Role of cardiovascular imaging in systemic autoimmune diseases

Simona Sitia, Luigi Gianturco, Livio Tomasoni, Maurizio Turiel

INTRODUCTION

Systemic autoimmune diseases represent a family of different pathologies with common pathogenetic mechanisms and occur as a consequence of the loss of physiological tolerance to self antigens. The targets of the autoantibodies are ubiquitous antigens, so that tissue damage is generalized, resulting in multiple organ involvement, including the heart. Circulating antibodies do not always play a pathogenetic role but they represent specific markers of ongoing tissue damage. The most frequent systemic autoimmune diseases are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary antiphospholipid syndrome, systemic sclerosis and systemic vasculitis. Patients affected by these diseases show an increased cardiovascular (CV) morbidity and mortality, only partially related to traditional CV risk factors and mainly due to enhanced atherosclerosis. In particular, CV disease occurs at a younger age than in the general population and often remains asymptomatic, at least in the early stages.

Abstract

Systemic autoimmune diseases are characterized by an excess of cardiovascular (CV) morbidity and mortality compared to the general population, mainly due to chronic inflammation that promotes the development of endothelial dysfunction and enhanced atherosclerosis. Early diagnosis of silent CV involvement is mandatory to improve the long term prognosis of these patients and CV imaging provides valuable information as a reliable diagnostic tool. Trans thoracic echocardiography, with several applications (e.g. coronary flow reserve evaluation, tissue Doppler imaging, speckle tracking and the transesophageal approach), represents a first line evaluation, in association with biomarkers of endothelial dysfunction, such as asymmetric dimethylarginine. Nuclear medicine provides useful information on myocardial perfusion. The aim of this editorial is to provide a brief but complete review of the diagnostic tools available for screening and follow up of CV involvement in systemic autoimmune diseases.

© 2010 Baishideng. All rights reserved.

Key words: Systemic autoimmune disease; Rheumatoid arthritis; Cardiovascular involvement; Echocardiography; Coronary flow reserve; Cardiac magnetic resonance; Computed tomography; Coronary angiography; Speckle tracking

Peer reviewers: Guenter Pilz, MD, Assistant Professor, FESC, Department of Cardiology, Clinic Agatharied, Academic Teaching Hospital, University of Munich, Norbert-Kerkel-Platz, D-83734 Hausham, Germany; Mustafa Yildiz, MD, PhD, Associate Professor, EC, Cardiologist, Internal Medicine Specialist and Physiologist, Department of Cardiology, Kartal Kosuyolu Yuksek Ihtisas Educational and Research Hospital, Istanbul 81410, Turkey

Sitia S, Gianturco L, Tomasoni L, Turiel M. Role of cardiovascular imaging in systemic autoimmune diseases. World J Cardiol 2010; 2(8): 237-242 Available from: URL: http://www.wjgnet.com/1949-8462/full/v2/i8/237.htm DOI: http://dx.doi.org/10.4330/wjc.v2.i8.237
The excess of CV morbidity and mortality could be explained by specific risk factors strictly related to autoimmune diseases, such as chronic inflammation, disease duration and activity and immunosuppressive therapy [glucocorticoids, methotrexate or anti-tumor necrosis factor α (TNFα)]\(^9\). All components of the heart can be potentially affected by several pathogenetic mechanisms involving valves, coronary arteries, conduction system, myocardium, endocardium and pericardium such that a wide spectrum of clinical manifestations can occur; e.g. pericarditis, myocarditis and myocardial fibrosis, rhythm and conduction disturbances, coronaryitis with ischemic heart disease, valvular diseases, pulmonary hypertension, syncope, diastolic or systolic heart failure\(^6\).

Several studies have shown that chronic inflammation plays an important role in the development of atherosclerotic plaque\(^7\) and endothelial dysfunction; in particular, a reduced bioavailability of nitric oxide (NO) seems to be the primum movens in this process\(^8\). Asymmetric dimethylarginine (ADMA) is widely recognized as the major endogenous inhibitor of NO-synthase and is considered an emerging CV risk factor. Elevated plasma ADMA levels have been found in patients affected by systemic autoimmune diseases, for example, in RA patients\(^9,10\).

Since CV damage in autoimmune diseases is characterized by adverse outcomes, an early identification of patients at higher risk is very important to improve long term prognosis. CV imaging techniques provide a reliable approach to CV involvement in systemic autoimmune diseases, both for screening, diagnosis and follow up. In this report, we analyze the different characteristics and applications of various imaging modalities, pointing out advantages and disadvantages.

**ULTRASOUND APPLICATIONS**

Ultrasound techniques are easy and useful diagnostic tools that enable detection of cardiac morphological and functional damage. Transthoracic echocardiography is a reliable, inexpensive and non-invasive technique that allows an accurate evaluation of valvular abnormalities, pericardial diseases and ventricular wall motion defects, while Doppler analysis is useful in studying left ventricular diastolic filling, valvular functioning and pulmonary pressures. Rexhepaj et al\(^11\) found significant differences in early diastolic flow velocity (E), atrial flow velocity (A) and E/A ratios in RA patients compared to a control group, suggesting that a subclinical impairment of left and right ventricular function is present in RA patients, when left ventricular thickness, dimensions and myocardial performance indexes were still normal.

A new clinical application of ultrasound imaging is transthoracic dipyridamole stress echocardiography with coronary flow reserve (CFR) evaluation (Figure 1). CFR is assessed in the distal left anterior descending coronary artery defined by the ratio between peak diastolic velocity during stress and at baseline (Figure 2). It is a highly sensitive (> 90%) diagnostic marker for coronary artery disease (CAD)\(^12,13\) and, when associated with evaluation of the regional wall motion analysis, it becomes also highly specific\(^14\). In literature reports, a value of CFR < 2 has been shown to accurately predict the presence of coronary stenosis\(^13\). In the absence of epicardial coronary stenosis, an abnormal CFR may reflect an impaired coronary microcirculation in patients with reperfused myocardial infarct, arterial hypertension with or without left ventricular hypertrophy, diabetes mellitus, hypercholesterolemia, syndrome X, hypertrophic cardiomyopathy and other diseases\(^15\). The assessment of CFR also has a prognostic value, in that a reduced CFR correlates with a negative prognosis\(^16\). Recently, new evidence underlined that, not only the binary (normal-abnormal) response in CFR, but the continuous spectrum of CFR values is a strong independent prognostic predictor in patients with known or suspected CAD\(^17\).

Hirata et al\(^18\) found a significant reduction of CFR in premenopausal women with SLE compared with age- and sex-matched controls. They concluded that microvascular impairment in SLE could be explained by functional alteration of the endothelium, which is responsible for the decrease in vasodilation in response to pharmacological stress. Turiel et al\(^10\) detected a significant impairment of CFR in 25 early RA patients, with disease duration less than 1 year and without any anti-rheumatic therapy. The reduced CFR in the absence of wall motion abnormalities at rest and during pharmacological stress showed a coro-
Coronary artery calcification (CAC) has long been known to occur as a part of the atherosclerotic process and there is good evidence that the extent of CAC reflects the total coronary atherosclerotic burden\(^{[26]}\). The Agatston coronary calcium score assesses the extent and the density of calcification in the coronary tree\(^{[27]}\). Electron-beam computed tomography (EBCT) has been recognized as a highly sensitive tool that is able to detect small amounts of calcium in the coronary arteries. Radiation doses received during an EBCT study are much lower than invasive coronary angiography\(^{[28]}\). Recent studies, using multislice computed tomography (CT) with administration of iodinate contrast medium to visualize the coronary artery lumen, demonstrated accuracy in the detection of CAD\(^{[29]}\). This technique plays a diagnostic role not only for the detection of significant coronary artery luminal narrowing but also for the study of the atherosclerotic plaque texture. Moreover, it allows coronary calcium scanning along the coronary tree\(^{[30]}\).

Kiani et al\(^{[31]}\) evaluated coronary calcium by means of helical CT in 200 asymptomatic SLE patients and they found increased coronary calcium significantly related with plasma ADMA levels. However, while echocardiography and, mainly, stress echocardiography provide functional evaluations of the heart and the coronary tree, EBCT is limited to an anatomical and morphological description, without any functional information.

As reported above, CT requires the administration of iodinated contrast medium, which could induce intolerance symptoms or renal impairment and, moreover, patients undergo ionizing radiation exposure, which is much higher than in invasive coronary angiography. To overcome these limitations, coronary magnetic resonance (MR) angiography has been introduced in clinical practice with non-invasive visualization of the epicardial coronary arteries in the majority of subjects. It has high sensitivity, negative predictive value and overall accuracy for detecting CAD, but it is not an exercise-dependent exam\(^{[32]}\). Moreover, coronary MR angiography has an unsuccessful rate of 13%-14% depending on patient's features and coronary arteries with diameters less than 1.5 mm are not well visualized, so that the diagnostic accuracy of distal coronary artery lesions is inferior to multislice CT\(^{[33]}\). A meta-analysis of 48 studies showed that multislice CT has higher sensitivity and specificity than MR for non invasive detection of coronary artery stenosis\(^{[34]}\). Moreover, MR imaging protocols are variable and the imaging procedure is time-consuming\(^{[35]}\).

Because of its non-invasiveness, MR angiography might be the most feasible imaging modality for the detection of CAD in patients with chronic kidney disease, as well as in young and asymptomatic patients. Panting et al\(^{[36]}\) demonstrated the high sensitivity of myocardial perfusion MR in the detection of subendocardial hypoperfusion in patients with syndrome X, characterized by chest pain with normal coronary arteries, but these results were not supported by Vermeltfoort et al\(^{[37]}\). Pilz et al\(^{[38]}\) confirmed the ability of MR to address the status of coronary microvascular impairment in the presence of normal epicardial vessels. In particular, coronary MR has been shown to be effective in detecting congenital coronary artery abnormalities\(^{[39]}\).

**Figure 3** Speckle tracking analysis of radial strain in a left ventricle short axis view.
Moreover, MR plays an important role in the diagnosis of myocardial inflammation that often coexists with different systemic autoimmune diseases. Edwards et al. detected a high prevalence of late gadolinium enhancement in the left ventricular myocardium, not related to coronary artery territories in patients with SLE and Wagner granulomatosis, raising the possibility that myocardial damage is due to a combination of subclinical inflammatory and immunological processes.

Finally, coronary angiography remains the gold standard for the diagnosis and therapy of coronary epicardial stenosis and the assessment of the presence, extent and site of atheromatous lesions, but because of its invasiveness and potential high risk, should not be used as a screening tool.

**NONINVASIVE IMAGING OF MYOCARDIAL PERFUSION**

Single-photon emission CT (SPECT) is the most widely available nuclear technique to assess myocardial perfusion at rest and during stress (maximal exercise or pharmacological stress) using diffusable radionuclides. While under normal conditions, myocardial blood flow during stress increases about 3 to 5 fold compared to during rest. In the presence of significant coronary stenosis, myocardial perfusion will not increase appropriately in the territory supplied by the stenotic artery, creating heterogeneous uptake. The available SPECT radionuclides are characterized by a rapid myocardial extraction and by a cardiac uptake proportional to blood flow. Although SPECT is very sensitive, specificity is relatively lower, mainly due to the occurrence of artifacts due to soft-tissue attenuation. Disadvantages of SPECT are represented by the need to use radioactive materials. However, the diagnostic applications are based on the ability to detect a hemodynamically significant flow-limiting stenosis.

Positron emission tomography (PET) has higher spatial resolution than SPECT and provides absolute quantitative measurements of physiologic parameters; moreover, it has high sensitivity and specificity for detection of myocardial ischemia. Myocardial perfusion by PET is particularly useful in reducing the number of false-positive SPECT studies because attenuation artifacts and allows a quantitative evaluation of myocardial blood flow.

The noninvasive study of myocardial perfusion by nuclear imaging could be a useful tool for the detection of subtle CV involvement in systemic autoimmune diseases, such as LES or RA, however, more study is required.

**USEFULNESS OF BIOMARKERS OF ENDOTHELIAL DYSFUNCTION**

In the field of systemic autoimmune disease, the new challenge for cardiology is the early diagnosis of subtle cardiac abnormalities in a preclinical stage. In addition to instrumental diagnostic tools, there is increasing evidence for a strict association between plasma levels of ADMA and CV disease in autoimmune diseases. Increased ADMA plasma levels have been demonstrated in different pathological conditions characterized by high CV risk, such as hypercholesterolemia, hypertriglyceridemia, peripheral arterial disease, hypertension, type 2 diabetes mellitus, acute coronary syndrome and end-stage renal disease. Recently, Kiani et al. described higher ADMA levels among SLE patients. In this group ADMA levels appeared to be associated with coronary calcification and poor prognosis. In contrast, Turiel et al. found that increased plasma ADMA levels in early RA patients who were free of anti-rheumatic therapy were associated with a subclinical impairment of coronary microcirculation. Interestingly, the same authors observed that after 18 mo of treatment with methotrexate or anti-TNFα agents, the improvement in inflammatory status and better control of disease activity were able to induce a significant amelioration of CFR.

Evaluation of the arterial distensibility and stiffness represents a good index of endothelial dysfunction and preclinical atherosclerosis. A reduced arterial distensibility disturbs coronary perfusion and has been related to increased CV risk. Yildiz reported a subclinical impairment of the aortic pulse wave velocity in chronic inflammatory rheumatic disorders, such as SLE, RA, psoriasis and systemic sclerosis, mainly due to the chronic inflammatory status.

**CONCLUSION**

CV involvement represents the most likely cause of morbidity and mortality in systemic autoimmune disease, with a large spectrum of clinical manifestations. However, the cardiologist should be able to make an early diagnosis of cardiac disease when it is still clinically silent. Echocardiographic techniques, with several applications, and in particular stress echocardiography with CFR evaluation, represent a first line approach for the assessment of endothelial dysfunction, such as ADMA, in addition to biomarkers. Nuclear medicine can provide a functional evaluation of myocardial perfusion, while CT and cardiac MR can be used to evaluate the morphological and anatomical integrity of coronary vessels. A careful study of CV function should be done in patients affected by systemic autoimmune diseases, early after diagnosis, to detect preclinical involvement and improve long-term prognosis.

**REFERENCES**

1. Sita S, Atzeni F, Sarzi-Puttini P, Di Bello V, Tomasoni L, Delfino L, Antonini-Canterin F, Di Salvo G, De Gennaro Colonna V, La Carrubba S, Carej S, Turiel M. Cardiovascular involvement in systemic autoimmune diseases. Autoimmun Rev 2009; 8: 281-286
2. Knockaert DC. Cardiac involvement in systemic inflammatory diseases. Eur Heart J 2007; 28: 1797-1804
3. Ribolli P, Gerosa M, Luzzana C, Catelli L. Cardiac involvement in systemic autoimmune diseases. Clin Rev Allergy Immunol 2002; 23: 247-261
4. Tanasescu C, Jurcut C, Jurcut R, Ginghina C. Vascular disease in rheumatoid arthritis: from subclinical lesions to cardiovascular risk. Eur J Intern Med 2009; 20: 348-354
van Zonneveld AJ, de Boer HC, van der Veer EP, Rabelink TJ. Inflammation, vascular injury and repair in rheumatoid arthritis. *Ann Rheum Dis* 2010; 69 Suppl 1: i57-60

Turiel M, Sitia S, Tomasoni L, Cicala S, Atzeni F, Gianiutro L, Longhi M, De Gennaro Coloma V, Sarzi-Puttini P. Cardiac involvement in rheumatoid arthritis. *Reumatismo* 2009; 61: 243-253

Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how “high-grade” systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2013; 108: 2957-2963

Arosio E, De Marchi S, Rigoni A, Prior M, Delva P, Lechi A. Forearm haemodynamics, arterial stiffness and microcirculatory reactivity in rheumatoid arthritis. *J Hypertens* 2007; 25: 1273-1278

Kiani AN, Mahoney JA, Petri M. Asymmetric dimethylarginine is a marker of poor prognosis and coronary calcium in systemic lupus erythematous. *J Rheumatol* 2007; 34: 1502-1505

Turiel M, Atzeni F, Tomasoni L, de Portu S, Delfino L, Bodini BD, Longhi M, Sitia S, Bianchi M, Ferrario P, Doria A, De Gennaro Coloma V, Sarzi-Puttini P. Non-invasive assessment of coronary flow reserve and ADMA levels: a case-control study of early rheumatoid arthritis patients. *Rheumatology* (Oxford) 2009; 48: 834-839

Rexhepaj N, Bajraktari G, Berisha I, Beqiri A, Shati F, Hima F, Elezi S, Ndrepapa G. Left and right ventricular diastolic functions in patients with rheumatoid arthritis without clinically evident cardiovascular disease. *Int J Clin Pract* 2006; 60: 683-688

Caiati C, Zedda N, Montaldo C, Montisci R, Iliceto S. Contrast-enhanced transthoracic second harmonic echo Doppler with adenosine: a noninvasive, rapid and effective method for coronary flow reserve assessment. *J Am Coll Cardiol* 1999; 34: 122-130

Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, Moriooka S. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. *Circulation* 1998; 97: 1557-1562

Rigo F, Richieri M, Pasanisi E, Cutaia V, Zanella C, Della Valentina P, Di Pede F, Raviele A, Picano E. Usefulness of coronary flow reserve over regional wall motion when added to dual-imaging dipyridamole echocardiography. *Am J Cardiol* 2003; 91: 269-273

Dimitrov PP. Coronary flow reserve-measurement and application: focus on transthoracic Doppler echocardiography. Boston/Dordrecht/London: Kluwer Academic Publishers, 2002

Rigo F, Gherardi S, Galderisi M, Pratali L, Cortigiani L, Sicari R, Picano E. The prognostic impact of coronary flow reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy. *Eur Heart J* 2006; 27: 1319-1323

Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Picano E, Sicari R. Implication of the continuous prognostic spectrum of Doppler echocardiographic derived coronary flow reserve on left anterior descending artery. *Am J Cardiol* 2010; 105: 158-162

Hirata K, Kadirvelu A, Kinjo M, Sciacca R, Sugikawa K, Otsuka H, Choy A, Chow SK, Yoshimura M, Yoshiyaka J, Homma S, Lang CC. Altered coronary vasomotor function in young patients with systemic lupus erythematosus. *Arthritis Rheum* 2007; 56: 1904-1909

Dandel M, Hetter C. Echocardiographic strain and strain rate imaging—clinical applications. *Int J Cardiol* 2009; 132: 11-24

Birdane A, Korkmaz C, Ata N, Cavusoglu Y, Kasiroglu T, Dogan SM, Gorenek B, Goktekin O, Unalir A, Timuralp B. Tissue Doppler imaging in the evaluation of the left and right ventricular diastolic functions in rheumatoid arthritis. *Echocardiography* 2007; 24: 485-493

Sitia S, Tomasoni L, Turiel M. Speckle tracking echocardiography: A new approach to myocardial function. *World J Cardiol* 2010; 2: 1-5

Turiel M, Muzzopappa S, Gottiardi B, Crema C, Sarzi-Puttini P, Rossi E. Evaluation of cardiac abnormalities and embolic sources in primary antiphospholipid syndrome by transesophageal echocardiography. *Lancet* 2000; 9: 406-412

Turiel M, Sarzi-Puttini P, Peretti R, Bonizzatto S, Muzzopappa S, Atzeni F, Rossi E, Doria A. Five-year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. *Am J Cardiol* 2005; 96: 574-579

Plastiras SC, Famboucas CA, Tzelepis GE, Toumanidis ST. Assessing mitral valve stenosis by real-time 3-dimensional echocardiography in systemic lupus erythematosus: a look inside the heart. *J Rheumatol* 2009; 36: 1843-1845

Marsan NA, Tops LF, Nihoyannopoulos P, Holman ER, Bax JJ. Real-time three dimensional echocardiography: current and future clinical applications. *Heart* 2009; 95: 1881-1890

Raggi P, Achenbach S. Computed tomography for atherosclerosis and coronary artery disease imaging. *Disc Med* 2010; 9: 98-104

Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827-832

Budoff MJ, Georgiou D, Brody A, Agatston AS, Kennedy J, Wolfkief C, Stanford W, Shields P, Lewis R, Janowitz WR, Rich S, Brundage BH. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation* 1996; 93: 898-904

Achenbach S, Moshage W, Ropers D, Nossen J, Daniel WG. Value of electron-beam computed tomography for the noninvasive detection of high-grade coronary-artery stenoses and occlusions. *N Engl J Med* 1998; 339: 1964-1971

Matsumoto N, Nagao K, Hirayama A, Sato Y. Non-invasive assessment and clinical strategy of stable coronary artery disease by magnetic resonance imaging, multislice computed tomography and myocardial perfusion SPECT. *Circ J* 2010; 74: 34-40

Kim WY, Danias PG, Stuber M, F lam SD, Plein S, Nagel E, Langerak SE, Weber OM, Pedersen EM, Schmidt M, Botnar RM, Manning WJ. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 2001; 345: 1863-1869

Schuij J, Dax JJ, Shaw LJ, de Roos A, Lamb HJ, van der Wall EE, Wijns W. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for non-invasive coronary angiography. *Am Heart J* 2016; 151: 404-411

Panting JR, Gatehouse PD, Yang GZ, Grothues F, Firmin DN, Collins P, Pennell DJ. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002; 346: 1948-1953

Vermeltfoort IA, Bondarenko O, Raimakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, van der Vis-Melsen MJ, Twisk JW, Beek AM, Teule GJ, van Rossum AC. Is subendocardial ischaemia present in patients with chest pain and normal coronary angiograms? A cardiovascular MR study. *Eur Heart J* 2007; 28: 1554-1558

Pilz G, Klos M, Ali E, Hoefling B, Schech R, Bernhardt P. Angiographic correlations of patients with small vessel disease diagnosed by adenosine-stress cardiac magnetic resonance imaging. *J Cardiovasc Magn Reson* 2008; 10: 8

Sato Y, Matsumoto N, Katsumi S, Kunimasa T, Yoda S, Tani S, Kunimoto S, Achenbach S, Saito S. Anomalous origin of the right coronary artery: depiction at whole-heart coronary magnetic resonance angiography. *Int J Cardiol* 2008; 127: 274-275

Mavrogeni S, Spargias K, Markussis V, Kolovou G, Demouiti E, Papadopoulou E, Stavridis G, Kaklamani L, Douskou M, Constantinoulakis P, Kokkinos DV. Myocardial inflammation in autoimmune diseases: investigation by cardiovascular...
magnetic resonance and endomyocardial biopsy. Inflamm Allergy Drug Targets 2009; 8: 390-397

38 Mavrogeni S, Manousakis M, Spargias K, Douskou M, Moutsopoulos H, Kaklamannis I, Cokkinos DV. Frequent detection of myocardial inflammation in autoimmune diseases. J Cardiovasc Mag Reson 2008; 10 Suppl 1: A302.

39 Edwards NC, Ferro CJ, Townend JN, Steeds RP. Myocardial disease in systemic vasculitis and autoimmune disease detected by cardiovascular magnetic resonance. Rheumatology (Oxford) 2007; 46: 1208-1209.

40 Turiel M, Peretti R, Sarzi-Puttini P, Atzeni F, Doria A. Cardiac imaging techniques in systemic autoimmune diseases. Lupus 2005; 14: 727-731.

41 Cuocolo A, Acampa W, Imbriaco M, De Luca N, Iovino GL, Salvatore M. The many ways to myocardial perfusion imaging. Q J Nucl Med Mol Imaging 2005; 49: 4-18.

42 Leppo JA, Meerdink DJ. Comparison of the myocardial uptake of a technetium-labeled isonitrile analogue and thallium. Circ Res 1989; 65: 632-639.

43 Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, Kelion AD, Al-Mohammad A, Prvulovich EM, Shaw LJ, Tweddel AC. Myocardial perfusion scintigraphy: the evidence. Eur J Nucl Med Mol Imaging 2004; 31: 261-291.

44 Petretta M, Costanzo P, Acampa W, Imbriaco M, Ferro A, Filardi PP, Cuocolo A. Noninvasive assessment of coronary anatomy and myocardial perfusion: going toward an integrated imaging approach. J Cardiovasc Med (Hagerstown) 2008; 9: 977-986.

45 Espinola Zavala N, Alexanderson E, Soto ME, Flores M, Amigo MC. [Analysis of the usefulness of contrast echocardiography and nuclear medicine in cardiovascular affection due to autoimmune diseases] Arch Cardioi Mex 2005; 75: 42-48.

46 Böger RH, Bode-Böger SM, Szuba A, Tsao PS, Chan JR, Tangphao O, Blaschke TF, Cooke JP. Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction: its role in hypercholesterolemia. Circulation 1998; 98: 1842-1847.

47 Lundman P, Eriksson MJ, Stühlinger M, Cooke JP, Hamsten A, Tornvall P. Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine. J Am Coll Cardiol 2001; 38: 111-116.

48 Böger RH, Bode-Böger SM, Thiele W, Junker W, Alexander K, Fröhlich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease. Circulation 1997; 95: 2068-2074.

49 Surdacki A, Nowicki M, Sandmann J, Tsikas D, Boeger RH, Bode-Boeger SM, Kruzelnicka-Kwiatkowska O, Kokot F, Dubiel JS, Frölich JC. Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. J Cardiovasc Pharmacol 1999; 33: 652-658.

50 Stühlinger MC, Abbasi F, Chu JW, Lamendola C, McLaughlin TL, Cooke JP, Reaven GM, Tsao PS. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA 2002; 287: 1420-1426.

51 Bae SW, Stühlinger MC, Yoo HS, Yu KH, Park HK, Choi BY, Lee YS, Pachinger O, Choi YH, Lee SH, Park JE. Plasma asymmetric dimethylarginine concentrations in newly diagnosed patients with acute myocardial infarction or unstable angina pectoris during two weeks of medical treatment. Am J Cardiol 2005; 95: 729-733.

52 MacAllister RJ, Rambausek MH, Vallance P, Williams D, Hoffmann KH, Ritz E. Concentration of dimethyl-L-arginine in the plasma of patients with end-stage renal failure. Nephrol Dial Transplant 1996; 11: 2449-2452.

53 Turiel M, Tomasoni L, Sità S, Cicala S, Gantanuro L, Ricci C, Atzeni F, De Gennaro Colonna V, Longhi M, Sarzi-Puttini P. Effects of Long-Term Disease-Modifying Antirheumatic Drugs on Endothelial Function in Patients with Early Rheumatoid Arthritis. Cardiovasc Ther 2010; Epub ahead of print.

54 Wang YX, Fitch RM. Vascular stiffness: measurements, mechanisms and implications. Curr Vasc Pharmacol 2004; 2: 379-384.

55 Yildiz M. Arterial distensibility in chronic inflammatory rheumatic disorders. Open Cardiovasc Med J 2010; 4: 83-88.