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Detection of Myocardial Viability with Nitrate Augmented Myocardial Perfusion Imaging: Literature Review

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Abstract

The incidence of coronary heart disease is increasing and the research for viability and its early detection will allow a better management and improvement of the prognosis. Studies have shown that nitrates improve the reversibility of defects on myocardial perfusion imaging.

The nitrates can be used routinely with ^{99m}Tc-MIBI and gives similar reversibility to ^{201}Tl with excellent prediction for left ventricular recovery.

^{99m}Tc-MIBI is better in detecting viability than DE-MRI with better sensitivity and specificity.

PET-CT imaging using ^{18}FDG is still the gold standard, although nitrate augmented ^{99m}Tc-MIBI allows us to overcome the artifacts observed in diabetic patients.

^{99m}Tc-MIBI with nitrates is an excellent alternative in the absence of particle accelerators and its routine use in screening allows early management of coronary heart disease, thus helping during post-insertion angiography of stent.

The aim of this work is to review the literature of the various works on the contribution of nitrates and to show their contribution in relation to other modalities.

Key words: Viability, ^{99m}Tc-MIBI, nitrate.

Introduction

Cardiovascular diseases are the leading cause of death in the world with an estimated mortality of 31% (source WHO).

Coronary heart disease is the failure of the coronary vessels to provide adequate blood flow to meet the oxygen needs to the heart muscle. And this oxygen deficit is responsible in the long run for myocardial ischemia or even necrosis at the origin of ventricular dysfunction.

The notion of myocardial viability has been widely explored and its mechanisms are well understood with concepts such as hibernation and stunning. This viability will become a very important concept in decision-making processes in the case of coronary insufficiency responsible of left ventricular dysfunction.

Although nitrates imaging has gained clinical acceptance in the detection of myocardial viability, the mechanism by which nitrates increase uptake is less understood. The mechanism was specified from the pharmacodynamics of nitrate and the pathophysiology of the hibernating myocardium. Nitrates increase myocardial blood flow to the hypoperfused myocardial segments by dilating the stenotic lumen. Nitrates selectively relax the epicardial vessels (conductance), thereby facilitating the flow of blood through collateral channels to area of myocardial ischemia. In addition, nitrates decrease LV preload and post-load, thereby decreasing sub-endocardial compressive forces and improving sub-endocardial perfusion [1].

Fujita et al. [2]. observed that in patients who had good collateral circulation, overall and regional function improved significantly after administration of sublingual nitroglycerin, while no change was recorded in patients with an occlusion but without collaterals. Attention has mainly been paid to the functional changes induced by the administration of nitrate. Aoki et al. demonstrated that in a non-infarcted myocardium with a good collateral network, acute administration of nitroglycerin reduced the extent and severity of the exercise-induced ^{201}Tl myocardial perfusion defect [3].

Single-photon emission computed tomography (SPECT) scintigraphy has contributed to the study and understanding of myocardial viability. Positron emission tomography (PET) marked a turning point in the assessment of myocardial viability with the fluoride-labeled fluoro-deoxy-glucose tracer 18. This radiopharmaceutical is often replaced by thallium in SPECT imaging. In the absence of a particle accelerator (cyclotron producing fluorine 18 and thallium 201), isn't ^{99m}Tc-MIBI associated with nitrates an alternative in the search for a viability of the heart muscle for a possible revascularization in case of stunning or hibernation?

This present study is a review of the literacy and aims to show the feasibility of the research for myocardial viability in the absence of a cyclotron and to allow the routine selection of patients who should benefit from a coronary angiography to localize the coronary lesions in order to carry out, if necessary, either an angioplasty, the pause. a stent or a bypass.

Methods

Several published reports (PubMed, Elsevier, NCBI…) were read and reviewed with nitrate augmented, SPECT, viability as key word, their results used to determine the most valuable tool for diagnosing and or monitoring patient with a history of myocardial infarction, functional or and left ventricular dysfunction.

For this assessment, a comparison were made between study were patient went for MPI augmented with nitrate compare to those with thallium reinjection, DE-RMI and the gold standard FDG-PET.

DISCUSSION

Nitrate augmented ^{99m}Tc-MIBI myocardial perfusion imaging has been introduced for the detection of myocardial viability for over 15 years, and is increasingly used in several nuclear medicine departement [4,5,6] around the world. The first study on myocardial perfusion imaging using nitrates was reported by He et al. [4]. In this study, the authors found 26% of LV segments with ^{201}Tl defect using the stress / reinjection protocol which became reversible when the reinjection examination was preceded by the administration of sublingual nitrates. These results were subsequently confirmed by two randomized, placebo-controlled studies [5,7]. Other studies have systematically shown that nitrates improved the reversibility of defects on myocardial perfusion imaging with ^{201}Tl (8,9), ^{99m}Tc-sestamibi [9,10], ^{99m}Tc-tetrofosmine [11, 12] and ^{99m}Tc-teboroxime [13, 4].

Several studies have evaluated the accuracy of the nitrate augmented ^{99m}Tc-MIBI myocardial perfusion test in predicting recovery of LV function after coronary revascularization. According to the data of these published studies, the sensitivity of ^{99m}Tc –Sestamibi under nitrates varies from 82 to 95%, while the specificity varies from 76 to 89%. Imaging with nitrates with ^{201}Tl has a sensitivity of 92% and a specificity of 78% [1]. The pooled data show a trend towards greater precision of ^{99m}Tc-sestamibi TEMP under nitrates for the prediction of recovery of left ventricular function compared to other conventional imaging protocols [14].

Regarding the prognostic value of ^{99m}Tc-MIBI SPECT, the assessment of myocardial viability in patients with left ventricular ischemic dysfunction using various modalities has been shown to have important implications in risk stratification and the prediction of cardiac events [13, 16]. Therefore, it is reasonable to consider that nitrate augmented ^{99m}Tc-MIBI TEMP is a useful tool for evaluating the outcome of coronary artery disease and left ventricular dysfunction.

Several study [17-24] have reported the prognostic value of myocardial perfusion imaging with nitrates. The majority of patients enrolled in these studies had a history of myocardial infarction (75 to 100%) and the left ventricular ejection fraction varied on average from 25 to 46%. Study protocols were variable, ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin has been used as a radiotracer. The type of nitrate administration was intravenous infusion or sublingual administration and the imaging protocol used was resting SPECT on nitrates, stress protocol or nitrate alone for the determination of myocardial viability.

The myocardial viability of the dysfunctional segments was objectified afterwards by an enhancement of the uptake after consumption of nitrate.

Studies have evaluated the predictions of event-free survival and have consistently shown the close relationship between myocardial viability assessed by myocardial perfusion imaging under nitrates and the occurrence of cardiac events.

For patients who received medical treatment after assessment of myocardial viability, event-free survival was lower in patients with viability detected by imaging with nitrates than in those who did not receive the addition of nitrates [19, 18, 20, 21]. Conversely, patients with detected viable myocardium would perform better if they underwent coronary revascularization than patients treated with drugs [22, 23, 6].

Therefore, nitrate augmented ^{99m}Tc-MIBI myocardial scintigraphy has provided important prognostic value in patients with coronary artery disease or left ventricular dysfunction, regardless of the study protocols used. These results agree with those reported by Allman & al. These studies also compared the ability of TEMP to nitrates in predicting cardiac events with other modalities.

Evangelista et al. [18] demonstrated that the administration of nitrates augmented ^{99m}Tc - MIBI significantly improved the prognosis of coronary artery disease, including clinical, functional, angiographic and resting TEMP data.

Regarding the diagnostic performance of TEMP under nitrates, previous studies have shown its diagnostic power by comparing it with conventional modalities including TEMP at ^{201}Tl and ^{99m}Tc.

The diagnostic performance of nitrate augmented ^{99m}Tc imaging compared to ^{18}F-FDG PET or dobutamine MRI (DE-MRI) was also done.

Slart et al. [15] demonstrated a high increase in blood flow after administration of nitrate in dysfunctional segments viable by PET.

Sorrentino et al. [24] compared the diagnostic and prognostic value between the TEMP pair with ^{99m}Tc under nitro derivative and FDG-TEP. They demonstrated that the administration of nitrates gave TEMP a performance comparable to ^{18}F-FDG (gold-standard) and this by comparing it with TEMP alone and TEMP under nitrates on the same group of patients. Eighty-nine patients with ischemic coronary artery disease and left ventricular dysfunction underwent both ^{99m}Tc –Tetrofosmin with nitrates SPECT and 18F-FDG PET. They were followed over an average period of 29 ± 19 months.

The results showed that without the addition of nitrates there is an 84% agreement between the ^{99m}Tc TEMP and the PET but when nitrates are administered the ^{99m}Tc TEMP is 99% concordant with the examination at ^{18}F-FDG [24].

Regarding the prognosis in this same study, event-free survival was 66% in patients with viability and 100% in patients without myocardial viability on SPECT on nitrates, 67% in patients with myocardial viability and 100% in patients without myocardial viability on PET. Therefore, technetium-labeled nitrates provide prognostic information comparable to that provided by ^{18}F-FDG imaging [24].

A previous study also showed that despite improved diagnostic accuracy in viability with FDG-PET, its prognostic value is not as superior to that of SPECT. In fact, the survival of patients whose treatment was based on viability assessed either by PET-FDG or by stress / rest SPECT with ^{99m}Tc-Sestamibi was not statistically different [25].

Although ^{18}F-FDG PET is still considered the gold standard in assessing myocardial viability, this technique sometimes suffers from several limitations. The quality of the ^{18}F-FDG PET image may be limited in some patients, especially in diabetics [26].

Furthermore, the limited availability and high cost of PET imaging precludes its wider clinical use. On the other hand, the administration of nitrates is simple, inexpensive and widely available, they should be administered before injection of ^{99m}Tc when the primary purpose of the study was to assess myocardial viability. Patients with ischemic left ventricular dysfunction who were considered candidates for coronary revascularization or heart transplantation may benefit from TEMP ^{99m}Tc-MIBI with nitrates.

However, nitrates should not be administered prior to exercise or pharmacological stress as they may reduce the extent and severity of myocardial perfusion abnormalities, thus leading to an underestimation of myocardial ischemia.

He et al. [22] studied a group of 36 patients with chronic myocardial infarction with LV dysfunction. All patients were subjected to both ^{99m}Tc TEMP and ^{18}F-FDG PET.

Dysfunctional segments with an uptake less than 55% of ^{99m}Tc at the first acquisition of SPECT or with an increase of uptake greater than or equal to 10% after administration of nitrates were considered viable. They demonstrated the concordance between ^{99m}Tc TEMP and ^{18}F-FDG PET to differentiate viable myocardial tissue from necrotic myocardial tissue in 82% of segments. Also the sensitivity and specificity of nitrate augmented ^{99m}Tc-MIBI were 81 and 86% in comparison with PET to ^{18}F-FDG. Giorgetti et al. [27] also identified a good diagnostic power of TEMP with nitrates in the evaluation of the reliability compared to PET with ^{18}F-FDG. However, it is the resting TEMP at ^{99m}Tc with nitrates that had the strongest agreement with PET (precision, 93%; sensitivity, 95%; specificity, 92%).

MRI under dobutamine (DE-MRI) has recently been proposed as a modality for the assessment of myocardial viability [28] because of its better spatial resolution than SPECT at ^{99m}Tc, DE-MRI can provide a direct visualization of the myocardial transmural extent of viable and non-viable tissue.

Giorgetti et al. [27] compared SPECT to ^{99m}Tc with DE-MRI in in-patients with severe post-ischemic LV dysfunction. They found that using DE-MRI when the uptake with ^{99m}Tc under nitrates was between 40 and 51%, the sensitivity, specificity and overall precision of the TEMP after injections of nitrates were respectively of 89, 78 and 84%, better than TEMP without nitrates for viability detection compared to DE-MRI, similar observations have been obtained from other studies [29, 30].

It was also observed through these studies that the TEMP with 99mTc under nitrates was significantly better performance than the TEMP with 99mTc without nitrates in comparison with the DE-IRM.

All these published data have shown that nitrate augmented ^{99m}Tc-MIBI myocardial perfusion imaging improves detection of myocardial viability and accurately predicts recovery of left ventricular function and clinical outcomes in patients with left ventricular dysfunction and coronary artery disease.

This reliable results of nitrate augmented ^{99m}Tc-MIBI TEMP, it is understandable that myocardial perfusion scintigraphy and the research of viability if necessary are the best choice before doing a coronary angiography. Indeed, in addition to the important diagnostic elements provided by MPI in the research for ischemia or necrosis. This myocardial viability research is relatively inexpensive non-invasive and non-operator dependent unlike echocardiography. Coronary angiography is above all an invasive examination and very expensive. It only allows an exploration of the anatomy of the coronary artery. Studies have shown the presence of a

coronary anomaly with satisfactory myocardial vascularization. In this case, this makes the indication for coronary angiography unnecessary. Moreover, this coronary angiography is relatively expensive and not accessible to most of patients with coronary artery disease. This coronary angiography should not be used for screening and should be reserved for the therapeutic act for revascularization after nitrate augmented ^{99m}Tc-MIBI.

Conclusion

Through this systematic review of the literature, we note that its data obtained on the intake of nitrates suggest that the use of the 99mTc-MIBI protocol associated with nitrate in SPECT cardiac imaging improves the detection of viable but hypoperfused segments. The results obtained are sometimes similar to those of the standard ^{201}Tl rest and redistribution protocol. Although the gold standard remains PET, SPECT with nitro derivatives is an alternative in regions without particle accelerators to produce ^{201}Tl or FDG.

Bibliography

1. **He ZX Verani MS. Evaluation of myocardial viability by myocardial perfusion imaging: should nitrates be used? J Nucl Cardiol 1998 et 5:527–532** . Evaluation of myocardial viability by myocardial perfusion imaging: should nitrates be used? [Revue] // J Nucl Cardiol . - 1998. - Vol. 5. - pp. 527-532.
2. **Fujita M, Yamanishi K, Hirai T, et al.** Significance of collateral circulation in reversible left ventricular asynergy by nitroglycerin in patients with relatively recent myocardial infarction. Am Heart J. 1990; 120:521–528.
3. **Aoki M, Sakai K, Koyanagi S, Takeshita A, Naka- mura M**. Effect of nitroglycerin on coronary col- lateral function during exercise evaluated by quan- titative analysis of thallium-201 single photon emission computed tomography. Am Heart J. 1991;121:1361–1366.
4. **He ZX Darcourt J, Guignier A, Guignier A, Ferrari E, Bussiere F, et al.** Nitrates improve detection of ischemic but viable myocardium by thallium-201 reinjection SPECT [Revue] // J Nucl Med 1993. - 1993. - Vol. 34. - pp. 1472-1477.
5. **He ZX Verani MS, Liu XJ. Nitrate-augmented myocardial imaging for** Nitrate-augmented myocardial imaging forassessment of myocardial viability. J Nucl Cardiol 1995; 2:352–357. [Revue] // J Nucl Cardiol . - 1995. - Vol. 2. - pp. 352-357.
6. **Yang Min-Fu & Keng, Felix & He, Zuo-Xiang.** Nitrate-augmented myocardial perfusion imaging for assessment of myocardial viability: Recent advances. [Article] //

Nuclear medicine communications. 30. 415-9. 10.1097/MNM.0b013e32832b2ed1. . - 2009. - pp. 415-419.

7. **Miyagawa M Kumano S, Sekiya M, Watanabe K, Hashida K, Shiode M, et al.** ssessment of myocardial viability by thallium-201 reinjection imaging withsublingual nitroglycerin. Kaku Igaku 1994; 31:943–950 [Revue] // Kaku Igaku. - 1994. - Vol. 31. - pp. 1943-1950.
8. **Oudiz RJ Smith DE, Pollak AJ, Mena J, Shapiro SM, Ginzton LE, et al** Nitrate-enhanced thallium 201 single-photon emission computedtomography imaging in hibernating myocardium. [Revue] // Am Heart J . - 1999. - Vol. 138. - pp. 369-375.
9. **Bisi G Sciagra R, Santoro GM, Fazzini PF. Rest technetium-99 m sestamibi** Rest technetium-99 m sestamibi tomography in combination with short-term administration of nitrates: feasibility and reliability for prediction of postrevascularization outcome of asynergic territories. [Revue] // J Am Coll Cardiol . - 1994; 24:1282–1289. - Vol. 24. - pp. 1282-1289.
10. **Li ST Liu XJ, Lu ZL, Zhu XD, Shi RF, Yang YJ, et al** The value of Tc-99 m MIBI SPECT during isosorbide dinitrate infusion in assessment of viable myocardium in patients with myocardial infarction. Ann Nucl Med 1996; 10:13–18. [Revue] // Ann Nucl Med 1996. - 1996. - Vol. 10. - pp. 13-18.
11. **Derebek E Kozan O, Durak H, Ergene O, Ozbilek E, Capa G, et al.** Sublingual nitrate plus 99Tcm-tetrofosmin infusion in the detection of severely ischaemic but viable myocardium: a comparative study with stress, [Revue] // Nucl Med Commun . - 1996. - Vol. 17. - pp. 864-871.
12. **Thorley PJ Bloomer TN, Sheard KL, Sivananthan UM.** Thorley PJ, Bloomer TN, She The use of GTN to improve the detection of ischaemic myocardium using 99Tcm-tetrofosmin [Revue] // Nucl Med Commun. - 1996. - Vol. 17. - pp. 669-674.
13. **Braunwald E Rutherford JD** Reversible ischemic left ventricular dysfunction:evidence for the hibernating myocardium. [Revue] // J Am Coll Cardiol . - 1986. - Vol. 8. - pp. 1467-1470.
14. **Bax JJ Poldermans D, Elhendy A, et al** Improvement of left ventricular ejection fraction, heart failure symptoms and prognosis after revascularization in patients with chronic coronary artery disease and viable myocardium detected by dobutamine stress echocardiography [Revue] // J Am Coll Cardiol. - 1999 . - 1 : Vol. 34. - pp. 163-9.

15. **Slart RH Agool A, van Veldhuisen DJ, Dierckx RA, Bax JJ.** Nitrate administration increases blood flow in dysfunctional but viable myocardium, leading to improved assessment of myocardial viability: a PET study. J Nucl Med 2006; 47:1307–1311 [Revue] // J Nucl Med 2006; 47:1307–1311. - 2006. - Vol. 47. - pp. 1307-1311.
16. **Camici PG Prasad SK, Rimoldi OE.** Stunning, hibernation, and assessment of myocardial viability. [Revue] // Circulation. - 2008. - Vol. 117. - pp. 103-114.
17. **Basu S Senior R, Raval U, Lahiri A.** Superiority of nitrate-enhanced 201Tl over conventional redistribution 201Tl imaging for prognostic evaluation after myocardial infarction and thrombolysis. [Revue] // Circulation . - Vol. 96. - pp. 2932-2937.
18. **Evangelista L Acampa W, Petretta M, Ferro A, Ricci F, Luongo L, et al.** Incremental prognostic value of cardiac single-photon emission computed tomography after nitrate administration in patients with ischemic left ventricular dysfunction. [Revue] // J Nucl Cardiol. - 2009. - Vol. 16. - pp. 38-44.
19. **Acampa W Evangelista L, Sorrentino AR, Petretta M, Luongo L, Cuocolo A.** Single-photon emission computed tomography after nitrate administration predicts cardiac events in patients with previous myocardial infarction and left ventricular dysfunction. [Revue] // J Card Fail . - 2007. - Vol. 13. - pp. 765-768.
20. **He ZX Yang MF, Liu XJ, Shi RF, Gao RL, Hu SS, et al** Association of myocardial viability on nitrate-augmented technetium-99 m hexakis2-methoxylisobutyl isonitrile myocardial tomography and intermediate-term outcome in patients with prior myocardial infarction and left ventricular dysfunction [Revue] // Am J Cardiol . - 2003. - Vol. 92. - pp. 696–699.
21. **Kostkiewicz M Olszowska M, Przewlocki T, Podolec P, Tracz W.** Prognostic value of nitrate enhanced Tc99 m MIBI SPECT study in detecting viable myocardium in patients with coronary artery disease. [Revue] // Int J Cardiovasc Imaging . - [s.l.] : Int J Cardiovasc Imaging 2003; 19:129–135., 2003. - Vol. 19. - pp. 129-135.
22. **He W Acampa W, Mainolfi C, Menna F, Sorrentino AR, Petretta M, et al.** . Tc-99 m tetrofosmin tomography after nitrate administration in patients with ischemic left ventricular dysfunction: relation to metabolic imaging by PET [Revue] // J Nucl Cardiol . - 2003. - Vol. 10. - pp. 599-60.
23. **Bosevski M Peovska I, Maksimovic J, Vavlukis M, Meskovska S.** Bosevski M, Peovska I, Maksimovic J, Vavlukis M, Meskovska S. Prognostic utility of carotid

ultrasound and cardiac SPECT imaging in coronary artery bypass patients. Nucl Med Rev [Revue] // Nucl Med Rev . - 2006. - Vol. 9. - pp. 12-17.

24. **Sorrentino AR Acampa W, Petretta M, Mainolfi C, Salvatore M, Cuocolo A** Comparison of the prognostic value of SPECT after nitrate administration and metabolic imaging by PET in patients with ischaemic left ventricular dysfunction. [Revue] // Eur J Nucl Med Mol Imaging. - 2007. - Vol. 34. - pp. 558-562.
25. **Siebelink HM Blanksma PK, Crijns HJ, Bax JJ, van Boven AJ, Kingma T, et al** No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomographyguided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. [Revue] // J Am Coll Cardiol . - 2001. - Vol. 37. - pp. 81-88.
26. **Vitale GD deKemp RA, Ruddy TD, Williams K, Beanlands RS.** Myocardial glucose utilization and optimization of (18)F-FDG PET imaging in patients with non-insulin-dependent diabetes mellitus, coronary artery disease, and left ventricular dysfunction. [Revue] // J Nucl Med . - 2001. - Vol. 42. - pp. 1730-1736.
27. **Giorgetti A Pingitore A, Favilli B, Kusch A, Lombardi M, Marzullo P.** Baseline/postnitrate tetrofosmin SPECT for myocardial viability assessment in patients with postischemic severe left ventricular dysfunction: new evidence from MRI [Revue] // J Nucl Med . - 2005. - Vol. 46.
28. **Kim RJ Wu E, Rafael A, Chen EL, Parker MA, Simoneti D, et al** The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction, N Engl J Med . - 2000. - Vol. 343. - pp. 1445-1453.
29. **Alfakih K Reid S, Jones T, Sivananthan M.** Assessment of ventricular function and mass by cardiac magnetic resonance imaging. [Revue] // Eur Radial . - 2004. - 10 : Vol. 14. - pp. 1813-22.
30. **Positano V Pingitore A, Giorgetti A, Favilli B, Santarelli MF, Landini L, et al.** A fast and effective method to assess myocardial necrosis by means of contrast magnetic resonance imaging. [Revue] // J Cardiovasc Magn Reson . - 2005. - Vol. 7. - pp. 487-494.