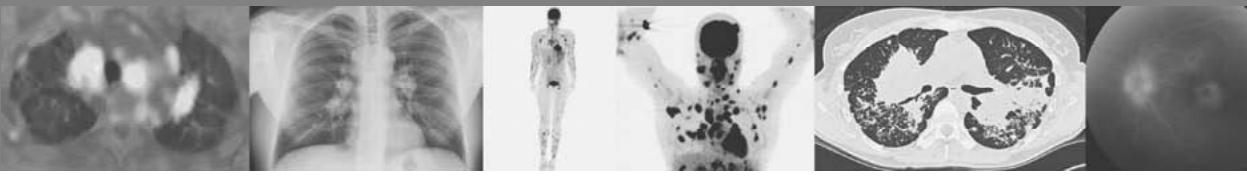
Chapter 2

Metaiodobenzylguanidine scintigraphy in pulmonary and cardiac disease



MJPG van Kroonenburgh, RLM Mostard, S Vöö

Curr Opin Pulm Med 2010;16:511-515

Abstract

Purpose of review

Nuclear medicine techniques have the capacity to investigate neuronal dysfunction at the synapse level. For instance, metaiodobenzylguanidine (MIBG) shows a similar uptake, storage and release as norepinephrine. Intravenously injected radiolabeled MIBG is able to reflect neuronal damage induced by inflammation and tumors. The purpose of this review is to evaluate the results and limitations of these neuronal imaging techniques in patients with pulmonary and cardiac diseases and to give an opinion about the clinical value of these new diagnostic tools.

Recent findings

MIBG neuronal images of the lungs and heart can show heterogeneous distribution patterns with either diminished or increased MIBG uptake and/or wash-out. These changes reflect changes in endothelial integrity, neuronal innervations and clearance of norepinephrine. Interest in the role of neurotransmitter involvement and the relation between endothelial cell integrity and vascularization is growing and of utmost importance to understand the effect on pathophysiology of diseases.

Summary

At this moment, there is no added clinical value to routinely use MIBG scanning of the lungs and the heart. This is partly due to the many unresolved questions such as what actually happens and which factors influence MIBG uptake and washout under normal physiological circumstances. But the technique, if standardized and when dynamic time acquisition is performed with the latest equipment, such as positron emission tomography (PET) and single photon emission computed tomography-computed tomography (SPECT-CT), has a tremendously great potential. It can unravel till now unknown relationships between innervation, vascularization and endothelial integrity. Other diagnostic tools like magnetic resonance imaging (MRI) and CT do not have this capacity, so the future looks bright for these new neuronal imaging techniques.

Introduction

In nuclear medicine, radiolabeled neurotransmitters are used as a diagnostic aid in clinical diagnosis. The visualization of neuroblastoma and pheochromocytoma by radiolabeled ^{123}I-metaiodobenzylguanidine scintigraphy (MIBG) is of great clinical value. ^{123}I-radiolabeled MIBG reflects adrenergic neuron integrity. MIBG and norepinephrine enter adrenergic cells through the same uptake mechanism and both are stored in the vesicles at the sympathetic nerve ending. In addition to this active uptake mechanism, MIBG, in contrast with norepinephrine, is also taken up by a diffusion type of pathway, which facilitates a substantial proportion of MIBG uptake into the adrenergic nerves. The uptake of MIBG is diminished by injury to adrenergic neurons, for instance induced by inflammation, and an increased sympathetic activity is associated with a more rapid rate of loss of MIBG.[1] Therefore radiolabeled MIBG is able to reflect neuronal dysfunction in different organs. The myocardium, lungs, adrenal glands, parotids, submandibular glands, uterus and intestines are all richly supplied with sympathetic nerves. A study from Nakayo et al.[2] suggested that serial measurements of time activity of radioiodinated MIBG in certain organs may be useful in the assessment of adrenergic neuropathy.

The lungs are able to extract circulating norepinephrine from the circulation, a process that is mediated by the pulmonary vascular endothelial cells. The extent to which the lungs are participating in the removal of these biogenic amines has been measured and it appears that approximately 25% of the circulating norepinephrine is extracted through the passage through the lungs in resting humans.[3] The focus on sympathetic innervations and/or removal of biogenic amines has led to questions as follows: is there an association between certain pulmonary diseases and adrenergic dysfunction? What is exactly the role of these innervations and why do the lungs play a role in the excretion of the biologically active amines? Is there any relation between chronic obstructive pulmonary disease (COPD) or pulmonary hypertension and neurogenic dysfunction and what is the effect of infectious disease? There are more questions than answers and the literature is scarce, but recently growing in numbers, indicating an awakening in interest in this area of science. Numerous sympathetic nerves innervate vessels in the lung.[4] Neurotransmitters released from sympathetic neurons can potentially affect endothelial cells and it has been hypothesized that the interaction between neuronal and endothelial cells may regulate vascular tone.[5,6] There remains a compelling need for investigating these kinds of innervations mechanism in the lungs and much is already learned from the innervations studies which have been done with radiolabeled MIBG in the heart.

Review

It is now well established that the lungs of many species actively take up circulating biogenic amines such as serotonin and norepinephrine.[7] Animal models showed that injured endothelial cells have a decreased ability to extract norepinephrine.[8] In 1999, Sakami et al.[9] compared MIBG imaging and plasma norepinephrine concentration between patients with COPD and normals. They showed that plasma norepinephrine in COPD was higher than in the controls and that patients with COPD have significant sympathetic nervous impairment of the left ventricle myocardium as a result of generalized sympathetic overactivity. It has been demonstrated that increased sympathetic activity can contribute significantly to myocardial infarction, arrhythmia and heart failure and that adrenergic blockade can be used as a therapy.[10]

Scintigraphy

Scintigraphic assessment showed evidence of diminished uptake of ^{123}I-MIBG in the lungs of patients suffering from COPD[9,11], but also in patients with pulmonary fibrosis[12], vasculitis[13], high altitude pulmonary edema[14,15], chronic hypoxia[16] and after radiotherapy.[17] In other diseases, increased or prolonged retention of MIBG have been shown. This was observed in patients with diabetes[18,19], in Behçet's disease[20], and in patients with chronic heart failure.[21] Furthermore the decreased lung washout rate of MIBG was related to the severity of pulmonary hypertension.[21] Increased or decreased uptake in the lungs, either homogeneous or not, is easily detected on a scintigram (Figure 2.1) and can be quantitated. It has been reported that plasma norepinephrine kinetics in sympathetic nerve terminals may change with age.[22,23]

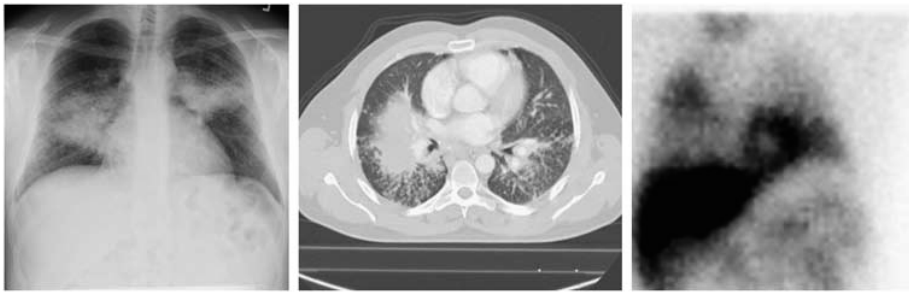


Figure 2.1 Metaiodobenzylguanidine and sarcoidosis.
Anterior chest radiograph, transaxial CT slice and planar anterior image of the thorax made of a patient with active sarcoidosis disease 4 h after intravenous injection of 185 Mbq ^{123}I-metaiodobenzylguanidine (MIBG). Note the remarkable irregular distribution of MIBG in the lungs.

Lung uptake of MIBG involves a sodium-dependent energy-requiring active transporter located in the endothelial cell membrane and changes in uptake can be due to changes in lung endothelial cell integrity of pre and postcapillary vessels and pulmonary veins.[24] Uptake by nerve endings is negligible.[25] After uptake in the endothelial cells, norepinephrine is rapidly degraded by monoamine oxidase and catechol *O*-methyl transferase (COMT).[24] In this way, the lungs are capable to regulate the amount of circulating norepinephrine. A decrease of around 20% in the uptake of MIBG in the lungs was observed both in a rat model after bleomycine[6] and in a rabbit model after amiodarone-induced pulmonary toxicity.[26] Because the lung endothelium has no vesicles and cannot store norepinephrine, the clearance of ^{123}I-MIBG from the lung is relatively rapid compared to that of the heart.[27] Of great interest in this respect is the study from Lee et al.[28] who investigated the characteristics and regulation of ^{123}I-MIBG transport in cultured pulmonary endothelial cells. A 50% percent wash-out was observed after 2 h. This time dependency is of importance and very few studies pay attention to this effect. As seen in Figure 2.2, uptake of MIBG in the lungs, 5 minutes after intravenous injection, has already shown different distribution patterns in patients with sarcoidosis. Lung uptake and washout of MIBG in sarcoidosis is diminished as described by Jonker et al.[29]

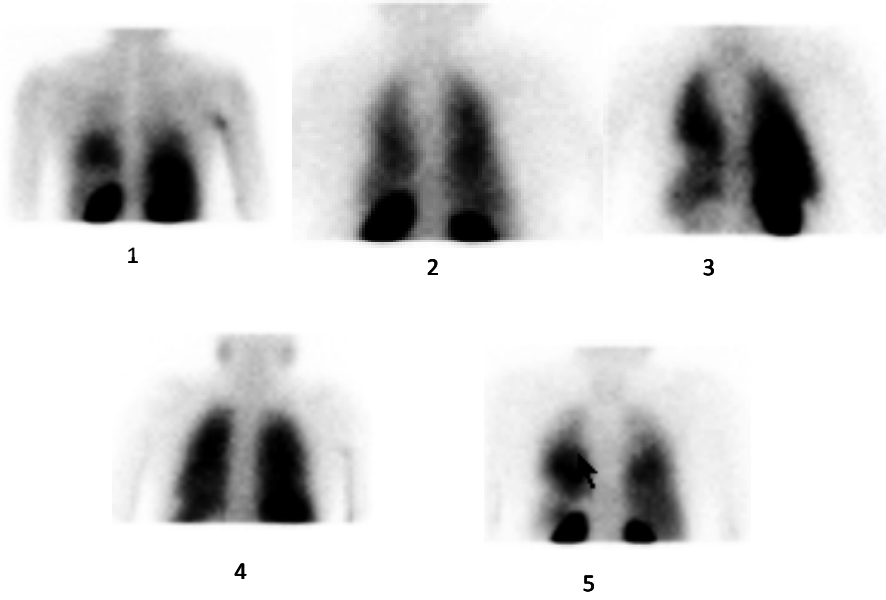


Figure 2.2 Dynamic metaiodobenzylguanidine scintigraphy.
Posterior images of the thorax made in five patients with sarcoidosis, directly (5 minutes) after intravenous injection of 185 Mbq ^{123}I-metaiodobenzylguanidine (MIBG). Arrows point to the heart uptake of MIBG. Note the different uptake patterns of MIBG in the lungs, reflecting different MIBG uptake in the endothelial cells of the lungs.

In sarcoidosis and other autoimmune diseases in which cardiac autonomic dysfunction is involved, a change in MIBG uptake can appear. Cardiac sympathetic nerves take up ^{123}I-MIBG. This permits visualization of the presynaptic sympathetic innervation of the heart. Defects on MIBG scans in sarcoidosis have been reported[30–33], but, to date, the underlying mechanism has remained unclear. One possible explanation postulated is that local ischemia or myocardial inflammation may play an important role. Recently, it was found that small fibre neuropathy (SFN) occurs frequently in sarcoidosis.[34] Moreover, an imbalance in sympathetic tone is considered to increase the propensity for developing ventricular arrhythmias in various cardiac diseases and conditions.[35] Autonomic dysregulation might contribute to fatal arrhythmias and unexplained sudden death in sarcoidosis. It is known from patients with neuropathy that the involvement of small autonomic nerve fibres is a predictor of cardiovascular mortality.[36,37] Sudden death is a rare, but dramatic complication.[38] In the case of sarcoidosis, it is thought to be due mainly to cardiac involvement. Active granulomatous infiltration and resulting myocardial fibrosis are considered to be the substrate. Cardiac sympathetic dysfunction, assessed by use of myocardial ^{123}I-MIBG scanning, appears to be heterogeneous in sarcoidosis patients and dependent on the presence or absence of SFN.[39] In 18 out of 47 (38%) of these cases, mild-to-moderate heterogeneity of ^{123}I-MIBG uptake in the myocardium was demonstrated. Cardiac sympathetic nervous system abnormalities detected by ^{123}I-MIBG have a predictive power in ventricular tachyarrhythmia, assessing prognosis in patients with chronic heart failure and assessing the risk of sudden death as shown in very recent studies.[40-42]

For correct interpretation of the results of MIBG scintigraphy, one should be aware of drug interference. Many drugs such as opioids, tricyclic antidepressants, sympathomimetics, antihypertensives and some anti-psychotics are known to interfere with the uptake and/or vesicular storage of ^{123}I-MIBG and those drugs should be discontinued for an adequate time prior to imaging.[43]

Conclusion

MIBG uptake and washout is a dynamic process and, therefore, implies appropriate timing for imaging and quantifying the neuronal accumulation. Imaging with MIBG in pulmonary diseases showed different patterns, probably related to disturbances in vascular endothelial function, but probably also related to the used imaging procedures and the vascularization status of the lungs and heart. Focusing on the lungs, we can say that changes in MIBG uptake and excretion can not be reliably differentiated on only one MIBG image, but serial or dynamic images are needed. Till now the imaging procedure has not been standardized, which makes interpretation and judging the clinical value difficult, if not impossible. Standardized, full dynamic acquisition with three-dimensional visualization of the MIBG uptake in the lung area

has never been performed. With single photon emission computed tomography-computed tomography (SPECT-CT) or positron emission tomography-computed tomography (PET-CT) with ^{124}I-MIBG, we have the tools to perform these studies of dynamic MIBG uptake in the lungs and heart in more detail. Lung perfusion and additional MIBG studies in humans has never been published. However, perfusion and MIBG studies from the heart often show mismatch of images, with normal perfusion of the heart and with clear innervation abnormalities observed by MIBG uptake. In our opinion, MIBG scanning of the lungs and heart is just started. However, the possibilities and instrumentation are available to investigate the relation between neuropathy and pulmonary and cardiac diseases in much more detail.

References

1. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques Jr. S. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987;28:1620-4.
2. Nakayo M, Shimabukuro K, Miyaji N, Shimada J, Shirono K, Sakata H, Yoshimura H, Yonekura R, Shinohara S. Rapid clearance if iodine-131 MIBG from the heart and liver in patients with adrenergic dysfunction and pheochromocytoma. *J Nucl Med* 1985;26:357-65.
3. Sole MJ, Drobac M, Schwartz L, Hussain N, Vaughan-Neil EF. The extraction of circulating catecholamines by the lungs in normal man and in patients with pulmonary hypertension *Circulation* 1979;60:160-3.
4. Fillenz M. Innervation of pulmonary and bronchial blood vessels. *J Anat* 1970;106:449-61.
5. Lincoln J, Burnstock G. An introduction to current research. In The Endothelium, Warren J (ed), new York, Wiley-Liss, Inc. 1990:21-32.
6. Miller VM. Interactions between neural and endothelial mechanisms in control of vascular tone. *NIPS* 1991;6:60-3.
7. Junod AF. 5-hydroxytryptamine and other amines in the lungs. In handbook of physiology. The respiratory system 1. 1985:337-49.
8. Slosman DO, Polla BS and Donath A. ^{123}I- MIBG pulmonary removal: a biochemical marker of minimal lung endothelial cell lesions. *Eur J Nucl Med* 1990;16:633-7.
9. Sakamaki F, Satoh T, Nagaya N, Kyotani S, Nakanishi N, Ishida Y. Abnormality of left ventricular sympathetic nervous function assessed by 123I-Metaiodobenzylguanidine imaging in patients with COPD. *Chest* 1999;116:1575-80.
10. Mark AL. Sympathetic dysregulation in heart failure mechanisms and therapy. *Clin Cardiology* 1995;18:13-18.
11. Arao T, Takabatake N, Sata M, Abe S, Shibata Y, Honma T, Takahashi K, Okada A, Takeishi Y, Kubota I. In vivo evidence of endothelial injury in chronic obstructive pulmonary disease by lung scintigraphic assessment of ^{123}I-Metaiodobenzylguanidine. *J Nucl Med* 2003;44:1747-54.
12. Takabatake N, Arao T, Sata M, Abe S, Inoue S, Shibata Y, Takeishi Y, Kubota I. Involvement of pulmonary endothelial cell injury in the pathogenesis of pulmonary fibrosis: clinical assessment by ^{123}I-MIBG lung scintigraphy. *Eur J Nucl Med Mol Imaging* 2005;32:221-8.
13. Yoshiike F, Koizumi T, Urushihata K, Hanaoka M,Kubo K. Reduced lung uptake of Iodine-123 Metaiodobenzylguanidine in patients with myeloperoxidase antineutrophil cytoplasmic antibodies-positive vasculitis. *Respiration* 2006;73:191-6.
14. Kotzumi T, Kubo K, Hanaoka M, Yamamoto H, Yamaguchi S, Fujii T, Kobayashi T. Serial scintigraphic assessment of iodine-123 Metaiodobenzylguanidine lung uptake in a patient with high altitude pulmonary edema. *Chest* 1999;116:1129-31.
15. Urushihata K, Koizumi T, Hanaoka M, Fujimoto K, Kubo K, Kobayashi T, Fujii T. Reduced lung uptake of iodine-123 metaiodobenzylguanidine in high-altitude pulmonary oedema. *Respirology* 2008;13: 897-902.
16. Richalet JP, Merlet P, Bourguignon M, Le-Trong JL, Kéromès A, Rathat C, Jouve B, Hot MA, Castaigne A, Syrota A. MIBG scintigraphic assessment of cardiac adrenergic activity in response to altitude hypoxia. *J Nucl Med* 1990;31:34-7.
17. Suga K, Kume N, Shimizu K, Nishigauchi K, Hara A, Motoyama K, Matsunaga N. Potential of iodine-123 metaiodobenzylguanidine single-photon emission tomography to detect abnormal functional status of the pulmonary neuroadrenergic system in irradiated lung. *Eur J Nucl Med* 1999;26:647-54.
18. Ünlü M, İnanir S. Prolonged lung retention of Iodine-123-MIBG in diabetic patients. *J Nucl Med* 1998; 39:116-8.
19. Murashima S, Takeda K, Matsumura K, Yamakado K, Sakuma H, Kitano T, Nakagawa T, Ichihara T, Yamakado T, Murata K. Increased lung uptake of Iodine-123-MIBG in diabetics with sympathetic Nervous dysfunction. *J Nucl Med* 1998;39:334-8.
20. Ünlü M, Akincioğlu C, Yamaç K and Önder M. Pulmonary involvement in Behçet's disease: evaluation of I123-MIBG retention. *Nucl Med Comm* 2001;22:1083-8.

21. Mu X, Hasegawa S, Yoshioka J, Maruyama A, Maruyama K, Paul AK, Yamaguchi H, Morozumi T, Hashimoto K, Kusuoka H, Nishimura T. Clinical value of lung uptake of iodine-123 metaiodobenzylguanidine (MIBG), a myocardial sympathetic nerve imaging agent, in patients with chronic failure. *Ann nucl Med* 2001;15:411-6.
22. Veith RC, Featherstone JA, Linares OA, Halter JR. Age differences in plasma norepinephrine kinetics in humans. *J Gerontol* 1986;41:319-24.
23. Kanzaki N, Soda R, Takahashi K, Sato K, Hayabara T, Kibata M, Takeda Y, Hiraki Y. Influence of age and gender on iodine-123 MIBG kinetics in normal lung. *Ann Nucl Med* 1998;12:225-9.
24. Nicholas TE, Strum JM. Angelo LS, Junod AF. Site and mechanism of uptake of 3H-1-norepinephrine by isolated perfused rat lungs. *Circ Res* 1974;35:670.
25. Sole MJ, Hussain MN. A simple specific radioenzymatic assay for the simultaneously measurement of pictogram quantities of norepinephrine, epinephrine and dopamine in plasma and tissues. *Biochem Med* 1977;18:301.
26. Durmuş-Altun G, Altun A, Aktas RG, Salihoglu YS, Yigitbasi NO. Use of iodine-123 metaiodobenzylguanidine scintigraphy for the detection of amiodarone induced pulmonary toxicity in a rabbit model: a comparative study with technetium-99m diethyltriaminepenta acetic acid radioaerosol scintigraphy. *Ann Nucl Med* 2005;19:217-24.
27. Morozumi T, Kusuoka H, Fukuchi K, Tani A, Uehara T, Matsuda S, Tsujimura E, Ito Y, Hori M, Kamada T, Nishimura T. Myocardial Iodine-123-metaiodobenzylguanidine images and autonomic nerve activity in normal subjects. *J Nucl Med* 1997;38:49-52.
28. Lee KH, Ko BH, Paik JY, Jung KH, Bae JS, Choi JY, Choe YS, Kim BT. Characteristics and regulation of 123I-MIBG transport in cultured pulmonary endothelial cells. *J Nucl Med* 2006;47:437-42.
29. Jonker GJ, Smulders NM, van Kroonenburgh MJ, Halders S, de Vries J, Faber CG, Drent M. Lung-uptake and -washout of MIBG in sarcoidosis. *Respir Med* 2008;102:64-70.
30. Smulders NM, Bast A, van Kroonenburgh MJ, Drent M. Improvement of cardiac sympathetic nerve function in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2008;25:140-2.
31. Imai E, Kaminaga T, Takada K, Kutomi K, Furui S. Radioactive defect on I-123 MIBG myocardial SPECT imaging in a patient with cardiac sarcoidosis. *Clin Nucl Med* 2002;27:729-30.
32. Matsuo S, Nakamura Y, Matsui T, Matsumoto T, Kinoshita M. Detection of denervated but viable myocardium in cardiac sarcoidosis with I-123 MIBG and Tl-201 SPECT imaging. *Ann Nucl Med* 2001; 15:373-5.
33. Misumi I, Kimura Y, Hokamura Y, Honda Y, Yasunaga T, Nakashima K, Takemura N, Asoshina M, Uranaka N, Takenaka S, Shima K. Scintigraphic detection of regional disruption of the adrenergic nervous system in sarcoid heart disease. *Jpn Circ J* 1996;60:774-8.
34. Hoitsma E, Marziniak M, Faber CG, Reulen JP, Sommer C, De Baets M, Drent M. Small fibre neuropathy in sarcoidosis. *Lancet* 2002;359:2085-6.
35. Wichter T, Matheja P, Eckardt L, Kies P, Schäfers K, Schulze-Bahr E, Haverkamp W, Borggrefe M, Schober O, Breithardt G, Schäfers M. Cardiac autonomic dysfunction in Brugada syndrome. *Circulation* 2002;105:702-6.
36. Tuck RR, McLeod JG. Autonomic dysfunction in Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry* 1981;44:983-90.
37. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med* 1980;92:308-11.
38. Ewing DJ, Boland O, Neilson JM, Cho CG, Clarke BF. Autonomic neuropathy, QT interval lengthening, and unexpected deaths in male diabetic patients. *Diabetologia* 1991;34:182-5.
39. Hoitsma E, Faber CG, van Kroonenburgh MJ, Gorgels AP, Halders SG, Heidendal GA, Kessels AG, Reulen JP, Drent M. Association of small fiber neuropathy with cardiac sympathetic dysfunction in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005;22:43-50.
40. Akutsu Y, Kaneko K, Kodamo Y, Li HL, Kawamura M, Asano T, Tanno K, Shinozuka A, Gokan T, Kobashi Y. The significance of cardiac sympathetic nervous system abnormality in the long-term prognosis of patients with a history of ventricular tachyarrhytmia. *J Nucl Med* 2009;50:61-7.
41. Jacobson AF, Lombard J, Banerjee G, Camici PG. ^{123}I- MIBG Scintigraphy to predict risk for adverse cardiac outcomes in heart failure patients: Design of two prospective multicenter international trials. *J Nucl Cardiol* 2009;16:113-21.

42. Tamaki S, Yamada T, Okuyama Y, Morita T, Sanada S, Tsukamoto Y, Masuda M, Okuda K, Iwasaki Y, Yasui T, Hori M, Fukunami M. Cardiac Iodine-123 metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left venrticular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2009;53:426-35.
43. Bombardieri E, Aktolun C, Baum RP, Bishof-Delaloye A, Buscombe J, Chatal JF, Maffioli L, Moncayo R, Mortelmans L, Reske SN. ^{131}I/^{123}I-Metaiodobenzylguanidine (MIBG) scintigraphy procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2003;30:132-9.