The Clinical Significance of the Prognostic Value of Radionuclide Methods in Known or Suspected Coronary Artery Disease. Established Knowledge and Recent Advances

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Nuclear cardiology was introduced in clinical practice in the early 1970s, and since then there has been a sustained growth of 15% per year[1]. Radionuclide methods allow for the accurate assessment of both relative myocardial perfusion and ventricular contractile function. Recently, a great deal of attention has been placed on risk stratification of patients with coronary artery disease. With this risk-based approach, the focus is not on the detection of coronary artery disease, but on identifying patients at high or low risk for major cardiac events in the future.

The diagnosis of coronary disease is the cornerstone for the therapeutic decision process. In patients with typical angina, medical treatment aims at relieving symptoms; interventional treatment (percutaneous coronary intervention or coronary artery bypass grafting) may be considered if conservative treatment fails to control symptoms. On the other hand, risk stratification addresses the cases in which symptoms are not the principal or the only criterion for selecting the appropriate therapeutic management. In the presence of atypical symptoms or mild angina, or in the absence of symptoms, improving the prognosis of patients may be the therapeutic criterion. Nevertheless, the therapeutic target may include both the relief of angina and the improvement of prognosis. Clearly, risk stratifying patients with coronary artery disease is the prerequisite for selecting the appropriate therapeutic strategy to improve prognosis.

The prognostic evaluation of patients with coronary artery disease is based on the prediction of future cardiac events. Cardiac events may be defined as hard events, including cardiac death (sudden or non-sudden) and nonfatal myocardial infarction, and soft events, namely severe angina pectoris, unstable angina, need for hospitalization, and requirement for revascularization in less than 3 months after the nuclear test. Obviously, although the latter may be of subjective concern, the former appear well-defined and therefore reliable end-points.

To date, accumulated data show that coronary artery bypass surgery prolongs survival, in relation to medical treatment, only in selected subsets of patients (multi-vessel disease, two-vessel disease with left anterior descending artery involvement, left-main disease, left ventricular dysfunction)[2,3]. Conversely, although there is no evidence persuasively supporting that invasive treatment reduces the risk for myocardial infarction, publications reported that aggressive lipid-lowering treatment may be beneficial in reducing future ischaemic events[4]. In particular, percutaneous coronary interventions do not ap-

pear superior to medical treatment in reducing the risk of major cardiac events; thus the former should be primarily applied in patients with single-vessel disease and angina refractory to antiischaemic medication[5,6]. Certainly, as considerable success is achieved by angioplasty in conjuction with stent implantation, percutaneous interventions may obviate bypass surgery in selected groups of patients[7].

Apparently, as the cardiac death rate of patients undergoing revascularization procedures is >1%, mildly symptomatic patients with a <1% mortality risk should not be candidates for revascularization to improve survival[8]. For purposes of risk assessment in patients with coronary artery disease (measured in cardiac mortality rate per year) it has been proposed that low risk is defined as <1%, intermediate risk refers to the 1%-3% range, and high risk is considered as >3%[9].

The most widely applied nuclear tests in cardiology are: a) myocardial perfusion imaging for the detection of jeopardized myocardium, and b) radionuclide ventriculography, for the measurement of ejection fraction and the assessment of segmental wall motion[10,11]. The recently introduced Gated SPECT technique for the combined assessment of myocardial perfusion, global ventricular function, and segmental contractility, has not yet convincingly shown that allows for accurate evaluation of the latter two aspects in moderate or severe ischaemic heart disease, that is in cases where this is particularly important, and it is no further commented[12].

Finally, it should be emphasized that in published reports the contribution of nuclear cardiology to the risk stratification of patients with coronary artery disease is undervalued[13]. This may primarily be due to the fact that high-risk patients, often identified by radionuclide techniques, are either more intensively treated, so that their prognosis may be improved, or withdrawn form the studies; thus, the positive predictive value of nuclear tests may appear diminished.

Physiologic basis of risk assessment in myocardial perfusion imaging

Myocardial perfusion imaging yields positive results in the presence of a haemodynamically significant coronary artery stenosis (>50%), which induces demand myocardial ischaemia at stress. The predictive power of myocardial nuclear imaging is based on the assessment of both the extent and the severity of myocardial perfusion abnormalities, which are generally considered to reflect the extent of coronary artery disease and the severity of atheromatic lesions in coronary vessels. However, it has been observed that most acute coronary syndromes occur in lesions causing less than <50% stenoses, as these are unstable and vulnerable to disruption, which may result in supply ischaemia in myocardium[14,15].

This paradox, to predict acute ischaemic events due to supply ischaemia with a method that in principle detects demand ischaemia, may be explained by the association of plaque instability with endothelial dysfunction. It is postulated that factors released at stress may result in vasodilation in stable, mild coronary stenoses, whereas they may stimulate vasoconstrictive response in mild coronary lesions with unstable plaques, associated with endothelial dysfunction[16,17]. This different response may yield defects in myocardial perfusion images, induced by mildly stenotic lesions with unstable atheromatic plaques[17]. Therefore, myocardial perfusion imaging may be able to discern endothelial dysfunction, which is associated with an increased risk of cardiac events. In this setting coronary angiography may detect anatomically insignificant stenoses, but not haemodynamically important. Certainly, stress induced myocardial ischaemia taken as criterion, cannot be interpreted as a false positive myocardial perfusion result.

Risk assessment in patients with chronic coronary artery disease

Data showing the prognostic power of radionuclide techniques in patients with coronary artery disease initially appeared in 1983[18,19,20]. Concordant with these results, a landmark study, published in 1986, undoubtedly demonstrated that the extent and severity of myocardial perfusion abnormalities are significant, independent variables for the prognosis of patients with angina[21]. This study also demonstrated that the greatest incremental information for prognosis was provided in patients with a high pre-test likelihood of coronary artery disease. Over time, a growing body of evidence substantiated the initial observations on the considerable predictive power of myocardial perfusion assessment in patients with suspected or known coronary artery disease, with either ^{201}Tl or ^{99m}Tc compounds[1,13,22].

Notably, in the presence of an extensive myocardial perfusion abnormality, cardiac mortality risk is increased 5-10 times, in comparison to a normal

result. Despite this, myocardial perfusion imaging possesses a low positive predictive value (≈10%) and therefore it may not be considered a powerful variable for clinical decision-making. However, as described below, a positive result may be successfully utilized for selecting the appropriate therapeutic strategy. Conversely, a normal or borderline abnormal myocardial perfusion is associated with a remarkably high negative predictive value (≈99%), which entails an annual cardiac event rate similar to that of the general population (<1%)[1,13,22]. This high negative predictive value may be the most clinically relevant aspect, as it practically obviates any further catheter-based investigation or treatment, provided that symptoms are minimal or easily controlled on antiischaemic medication. Moreover, it has been reported that myocardial perfusion imaging retains its high negative predictive value when combined with submaximal exercise or even in the presence of multivessel disease[23,24,25]. Thus, low risk for adverse events may be related with multi-vessel involvement, whereas high risk may be associated with one-vessel disease. In addition, it is worth mentioning that the majority of patients enrolled in the prognostic studies were on antiischaemic medication during the nuclear tests.

Studies demonstrated that myocardial perfusion imaging provides considerable predictive power over clinical or exercise test variables, which are easier and cheaper to obtain[21,26,27]. Indeed, it was found that ^{201}Tl SPECT myocardial perfusion assessment provides significant prognostic information over clinical markers alone or clinical plus exercise information[27]. Importantly, it was shown that no incremental prognostic information was provided by catheterization findings, once clinical data, exercise test variables and myocardial perfusion results were known.

It has been previously shown that radionuclide ventriculography parameters, mainly the ejection fraction at rest and during exercise and its change from rest to exercise, are significant prognostic variables in patients with coronary artery disease[28,29]. It appears that an ejection fraction at rest or during exercise <35% bears an unfavorable prognosis. In most cases resting ejection fraction provides significant prognostic information, as it possesses 80%-85% of the prognostic value of exercise ejection fraction[13].

Numerous myocardial perfusion and radionuclide ventriculography studies, comprising tens of thousands of patients, have undoubtedly documented the effectiveness of nuclear cardiology techniques in predicting adverse events in patients with coronary artery disease, and resulted in the incorporation of nuclear tests in ACC/AHA/ACP-ASIM Guidelines[9]. High risk (>3% annual cardiac mortality rate) are considered a resting or exercise left ventricular ejection fraction <35%, a stress induced large defect (particularly if anterior), stress induced multiple perfusion defects of moderate size, and a stress induced moderate perfusion defect or a large "fixed" perfusion defect with either left ventricular dilation or increased lung ^{201}Tl uptake. Moderate risk (annual cardiac death rate 1%-3%) constitutes a resting left ventricular ejection fraction 35%-49% or a stress induced moderate perfusion defect without left ventricular dilation or increased lung ^{201}Tl uptake. Finally, a normal or mildly abnormal myocardial perfusion result signifies a low risk (<1% annual cardiac mortality rate).

Exercise electrocardiography is not an obsolete test. In fact, there is an interplay among exercise testing and myocardial perfusion assessment results[9,13]. However, myocardial perfusion imaging is clearly superior as a single prognostic variable, it provides considerable incremental information over exercise data, and it can more effectively identify patients at low or high risk[30].

The importance of radionuclide tests in the assessment of patients unable to exercise or with abnormal resting electrocardiograms (left bundle branch block, left ventricular hypertrophy, digoxin, Wolf-Parkinson-White syndrome) is apparent. However, the application of nuclear cardiology tests in cases with an interpretable exercise electrocardiography remains controversial, as clinical data and exercise testing may be considered adequate in this setting. Myocardial perfusion imaging should not be performed in patients with a low likelihood of coronary artery disease post-exercise testing, as the cost per cardiac event predicted was found excessively high[31]. On the other hand, in patients with an intermediate or high likelihood of disease on the basis of exercise electrocardiography, myocardial perfusion assessment may subsequently stratify this group into subsets with low or high risk for major cardiac events in the future[30,31]. In particular, it appears reasonable to pursue further nuclear testing in patients with an intermediate risk post-exercise testing in whom the cardiac mortality rate is in the range of 1%-3%[9,32].

Finally, it should be added that as coronary artery disease may progress over time, particularly in the absence of intensive medical therapy, the low risk associated with a normal myocardial perfusion scan remains valid for no more than two years[1].

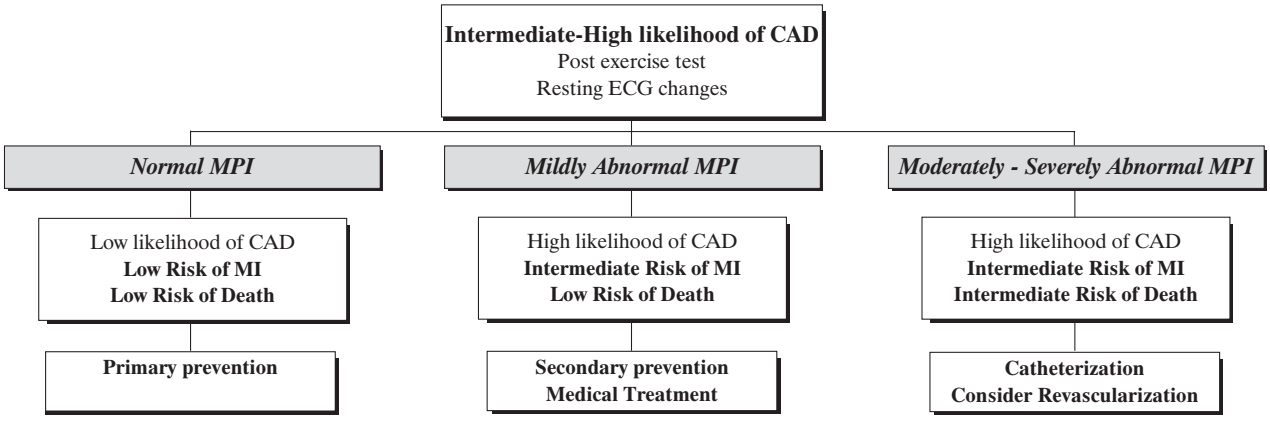

Figure 1. Diagnostic and therapeutic strategy in patients with coronary artery disease, based on myocardial perfusion imaging (CAD: coronary artery disease, ECG: electrocardiography, MPI: myocardial perfusion imaging, MI: myocardial infarction).

The prognostic value of radionuclide methods in the selection of the therapeutic strategy in patients with chronic coronary artery disease

Published data demonstrated that catheterization rates closely parallel myocardial perfusion imaging results[33,34]. Moreover, similar satisfactory outcomes with either medical or invasive strategy were reported in patients with non-extensive ischaemic heart disease, as assessed by myocardial perfusion scans[35]. Myocardial perfusion imaging reliability was further strengthened by data demonstrating a low mortality rate in patients with severe ischaemic heart disease having undergone revascularization, as opposed to patients with extensive myocardial perfusion abnormalities and medically treated[36]. In this remarkable publication both cardiac mortality rate and acute myocardial infarction risk, as a function of myocardial perfusion assessment, were also investigated. It was observed that patients with mild ischaemic heart disease were at intermediate risk for acute myocardial infarction (2.7% per year), whereas in patients with moderate or severe ischaemic heart disease the risk was high (2.9% and 4.2% per year respectively). Conversely, despite the fact that cardiac death rate was increased in patients with moderate or severe ischaemic heart disease (2.3% and 2.9% per year respectively), mild ischaemic heart disease was associated with a low mortality risk (0.8% per year). Finally, patients with normal or equivocally abnormal myocardial perfusion had a low annual risk for both cardiac death and myocardial infarction (0.3% and 0.5% respectively). On the basis of risk stratification by myocardial perfusion imaging, an optimized management strategy may be proposed for patients with intermediate or high likelihood of coronary artery disease before nuclear testing (Figure 1). Patients with moderate or severe myocardial perfusion abnormalities face a high risk for cardiac death per year; therefore, coronary angiography with consideration of revascularization is recommended, as the latter may improve their prognosis. Similar strategy is recommended in patients with refractory symptoms, despite intensive medical treatment. However, patients with mildly abnormal myocardial perfusion are at increased risk only for acute myocardial infarction (>1% per year); therefore, medical treatment may be the optimal therapy in this subset, as invasive procedures do not appear to reduce the risk of myocardial infarction.

Apparently, risk stratification by nuclear cardiology techniques may substantially affect the therapeutic management and the outcome of patients with coronary artery disease. In particular, myocardial perfusion assessment may identify patients in whom coronary revascularization may be beneficial, from others in whom invasive treatment does not improve their prognosis[36].

Risk stratification after invasive revascularization

Despite the fact that nuclear tests may define the presence, location and severity of myocardial ischaemia before percutaneous coronary interventions, it has been noted that a substantial proportion of patients is not submitted even to exercise testing before the procedure. Indeed, it was reported that only 29% of patients having undergone percutaneous interventions had been previously submitted to an exercise tolerance test[37].

Significant restenosis after percutaneous coronary interventions is not necessarily heralded by angina[38]. It has been demonstrated that myocardial perfusion assessment may accurately detect the presence of restenosis, regardless of whether recurrent symptoms are present[39]. Recent publications have suggested that myocardial perfusion imaging remains similarly effective in detecting restenosis in angioplasty with stent implantation[40]. Although few data exist on the prognostic value of radionuclide tests after percutaneous interventions, particularly in asymptomatic patients, it appears that an abnormal myocardial perfusion is associated with an increased cardiac event rate[38].

In patients with single-vessel disease and angina or interpretable exercise electrocardiography before a percutaneous coronary procedure, post-intervention assessment may be based on symptoms and standard exercise testing. Myocardial perfusion imaging can be useful in multi-vessel disease in defining the culprit vessel and assessing the extent of ischaemia. In asymptomatic patients radionuclide testing 3-6 months after angioplasty is recommended[41]. Whenever moderate or severe myocardial ischaemia is detected, subsequent catheterization is the logical approach. Otherwise, repeat nuclear testing 1-2 years after the initial radionuclide assessment is recommended, similar to the management of chronic coronary artery disease.

It is known that by 10 years after coronary bypass surgery 75% of vein grafts are occluded or severely stenosed, whereas better results are achieved if internal mammary arteries are used[42]. Using a 5-year cutoff point after surgical revascularization, myocardial perfusion assessment has been shown to be particularly useful for the prediction of major cardiac events, even in patients with no symptoms[43,44]. The recommended strategy for the post-coronary surgery assessment, formed from a synthesis of up to date published reports, is as follows: When angina reoccurs at any time following coronary bypass surgery, myocardial perfusion imaging may be used, as it may define the presence of ischaemia and assess its extent. In addition, myocardial perfusion assessment is recommended 5 years after bypass surgery in all asymptomatic patients[45]. If myocardial perfusion scan shows an considerable area of induced ischaemia or ischaemic, albeit viable myocardium, further invasive treatment should be considered. In this setting, illustration of coronary anatomy is necessary to decide whether to proceed percutaneously or surgically.

Risk stratification in acute coronary syndromes

Although the diagnosis of acute myocardial infarction is often straightforward, in many cases is not. Clinical presentation, electrocardiography and biochemistry are the main tools for the assessment. However, electrocardiography, for example, may not be diagnostic in one third of patients with acute myocardial infarction presenting in the emergency department, and a considerable proportion of patients with myocardial infarction may be missed[46]. It is therefore important to distinguish patients with non-diagnostic electrocardiograms who may benefit from early intervention, from those who do not require intensive care.

Published data have demonstrated that in chest pain units, where rapid investigation protocols are applied, a distinctly lower proportion of myocardial infarctions are missed (from 4% to 0.4%). In parallel, both the admission rate and the cost per patient are reduced[47,48]. Radionuclide methods may play a pivotal role in these units[49,50]. Interestingly, it has been found that even when troponin measurements are utilized, cardiac radionuclide imaging and enzyme tests provide complementary information[51].

A resting ^{99m}Tc-MIBI study in patients presenting with chest pain and non-diagnostic electrocardiograms may predict a high likelihood for acute myocardial infarction, need for catheterization and primary revascularization, and final diagnosis of coronary artery disease[52]. Compiled data disclose an average sensitivity of 98% and a specificity of 69% in detecting acute coronary syndromes in patients with an abnormal resting myocardial perfusion[1]. It thus appears that a normal myocardial perfusion scan possesses a high negative predictive value, and in the absence of other compelling evidence these patients may be discharged or subsequently investigated for induced ischaemia with stress testing, with or without radionuclides.

The assessment of patients having suffered an acute coronary event is drawing particular attention. Guidelines suggest that in post-myocardial infarction patients with a low or intermediate clinical risk, exercise testing (without or preferably with perfusion imaging) may be effective in risk stratification, subsequent catheterization referral, and therapeutic decisions[53]. This recommendation for selective catheterization is based on several publications, among which the TIMI IIIB study is the most widely quoted[54]. Notably, radionuclide methods were not used in a

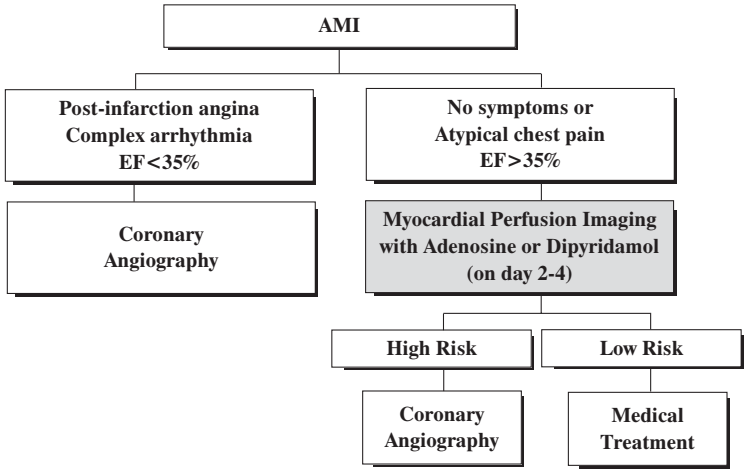

Figure 2. Strategy of diagnostic approach and therapeutic management after an acute myocardial infarction (AMI), (EF: ejection fraction).

standardized manner in these studies. Recent results, with a standardized approach of nuclear cardiology techniques, have demonstrated that a similar selective catheterization strategy may be beneficial in patients with non-Q acute myocardial infarction[55]. Interestingly, recently published data support invasive strategy in all patients with non ST-elevation acute coronary syndromes[56]. However, no risk stratification based on clinical markers was employed in this study. Moreover, the prognostic assessment in the conservative treatment group was based on any non-invasive modality available, without exclusively using the most effective test according to literature, namely myocardial perfusion imaging. With careful non-invasive risk stratification, that study might augment previous results[54,55].

Publications in the post-thrombolytic era (>1985), disputed the prognostic value of radionuclide methods[57,58]. These studies, however, generally included low-risk patients, as high-risk patients tended to receive catheter-based management, many of them because of an abnormal myocardial perfusion result[58,59]. Recent work suggested that myocardial perfusion imaging with pharmacological stress may be safely performed 2-4 days after an acute myocardial infarction, and it can separate patients at high or low risk for cardiac events[60,61,62]. Furthermore, the prognostic significance of ejection fraction in post-myocardial infarction patients was demonstrated in a meta-analysis[63]. It has also been shown that in patients having suffered a myocardial infarction, very early myocardial perfusion assessment with pharmacological stress can predict early and late cardiac events, with superior prognostic value compared to submaximal exercise testing[64]. Adoption of this strategy may allow for management decisions to be made earlier in selected subsets of patients, with substantial cost savings associated with a shorter hospital stay[65]. Moreover, recently published data support that a radionuclide guided selective catheterization strategy may be extended to patients with an intermediate to high risk after myocardial infarction[66].

One of the major dilemmas in patients with a myocardial infarction is the use and timing of cardiac catheterization. Currently, most post-myocardial infarction patients are routinely referred for coronary angiography[53]. An alternative strategy, advocated by clinical guidelines, is to submit to catheterization patients with post-infarction angina, complex arrhythmias, or a low ejection fraction (<35%)[67]. In patients with an uncomplicated hospital course, a non-invasive approach is recommended to identify patients in whom catheter-based management may be decided (Figure 2). First, left ventricular function assessment is recommended, as it has been proven the most powerful variable for predicting cardiac death[63]. Once ejection fraction is reasonably preserved (>35%), early myocardial perfusion assessment with pharmacological stress, performed 2-4 days after the index event, may provide considerable prognostic information and it may allow for early dis-

charge of low-risk patients[64,67]. Patients at high risk are candidates for cardiac catheterization with consideration for early revascularization.

Assessment of myocardial viability

Several large trials have demonstrated that coronary artery bypass grafting may prolong survival in patients with multi-vessel disease and resting left ventricular dysfunction[68,69]. However, as in these patients coronary surgery is associated with an increased risk, identifying patients expected to benefit from this intervention is of outmost importance; otherwise, patients should be candidates for heart transplantation[70]. Indeed, published data have shown that in patients with left ventricular dysfunction and viable myocardium medical treatment is associated with reduced survival[71]. Conversely, the outcome of patients with a low ejection fraction and a considerable area of viable myocardium is improved, if submitted to bypass surgery, compared to those managed medically[72]. Nevertheless, myocardial viability assessment may be entangled by the difficulty in accurately evaluating the bypass surgery result; moreover, there is no unanimously approved criterion for this assessment. The conception of myocardial viability implies the presence of asynergic segments and it has been associated with stunning and hibernation.

Myocardial stunning may be due to a prolonged and severe ischaemic insult, with subsequent restoration of coronary flow, which is associated with reduction in contractile function of the affected segment[73]. This may occur in the setting of an acute myocardial infarction with restoration of the vessel patency (spontaneous or therapeutic thrombolysis, primary revascularization). In these circumstances, myocardial perfusion imaging with resting injection of the tracer, is normal or almost normal in the asynergic segment. Whether induced ischaemia may appear at stress depends on the presence of a significant stenotic lesion in the insult-related artery. These findings are consistent with improvement of regional wall motion over time. If stunning occurs after prolonged exercise in the presence of a high-grade coronary stenosis, resting myocardial perfusion is normal. However, marked perfusion defects and focal asynergy appear during exercise[74]. In these patients revascularization offers a high probability of improvement in exercise coronary flow and segmental contractility, as well as post-exercise regional wall motion.

In myocardial hibernation functional down-regulation follows long-standing reduction of blood flow[69,75]. In these cases, myocardial perfusion with resting injection of the tracer is mildly to severely reduced[75]. In delayed imaging (rest-redistribution ^{201}Tl study) improvement of the initial defect is expected. Conversely, at stress a greater degree of reduction in perfusion would appear (stress-rest study). Myocardial segments with defect resolution in delayed imaging, namely reversible defects, or with reduced uptake of the perfusion tracer, albeit >50% of the maximal, are considered viable[76]. This is associated with an increased likelihood of left ventricular function improvement with revascularization[76]. Certainly, dobutamine echocardiography may detect contractile reserve in hibernating segments, which has also been reported to predict improvement in left ventricular function after revascularization[77].

Notably, improvement of the left ventricular ejection fraction was observed in one third of patients having undergone revascularization, 2 to 3 months after the procedure[1]. However, it is not known whether this result is sustained at e.g. 12 months, or if a different proportion of patients have improved, similar, or reduced ejection fraction. From only few available published data, the hypothesis that the beneficial result of revascularization is due to left ventricular function improvement cannot be supported[78,79]. In fact, in an interesting report it was observed that prolonged survival in patients with left ventricular dysfunction and submitted to bypass surgery was not associated with a change in their ejection fraction[80]. It thus appears that the reversibility of left ventricular dysfunction, namely improvement of the ejection fraction, may not be a reliable basis for the assessment of myocardial viability, as no data document this hypothesis[78,80,81]. On the other hand, clinical outcome taken as viability criterion, that is prolonged survival and improved quality of life, regardless of potential increase in ejection fraction, a substantial body of evidence shows that bypass grafting may be beneficial in patients with left ventricular dysfunction in the presence of viable myocardium[81,82]. This may be due to limitation of the ischaemic substrate, which may reduce the likelihood of severe arrhythmias or acute ischaemic events, or in favorable remodeling of the left ventricle. It is also worth mentioning that a considerable area of viable myocardium (>20%-30% of myocardial outline in various modalities) should be present to expect improved outcome after revascula-

rization[76,77]. Finally, with prolonged survival and improvement in quality of life as criteria, no convincing data document that the presence of contractile reserve in asynergic myocardial segments, as assessed by dobutamine echocardiography, may reliably predict the clinical outcome after revascularization.

Cost-effective implications

Several reports have demonstrated that radionuclide methods may contribute in substantially reducing the cost of diagnosis, follow-up, hospitalization, and therapeutic management of patients with coronary artery disease[83,84]. A 17% reduction in catheterization rates and cost savings ranging from 22% to 55% have been reported when coronary angiography was limited to patients with moderate or severe ischaemic heart disease[36]. In a large multi-center trial, comparing a direct cardiac catheterization approach to a selective catheterization strategy, based on myocardial perfusion assessment, in patients with chronic stable angina, a substantial reduction in both the early (diagnostic) and follow-up costs was found, ranging from 31% to 50%[84]. Moreover, the selective catheterization strategy was associated with a reduced rate of revascularization by 50%, whereas the outcome was identical in both groups of patients. Similar cost savings, ranging from 20% to 57% per patient, have been reported with resting ^{99m}Tc-MIBI SPECT imaging used in patients presenting with chest pain, as both the admission rate and hospital stay may be reduced[52,85].

Positron emission imaging and other non-invasive modalities

For purposes of completeness, it is mentioned that positron emission tomography (PET) is considered the optimal nuclear technique for the investigation of coronary artery disease. Several studies underscore the usefulness of PET, mainly in myocardial viability assessment[86]. However, up to date reports do not show an unequivocal advantage of PET over conventional nuclear cardiology techniques in routine clinical practice[87].

Wide clinical approval of other competitive non-invasive modalities, such as stress echocardiography, magnetic resonance imaging, and electron beam computerized tomography, is not supported by a large data basis, as yet[88,89,90]. Conversely, nuclear cardiology has been successfully tested for many years and a substantial body of evidence strongly supports its clinical usefulness in patients with coronary artery disease.

Conclusion

A large body of evidence documents that nuclear methods are highly effective in the prognostic assessment and the therapeutic management of patients with coronary artery disease. The greatest incremental information for risk stratification is provided in patients with intermediate or high likelihood of coronary artery disease, which signifies that the application field of radionuclide techniques is expanded, compared to their diagnostic utility. The favorable cost-effectiveness ratio with routine nuclear cardiology use in clinical practice is particularly emphasized.

Nuclear tests effectively identify patients with coronary artery disease who may benefit from revascularization, from others in whom medical treatment may be the optimal therapeutic strategy[36]. Thus, nuclear cardiology methods allow for the non-invasive selection of the appropriate treatment, particularly when symptoms are not the principal therapeutic criterion. Moreover, radionuclides may limit the routine diagnostic or prognostic use of coronary angiography, ideally referring for catheterization only patients in whom knowledge of coronary anatomy is necessary in the consideration of interventional revascularization[91].

All these are consistent with the current medical environment featured by cost-effectiveness considerations, significant advances in medical treatment, enrichment of therapeutic options, and realization of overuse of invasive procedures in patients with coronary artery disease[92,93].

References

1. Berman DS, Hayes SW, Shaw LJ, Germano G: Recent advances in myocardial perfusion imaging. Curr Probl Cardiol 2001; 26: 1-140.
2. Alderman EL, Bourassa MG, Cohen LS, et al: Ten-year follow-up of survival and myocardial infarction in the randomized Coronary Artery Surgery Study. Circulation 1990; 82: 1629-1646.
3. Detre KM, Akaro P, Hultgren H, et al: Long-term mortality and morbidity results of the Veterans Administration randomized trial of coronary artery bypass surgery. Circulation 1985; 72(suppl V): V-84-V-89.
4. Pitt B, Waters D, Brown WV, et al: Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 1999; 341: 70-76.

5. Parisi AF, Folland ED, Hartigan P, et al: A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. N Engl J Med 1992; 326: 10-16.
6. Bucher HC, Hengstler P, Schindler C, Guyatt GH: Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. BMJ 2000; 321: 73-77.
7. Rodriguez A, Bernardi V, Navia J, et al: Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple Vessel Disease (ERACI II): 30-Day and One-Year Follow-up Results. J Am Coll Cardiol 2001; 37: 51-58.
8. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996; 335: 217-225.
9. Gibbons R, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol 1999; 33(7): 2092-2197.
10. Iskandrian AS, Verani MS: Nuclear Cardiac Imaging, Principles and Applications, 2nd ed. F.A. Davis Company, Philadelphia 1996, pp 29-45.
11. Borer JS: Measurement of ventricular function and volume, in Zaret BL, Beller GA (eds): Nuclear Cardiology, State of the Art and Future Directions, 2nd ed. Mosby, St Louis, 1999, pp 201-215.
12. Anagnostopoulos C, Underwood SR: Simultaneous assessment of myocardial perfusion and function: how and when? (review) Eur J Nucl Med 1998; 25(6): 555-558.
13. Iskandrian AS, Verani MS: Nuclear Cardiac Imaging, Risk assessment, 2nd ed. F.A. Davis Company, Philadelphia 1996, pp 242-278.
14. Davies JM, Thomas AC: Plaque fissuring-the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985; 53: 363-373.
15. Little WC, Constantinescu M, Applegate RJ, et al: Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988; 78: 1157-1166.
16. Golino P, Piscione F, Willerson JT, et al: Divergent effects of serotonin on coronary artery dimensions and blood flow in patients with coronary atherosclerosis and control patients. N Engl J Med 1991; 324: 641-648.
17. Hasdai D, Gibbons RJ, Holmes DR Jr, et al: Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. Circulation 1997; 96: 3390-3395.
18. Brown KA, Boucher CA, Okada RD, et al: Prognostic value of exercise thallium-201 imaging in patients presenting for evaluation of chest pain. J Am Coll Cardiol 1983; 1: 994-1001.
19. Gibson RJ, Watson DD, Craddock GB, et al: Prediction of cardiac events after uncomplicated myocardial infarction: A prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983; 68: 321-336.
20. Jones RH, Floyd RD, Austin EH, Sabiston DC Jr: The role of radionuclide angiocardiography in the preoperative prediction of pain relief and prolonged survival following coronary artery bypass grafting. Ann Surg 1983; 197: 743-754.
21. Ladenheim ML,Pollock BH, Rozanski A, et al: Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986; 7: 464-471.
22. Brown KA: Prognosis in stable coronary artery disease, in Zaret BL, Beller GA (eds): Nuclear Cardiology, State of the Art and Future Directions, 2nd ed. Mosby, St Louis, 1999, pp 331-345.
23. Brown KA, Rowen M: Impact of antianginal medications, peak heart rate and stress level on the prognostic value of a normal exercise myocardial perfusion imaging study. J Nucl Med 1993; 34: 1467-1471.
24. Brown KA, Rowen M: Prognostic value of a normal exercise myocardial perfusion imaging study in patients with angiographically significant coronary artery disease. Am J Cardiol 1993; 71: 865-867.
25. Abdel Fattah A, Kamal AM, Pancholy S, et al: Prognostic implications of normal exercise tomographic thallium images in patients with angiographic evidence of significant coronary artery disease. Am J Cardiol 1994; 74: 769-771.
26. Pollock SG, Abbott RD, Boucher CA, et al: Independent and incremental prognostic value of test performance in hierarchical order to evaluate patients with suspected coronary artery disease. Validation of models based on these tests. Circulation 1992; 85(1): 237-248.
27. Iskandrian AS, Chae SC, Heo J, et al: Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993; 22: 665-670.
28. Jones RH, Johnson SH, Bigelow C, et al: Exercise radionuclide angiocardiography predicts cardiac death in patients with coronary artery disease. Circulation 1991; 84(3suppl): I52-I58.
29. Miller TD, Talierco CP, Zinsmeister AR, et al: Risk stratification of single or double vessel coronary artery disease and impaired left ventricular function using exercise radionuclide angiography. Am J Cardiol 1990; 65: 1317-1321.
30. Hachamovitch R, Berman DS, Kiat H, et al: Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. Circulation 1996; 93: 905-914.
31. Berman DS, Hachamovitch R, Kiat H, et al: Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emissio computed tomography. J Am Coll Cardiol 1995; 26: 639-647.
32. Gibbons R, Chatterjee K, Daley J, et al: ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: executive summary and recommendations. Circulation 1999; 99(21): 2829-2948.
33. Bateman TM, O' Keefe JH Jr, Dong VM, et al: Coronary angiographic rates after stress single-photon emission computed tomographic scintigraphy. J Nucl Cardiol 1995; 2: 217-223.
34. Nallamothu N, Pancholy SB, Lee KR, et al: Impact of exercise single-photon emission computed tomographic thallium imaging on patient management and outcome. J Nucl Cardiol 1995; 2: 334-338.
35. O'Keefe JH Jr, Bateman TM, Ligon RW, et al: Outcome of medical versus invasive treatment strategies for non-high-risk ischemic heart disease. J Nucl Cardiol 1998; 5: 28-33.

36. Hachamovitch R, Berman DS, Shaw LJ, et al: Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998; 97: 535-543.
37. Topol EJ, Ellis SG, Cosgrove DM, et al: Analysis of coronary angioplasty practice in the United States with an insurance-claims data base. Circulation 1993; 87: 1489-1497.
38. Pfisterer M, Rickenbacher P, Kiowski W, et al: Silent ischemia after percutaneous transluminal coronary angioplasty: incidence and prognostic significance. J Am Coll Cardiol 1993; 22: 1446-1454.
39. Hecht HS, Shaw LJ, Chin HL, et al: Silent ischemia after coronary angioplasty: evaluation of restenosis and extent of ischemia in asymptomatic patients by tomographic thallium-201 exercise imaging and comparison with symptomatic patients. J Am Coll Cardiol 1991; 17: 670-677.
40. Kosa I, Blasini R, Schneider-Eicke J, et al: Myocardial perfusion scintigraphy to evaluate patients after coronary stent implantation. J Nucl Med 1998; 391307-1311.
41. Miller DD, Verani MS: Current status of myocardial perfusion imaging after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1994; 24: 260-266.
42. FitzGibbon GM, Leach AJ, Kafka HP, et al: Coronary bypass graft fate: long-term angiographic study. J Am Coll Cardiol 1991; 17: 1075-1080.
43. Palmas W, Bingham S, Diamond GA, et al: Incremental prognostic value of exercise thallium-201 myocardial single-photon emission computed tomography late after coronary artery bypass surgery. J Am Coll Cardiol 1995; 25: 403-409.
44. Lauer MS, Lytle B, Pashkow F, et al: Prediction of death and myocardial infarction by screening with exercise thallium testing after coronary-artery-bypass grafting. Lancet 1998; 351: 615-622.
45. Zellweger MJ, Lewin HC, Lai S, et al: When to stress patients after coronary artery bypass surgery? Risk stratification in patients early and late post-CABG using stress myocardial perfusion SPECT: Implications of appropriate clinical strategies. J Am Coll Cardiol 2001; 37: 144-152.
46. Lee TH, Juarez G, Cook EF, et al: Ruling out acute myocardial infarction. A Prospective multicenter validation of a 12-hour strategy for patients ay low risk. N Engl J Med 1991; 324: 1239-1246.
47. Graff LG, Dallara J, Ross MA, et al: Impact on the care of the emergency department chest pain patient from the chest pain evaluation registry (CHEPER) study. Am J Cardiol 1997; 80: 563-568.
48. Gomez MA, Anderson JL, Karagounis LA, et al: An emergency department-base protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: results of a randomized study (ROMIO). J Am Coll Cardiol 1996; 28: 25-33.
49. Varetto T, Cantalupi D, Altieri A, et al: Emergency room technetium-99m sestamibi imaging to rule out acute myocardial ischemic events in patients with nondiagnostic electrocardiograms. J Am Coll Cardiol 1993; 22: 1804-1808.
50. Hilton TC, Fulmer H, Abuan T, et al: Ninety-day follow-up of patients in the emergency department with chest pain who undergo initial single-photon emission computed tomographic perfusion scintigraphy with technetium 99m-labeled sestamibi. J Nucl Cardiol 1996; 3: 308-311.
51. Kontos MC, Jesse RL, Anderson FP, et al: Comparison of myocardial perfusion imaging and cardiac troponin I inpatients admitted to the emergency department with chest pain. Circulation 1999; 99: 2073-2078.
52. Heller GV, Stowers SA, Hendel RC, et al: Clinical value of acute rest technetium-99m tetrofosmin tomographic myocardial perfusion imaging in patients with acute chest pain and nondiagnostic electrocardiograms. J Am Coll Cardiol 1998; 31: 1011-1017.
53. Ryan TJ, Anderson JL, Antman EM, et al: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the ACC/AHA Task Force on Practice Guidelines (Committee in Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996; 28: 1328-1428.
54. Anderson HV, Cannon CP, Stone PH, et al: One-year results of the thrombolysis in myocardial infarction (TIMI) IIIB clinical trial. J Am Coll Cardiol 1995; 26: 1643-1650.
55. Boden WE, O'Rourke RA, Crawford MH, et al: Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veteran Affairs Non-Q-Wave Infarction Strategy in Hospital (VANQWISH) Trial Investigators. N Engl J Med 1998; 338: 1785-1792.
56. Cannon PC, Weintraub WS, Demopoulos LA, et al: Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban (TACTICS). N Engl J Med 2001; 344: 1879-1887.
57. Krone RJ, Gregory JJ, Freeland KE, et al: Limited usefulness of exercise testing and thallium scintigraphy in evaluation of ambulatory patients several months after recovery from an acute coronary event: Implications for management of stable coronary heart disease. J Am Coll Cardiol 1994; 24: 1274-1281.
58. Verani MS: Risk assessment after myocardial infarction: have the rules changed with thrombolytic therapy? J Nucl Cardiol 1996; 3: S50-S59.
59. Brown KA: Noninvasive risk stratification: Right question, wrong study. J Nucl Cardiol 1994; 1: 112-113.
60. Dakik HA, Mahmarian JJ, Kimball KT, et al: Prognostic value of exercise 201Tl tomography in patients treated with thrombolytic therapy during acute myocardial infarction. Circulation 1996; 94: 2735-2742.
61. Heller GV, Brown KA, Landin RJ, et al: Safety of early intravenous dipyridamole technetium 99m sestamibi SPECT myocardial perfusion imaging after uncomplicated first myocardial infarction. Early Post MI IV Dipyridamole Study (EPIDS). Am Heart J 1997; 134: 105-111.
62. Mahmarian JJ, Mahmarian AC, Marks GF, et al: Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995; 25: 1333-1340.
63. Shaw LJ, Peterson ED, Kesler K, et al: A meta-analysis of predischarge risk stratification after acute myocardial infarction with stress electrocardiographic, myocardial perfusion, and ventricular function imaging. Am J Cardiol 1996; 78: 1327-1337.
64. Brown KA, Heller GV, Landin RS, et al: Early dipyridamole Tc-99m SPECT imaging after acute myocardial infarction predicts in-hospital and post-discharge cardiac events: Comparison with submaximal exercise imaging. Circulation 1999; 100: 2060-2066.

65. Wackers JT, Zaret BL: Risk stratification soon after acute infarction [editorial]. Circulation 1999; 100: 2040-2042.
66. Dakik H, Kleiman N, Farmer J, et al: Intensive medical therapy versus coronary angioplasty for suppression of myocardial ischemia in survivors of acute myocardial infarction. Circulation 1998; 98: 2017-2023.
67. Peterson ED, Shaw LJ, Califf RM: Risk stratification after myocardial infarction. ACP Position Paper. Clinical Guideline Part I. Ann Intern Med 1997; 126: 561-582.
68. Abraham WT, Bristow MR: Specialized centers for heart failure management. Circulation 1997; 96: 2755-2757.
69. Rahimtoola SH: Importance of diagnosing hibernating myocardium: How and in whom? J Am Coll Cardiol 1997; 30: 1701-1706.
70. Mickleborough LL, Maruyama H, Takagi Y, et al: Results of revascularization in patients with severe left ventricular dysfunction. Circulation 1995; 92(9suppl): II73-II79.
71. Gioia G, Milan E, Giubbini R, et al: Prognostic value of tomographic rest-redistribution thallium 201 imaging in medically treated patients with coronary artery disease and left ventricular dysfunction. J Nucl Cardiol 1996; 3: 150-156.
72. Pagley PR, Beller GA, Watson DD, et al: Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 1997; 96: 793-800.
73. Braunwald E, Kloner RA: The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982; 66: 1146-1149.
74. Johnson LL, Verdesca SA, Aude WY, et al: Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. J Am Coll Cardiol 1997; 30: 1641-1648.
75. Elsasser A, Schlepper M, Klovekorn WP, et al: Hibernating myocardium: an incomplete adaptation to ischemia. Circulation 1997; 96: 2920-22931.
76. Bax JJ, Vanoverschelde J-LJ, van der Wall EE: Assessment of myocardial viability with thallium-201, in Iskandrian AS, van der Wall EE (eds): Myocardial Viability, 2nd Completely Revised Edition. Kluwer Academic Publishers, Dordrecht, 2000, pp 73-89.
77. Chaudry FA, Galatro K: Echocardiographic assessment of reversible left ventricular dysfunction, in Iskandrian AS, van der Wall EE (eds): Myocardial Viability, 2nd Completely Revised Edition. Kluwer Academic Publishers, Dordrecht, 2000, pp 155-175.
78. Jacobson AF, Tow DE, Lapsley D, Khuri S: Changes in septal regional ejection fraction early and late following coronary artery bypass grafting in patients without postoperative myocardial infarction. Nucl Med Commun 1992; 124: 1190-1195.
79. Cuocolo A, Nicolai E, Petretta M, et al: One-year effect of myocardial revascularization on resting left ventricular function and regional thallium uptake in chronic CAD. J Nucl Med 1997; 38: 1684-1692.
80. Samady H, Elefteriades JA, Abbott BG, et al: Failure to improve left ventricular function after coronary revascularization for ischemic cardiomyopathy is not associated with worst outcome. Circulation 1999; 100: 1298-1304.
81. Iskandrian AE: Viability assessment: clinical application, in Iskandrian AE, van der Wall (eds): Myocardial Viability, 2nd Completely Revised Edition, Kluwer Academic Publishers, Dordrecht, 2000, pp 199-227.
82. Iskander S, Iskandrian AE: Prognostic utility of myocardial viability assessment. Am J Cardiol 1999; 83: 696-702.
83. Underwood SR, Godman B, Salyani S, et al: Economics of myocardial perfusion imaging in Europe – The EMPIRE study. Eur Heart J 1999; 20: 157-166.
84. Shaw LJ, Hachamovitch R, Berman DS, et al: The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. J Am Coll Cardiol 1999; 33: 661-669.
85. Radensky PW, Hilton TC, Fulmer H, et al.: Potential cost effectiveness of initial myocardial perfusion imaging for assessment of emergency department patients with chest pain. Am J Cardiol 1997; 79: 595-599.
86. Schelbert HR: The usefulness of Positron Emission Tomography. Curr Probl Cardiol 1998; 23: 69-124.
87. Siebelink H-M J, Blanksma PL, Crijns HJG, et al: No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management. A prospective randomized comparison of patients with suspicion of jeopardized myocardium. J Am Coll Cardiol 2001; 37: 81-88.
88. ACA/AHA Guidelines for the Clinical Application of Echocardiography. Circulation 1997; 95: 1686-1744.
89. Task Force of the European Society of Cardiology, in collaboration with the Association of European Paediatric Cardiologists: The clinical role of magnetic resonance in cardiovascular disease. Eur Heart J 1998; 19: 19-39.
90. Detrano RC, Doherty TM, Davies MJ, Stary HC: Predicting coronary events with coronary calcium: Pathophysiologic and clinical problems. Curr Probl Cardiol 2000; 25: 369-404.
91. Wackers FJT, Zaret BL: Radionuclide stress myocardial perfusion imaging: The future gatekeeper for coronary angiography. J Nucl Cardiol 1995; 2: 358-359.
92. Rouleax JL, Moye LA, Pfeffer M, et al: A comparison of management patterns after acute myocardial infarction in Canada and the United States. N Engl J Med 1993; 328: 779-784.
93. Lange RA, Hillis LD: Use and overuse of angiography and revascularization for acute coronary syndromes [editorial]. N Engl J Med 1998; 338: 1838-1839.