmural)
   Site: anterior, lateral, septal, apical, inferior; combined and/or simultaneous.
   Reversibility (Ischemia).
   Fixed defect (infarction)
   Mixed (necrosis and ischemia)
   Reverse-Reversibility [2*]
2. **Responsible artery (ies)**
   Correlate location and degree of ischemia with artery involved.
   The residual flow with high sensitivity can be inferred in the involved artery[3*]
3. **Viable myocardium:** Stunned/Hibernating: Redistribution/reinjection protocol TI-201 SPECT/18FDG[4*]
4. **Assessment of microcirculation and collateral circulation:**
   Associated epicardial coronary arteries obstruction and normal coronaries.
5. **Left Ventricular Dysfunction:**
   Ejection fraction
   Post stress LV cavity
   Thallium retention at pulmonary level
6. **GATED SPECT: Simultaneous assessment of myocardial perfusion and LV function:**
   Global and regional wall mobility, systolic thickness, ejection fraction, diastolic volumes.
7. **Ventriculogram:**[5*] **Determines global and regional EF, with preciseness and highly reproducible.**
   Diastolic function.
8. **Right Ventricle:** Myocardium in risk, ischemia and/or infarction, dilatation and dysfunction; EF.
9. **Assessment of revascularization and reperfusion treatment effectiveness**[6*]
   Saved myocardium (with pre-procedure and post-examinations).
10. **Post-treatment coronary restenosis assessment of revascularization.**

[*] Quantifies objectively, directly and reliably the comprised myocardium, it is the most precise method.
Relates objectively risk area with morbi-mortality., risk area > 1% = 7% mortality; Area < 12% = null mortality.[37]

[2*] Reverse. Reversibility: recanalization of involved artery, collateral circulation, artefact, infarct scar, microcirculation.

[3*] Ischemia presence and degree (objective) allow hemodynamist decide to dilate or not, compromised vessel based on functional repercussion.

[4*] With TI-201 protocol, 90% preciseness to determine presence of viable tissue SPECT-18 FDG, increases to 100% and together with PET represent the "gold standard" for the direct study of cellular metabolism and viability.[20,21]

[5*] Represents the gold standard.

[6*] Surgical or with angioplasty and reperfusion with thrombolysis

LV = Left ventricle; SPECT/18FDG: Single Photon Emission Computarized Tomography/18 fluoro-deoxi-glucose; EF: ejection fraction.

tigraphic examinations offer an alternative option and should be the starting point and be considered the **"single best test"**

- Patient's care upon admittance to the Emergency Unit has been substantially and dramatically modified due to this "technological simplification", that allows for decision making in a fast and efficient way with a high degree of reliability.
- By reducing in-patient time and admittance frequency, the cost-benefit ratio is greatly improved.[44,45]
- Nuclear Cardiology opens a dramatic road for the specific case of acute myocardium infarction allowing for fast and reliable diagnosis, focused therapy, and patient reference to adequate hospital services, with greater efficiency and lower cost.[45-47]
- The relative ease for nuclear technology use prompts the convenience of its daily use in emergency services. Therefore it is considered wise to have the necessary facilities nearby, even inside the emergency room itself (Chest Pain Unit).
- As part of this proposal, the development of educational programs, both for physicians and the public, to create an awareness on the need for an early diagnosis and, consequently, an efficient patient treatment, is required.

Corollary: The ultimate goal is to obtain an urgent diagnosis of excellence while treating a patient, at an appropriate and competitive cost.

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