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# Non-Invasive Study of Coronary Circulation by Means of a Transthoracic Dipyridamole Stress Echocardiography with Coronary Flow Reserve Evaluation

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Vincenzo Gianturco and Bruno Dino Bodini

Additional information is available at the end of the chapter

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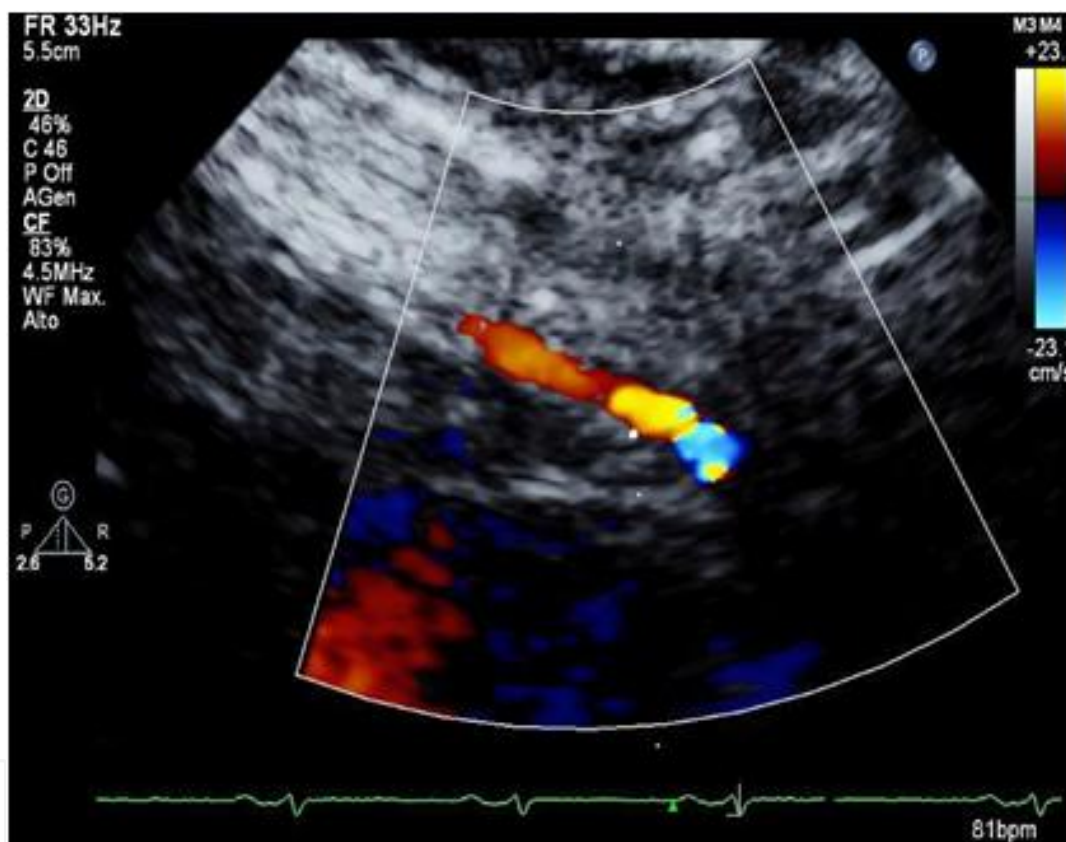
## 1. Introduction

Ultrasound techniques represent easy and useful diagnostic tools able to detect cardiac morphological and functional damage.

Transthoracic echocardiography is a reliable, cheap and non-invasive technique that allows an accurate evaluation of valvular abnormalities, pericardial diseases and ventricular wall motion defects, while Doppler analysis is useful to study left ventricular diastolic filling, valvular functioning and pulmonary pressures. Rexhepaj et al [1] found significant differences in early diastolic flow velocity (E), atrial flow velocity (A) and E/A ratio in rheumatoid arthritis (RA) patients compared to the 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 represented by the transthoracic dipyridamole stress echocardiography with coronary flow reserve (CFR) evaluation. CFR is assessed in the distal left anterior descending coronary artery (LAD) defined by the ratio between peak diastolic velocity during stress and at baseline (Fig. 1-2). It is a highly sensitive (>90%) diagnostic marker for coronary artery disease (CAD)[2, 3] and, when associated with the evaluation of the regional wall motion analysis, it becomes also highly specific [4]. In literature reports, a value of CFR < 2 has been shown to accurately predict the presence of coronary stenosis. In 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 [5]. The assessment of CFR has also a prognostic value, so that a reduced CFR correlates with a negative prognosis [6]. Recently, new evidence underlined that not only the binary (normal-abnormal) response in CFR but the continuous spectrum of CFR value is a strong independent prognostic predictor in patients with known or suspected CAD [7].



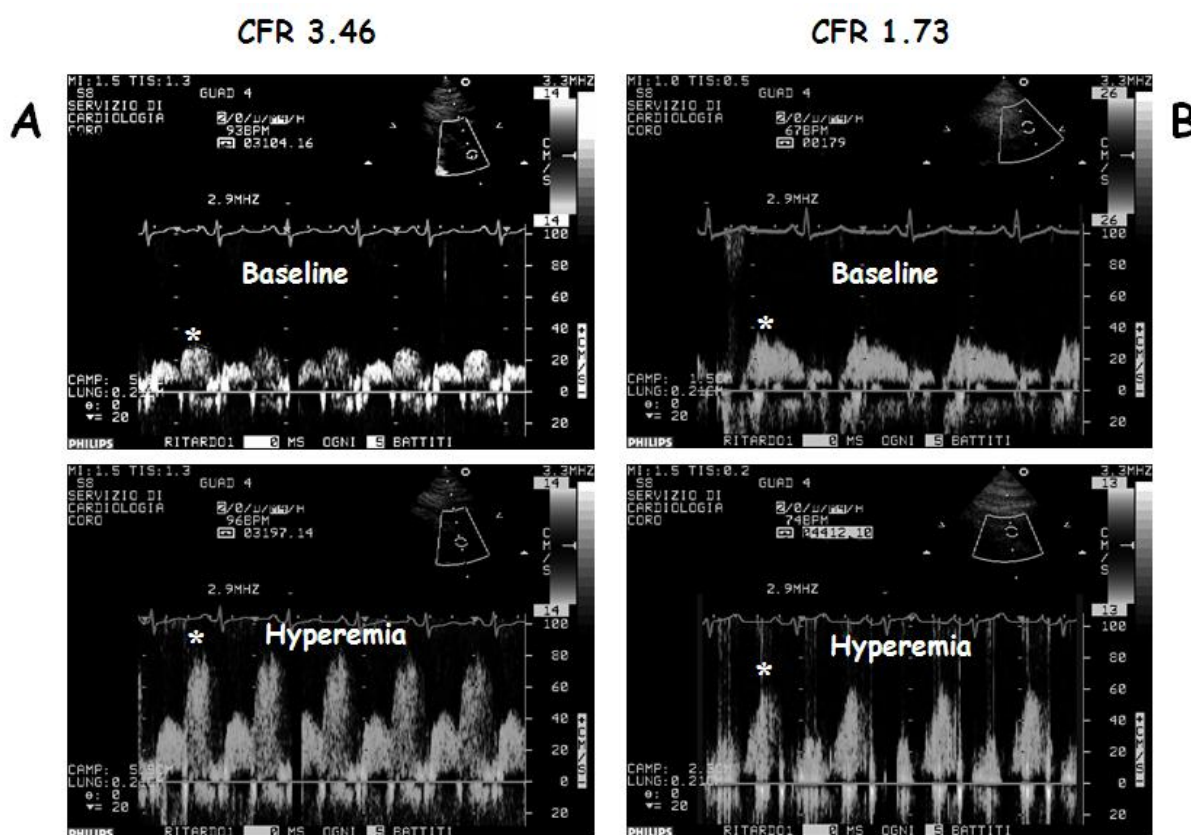
**Figure 1.** Distal left anterior descending (LAD) flow at color-Doppler.

Hirata et al [8] 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 endothelium which is responsible for the decrease vasodilation in response to pharmacological stress.

Turiel et al. 9 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 absence of wall motion abnormalities at rest and during pharmacological stress showed a coro-

nary microcirculation involvement present in early RA and was associated with endothelial dysfunction.

Tissue Doppler Imaging (TDI) represents a new imaging modality which allows the measurement of myocardial velocities. Till now, TDI has been considered a reliable tool for the assessment of myocardial deformation, but this method is limited by angle-dependency and only deformation along the ultrasound beam can be derived from velocities, while myocardium deforms simultaneously in 3 dimensions [10]. Recently, Birdane et al [11] demonstrated that RA patients had a significant impairment of TDI biventricular diastolic functional parameters compared to healthy controls depending on age and use of steroids. To overcome TDI limitations, speckle tracking analysis has been introduced to evaluate myocardial strain along the longitudinal, circumferential and radial axis [12].



**Figure 2.** Doppler sampling of LAD: ratio between peak diastolic velocity during stress and at baseline.

Another very useful application of echocardiography in systemic autoimmune diseases is the echo transesophageal approach which is widely recognized as more sensitive than the transthoracic evaluation for the detection of valvular lesions [13] and identification of intracardiac masses.

In particular, Turiel et al [14] observed a large prevalence (61%) of valvular thickening or vegetations and/or potential embolic sources by transesophageal echocardiographic approach in 56 patients with primary antiphospholipid syndrome followed up for 5 years.

## 2. Utility of coronary flow reserve assessment in systemic autoimmune diseases

Patients suffering from systemic autoimmune diseases (SADs), especially RA, present higher risk of acute myocardial infarction and stroke [15], correlated with disease duration [16] with higher frequency of silent myocardial infarction and sudden death compared to general population [17]. This increase in cardiovascular (CV) risk seems not depending on traditional risk factors, thus suggesting a dominating role of RA-related risk factors [18, 19]. During these last years, attempts of explaining the accelerated atherosclerosis pathogenic pathways in RA were made; Attention particularly focused importance of chronic systemic inflammatory process with high pro-inflammatory cytokines plasmatic levels. Presence of pro-atherogenic alterations such as dislipidemy, insulin-resistance, trombofilia and oxidative stress look favoring development of endothelial dysfunction that may be the initial stage of the atherosclerotic process [20, 21]. Arosio et al. [22], showed a reduced vasodilatation endothelium-dependant, changes in micro circle reactivity and an increased arterial stiffness in RA female patients.

Today non invasive evaluation of carotid median intimal thickness (IMT) is considered an early atherosclerosis clinical marker [23]. Kumeda et al. [24] observed in RA patients an increased IMT of common carotid and femoral artery, related to disease severity and duration. According to these evidences, Ciftci et al. [25] confirmed increased IMT and presence of reduced coronary flow reserve (CFR) in RA patients, correlating CV risk to disease duration. Moreover, Chung et al. [26], studied extension of coronary calcifications with CT, showing that patient with a long history of RA presents greater prevalence and severity of coronary calcifications compared to patients with early RA, also correlated with smoking and increase eritrosedimentation rate (ESR).

Nowadays, trans-thoracic echocardiographic evaluation of CFR by pharmacological stress (adenosine or dipyridamole) is considered a very useful exam as diagnose marker highly sensible (>90%) for coronary disease [27]. If associated with LV regional kinesis evaluation, acquires high specificity too. CFR value < 2 measured about at middle-distal tract of left anterior descending artery can accurately predict the presence of coronary significative stenosis. If epicardial vessels are free from significant stenosis a reduced CFR can be evidence of an alteration in coronary microcirculation in patients with reperfused myocardial infarction, high blood pressure with or without LV hypertrophy, diabetes mellitus, hypercholesterolemia, X syndrome, hypertrophic cardiomyopathy and collagen diseases. CFR measure has prognostic value in different pathologic conditions too [28].

Turiel et al. [29] showed a statistically significative variation of CFR among RA patients related with disease duration.

Endothelium function can be also studied through measure of asymmetric dimethylarginine (ADMA) plasmatic levels. Many clinical evidences support a close association between ADMA level and CV involvement in patients autoimmune diseases [30].

Higher ADMA plasmatic levels are reported in many conditions associated with high CV risk such as hypercholesterolemia, hypertriglyceridemia [31], peripheral artery disease [32], diabetes mellitus type II [33], acute coronary syndrome [34], chronic renal failure [35]. Moreover, Surdacki et al [36] evidenced in RA patient an association between high ADMA plasmatic levels and increased IMT at common carotid artery. Turiel et al. [37] observed an inverse correlation between ADMA and CFR in early stages of RA thus indicating a subclinical heart involvement already present at the beginning of the development of the disease.

Many clinical trials evidenced potential effects against atherosclerosis of therapies lead with disease modifying anti-rheumatic drugs (DMARDs), going beyond the simple control of inflammatory process and of disease activity (Tab. 1). In particular Hurlimann et al. [38] showed that anti-TNF $\alpha$  can not only reduce disease activity indexes, but also increase endothelial function in RA. Moreover, Sitia et al. [39] observed that long time treatment with DMARDs can reverse endothelial dysfunction, in early stages of disease.

Farmaco	Posologia	Tempo approssimativo per l' azione	Documentazione attività ref.	Costo per terapia annuale (\$ )
Idrossiclorochina	200 mg 2 volte al giorno	2 - 6 mesi	11,12	1.056
Oro intramuscolo	25-50 mg i.m. ogni 2-4 sett	3 - 6 mesi	13	198
Azatioprina	50-150 mg al giorno	2 - 3 mesi	14	579 - 1.737
D-penicillamina	250-750 mg/die	3 - 6 mesi	15	865 - 2.595
Ciclosporina	25-4 mg/Kg/die	2 - 4 mesi	16	4.432 - 8.859
Methotrexate	7,5-20 mg/sett i.m o per os	1 - 2 mesi	17,18	orale 697 -1.859 i.m. 419 - 806
Sulfasalazina	100 mg 2-3 volte die	1 - 3 mesi	19 - 21	509 - 763
Leflunomide	20 mg al giorno	4 - 12 sett.	22,23	2.938
Infliximab (+ Methotrexate)	3-10 mg/Kg i.v. ogni 8 sett	da pochi giorni a 4 mesi	24 - 26	13.940 - 36.694
Etanercept	25 mg sc 2 volte/sett.	da pochi giorni a 4 sett.	27 - 29	15.436
Anakinra	100 mg sc quotidie	-	30,31	-

**Table 1.** Disease modifying anti-rheumatic drugs (DMARDs) in common use. (From American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 2002; 46: 328-46, modified).

In addition, Mäki-Petäjä et al. [40] in a recent study confirmed the efficacy of associating ezetimibe and simvastatin in reducing the inflammatory process, but also in improving aortic stiffness in RA. Anyway, the possible validation of efficacy of the therapy with statin and/or biological drugs in modifying the evolution of atherosclerosis needs further perspective clinical trials.

### 3. Conclusions

Subclinical CV involvement related to specific and non-specific risk factors is frequent in systemic autoimmunity diseases. It begins rapidly after the onset of the disease and progresses with disease duration. All cardiac structures may be affected, and the cardiac complications include a variety of clinical manifestations. As CV involvement is associated with an unfavorable prognosis, the early detection of subclinical cardiac involvement in asymptomatic SADs patients is essential and then modern techniques nowhere existing and in this chapter illustrated are very very important to reach such goal.

### Conflict of interest

None

### Author details

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### References

- [1] NoneRexhepaj N, Bajraktari G, Berisha I, Beqiri A, Shatri F, Hima F, Elezi S, Ndrepepa G. Left and right ventricular diastolic functions in patients with rheumatoid ar-

- thritus without clinically evident cardiovascular disease. *Int J Clin Pract* 2006; 60: 683-688.
- [2] Caiati C, Zedda N, Montaldo C, Montisci R, Ruscazio M, Lai G, Cadeddu M, Meloni L, 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.
- [3] Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, Morioka S. Non invasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. *Circulation* 1998; 97: 1557-1562.
- [4] 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.
- [5] Dimitrow PP. *Coronary flow reserve-measurement and application: focus on transthoracic Doppler echocardiography*. Boston/Dordrecht/London: Kluwer Academic Publishers. 2002.
- [6] 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-ischemic dilated cardiomyopathy. *Eur Heart J* 2006;27:1319-1323.
- [7] 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.
- [8] Hirata K, Kadirvelu A, Kinjo M, Sciacca R, Sugioka K, Otsuka R, Choy A, Chow SK, Yoshiyama M, Yoshikawa J, Homma S, Lang CC. Altered coronary vasomotor function in young patients with Systemic Lupus Erythematosus. *Arthritis and Rheum* 2007; 56: 1904-1909.
- [9] Turiel M, Tomasoni L, Sitia S, Cicala S, Gianturco L, Ricci C, Atzeni F, De Gennaro Colonna V, Longhi M, Sarzi-Puttini P. Effects of long-term disease-modifying anti-rheumatic drugs on endothelial function in patients with early rheumatoid arthritis. *Cardiovasc Ther*. 2010 Oct;28(5):e53-64.
- [10] Dandel M, Hetzer R. Echocardiographic strain and strain rate imaging – Clinical applications. *Int J Cardiol* 2009; 132: 11-24.
- [11] Birdane A, Korkmaz C, Ata N, Cavusoglu Y, Kasifoglu 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.
- [12] Sitia S, Tomasoni L, Turiel M. Speckle tracking echocardiography: a new approach to myocardial function. *World J Cardiol* 2010; 2: 1-5.



- [13] Turiel M, Muzzupappa S, Gottardi B, Crema C, Sarzi-Puttini P, Rossi E. Evaluation of cardiac abnormalities and embolic sources in primary antiphospholipid syndrome by transesophageal echocardiography. *Lupus* 2000;9: 406-412.
- [14] Turiel M, Sarzi-Puttini P, Peretti R, Bonizzato S, Muzzupappa 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.
- [15] Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, Canning C, Schneeweiss S. Patterns of cardiovascular risk in rheumatoid arthritis. *Ann Rheum Dis.* 2006;65:1608-12.
- [16] Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, Stampfer MJ, Curhan GC. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation.* 2003;107:1303-7.
- [17] Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, Gabriel SE. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum.* 2005;52:402-11.
- [18] Del Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum.* 2001;44:2737-45.
- [19] Del Rincón I, O'Leary DH, Freeman GL, Escalante A. Acceleration of atherosclerosis during the course of rheumatoid arthritis. *Atherosclerosis.* 2007;195:354-60.
- [20] Voskuyl AE. The heart and the cardiovascular manifestations in rheumatoid arthritis. *Rheumatology* 2006;45:iv4-7.
- [21] Dhawan SS, Quyyumi AA. Rheumatoid arthritis and cardiovascular disease. *Curr Atheroscler Rep.* 2008 Apr;10(2):128-33.
- [22] Arosio E, De Marchi S, Rigoni A, Prior M, Delva P, Lech A. Forearm haemodynamics, arterial stiffness and microcirculatory reactivity in rheumatoid arthritis. *J Hypertens.* 2007;25:1273-8.
- [23] Sidhu PS, Allen PL. Ultrasound assessment of internal carotid artery stenosis. *Clin Radiol* 1997;52: 654-8.
- [24] Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, Ishimura E, Inui K, Yutani Y, Miki T, Shoji T, Nishizawa Y. Increased thickness of arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002; 46:1489-97.
- [25] Ciftci O, Yilmaz S, Topcu S, Caliskan M, Gullu H, Erdogan D, Pamuk BO, Yildirim A, Muderrisoglu H. Impaired coronary microvascular function and increased intima-media thickness in rheumatoid arthritis. *Atherosclerosis* 2008; 198: 332-7.

- [26] Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, Pincus T, Avalos I, Stein CM. Increased coronary-artery atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2005;52: 3045-53.
- [27] Kerekes G, Soltész P, Nurmohamed MT, Gonzalez-Gay MA, Turiel M, Végh E, Shoenfeld Y, McInnes I, Szekanecz Z. Validated methods for assessment of subclinical atherosclerosis in rheumatology. *Nat Rev Rheumatol* 2012; 8(4): 224-34.
- [28] Sitia 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, Carerj S, Turiel M. Cardiovascular involvement in systemic autoimmune diseases. *Autoimmunity Rev* 2009; 8: 281-286.
- [29] Atzeni F, Sarzi-Puttini P, Delfino L, et al. Decreased coronary flow reserve in patients with rheumatoid arthritis. *Ann Rheum Dis* 2004;63:S196.
- [30] De Gennaro Colonna V, Pascale V, Bianchi M, Ferrario P, Morelli F, Pascale W, Tomasoni L, Turiel M. Asymmetric dimethylarginine (ADMA): an endogenous inhibitor of nitric oxide synthase and a novel cardiovascular risk molecule. *Medical Science Monitor* 2008; 15(4): 91-101.
- [31] Lundman P, Eriksson MJ, Stuhlinger 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: 111-6.
- [32] Boger RH, Bode-Boger SM, Thiele W, Junker W, Alexander K, Frölich JC. Biochemical evidence for impaired nitric oxide synthesis in patients with peripheral arterial occlusive disease. *Circulation* 1997; 95:2068-74.
- [33] Stuhlinger 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: 1420-6.
- [34] Bae SW, Stuhlinger 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: 729-33.
- [35] 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: 2449-52.
- [36] Surdacki A, Martens-Lobenhoffer J, Wloch A, Marewicz E, Rakowski T, Wieczorek-Surdacka E, Dubiel JS, Pryjma J, Bode-Böger SM. Elevated plasma asymmetric dimethyl-L-arginine levels are linked to endothelial progenitor cell depletion and carotid atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 809-19.
- [37] Turiel M, Tomasoni L, Delfino L, Bodini B, Bacchiani G, Atzeni F, Sarzi-Puttini P, De Gennaro Colonna V. Clinical implications of assessing coronary flow reserve and

plasma asymmetric dimethylarginine in early rheumatoid arthritis. *Eur J Echocardiogr* 2007; 8: S35.

- [38] Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, Béchir M, Spiekler LE, Neidhart M, Michel BA, Gay RE, Lüscher TF, Gay S, Ruschitzka F. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002; 106: 2184-7.
- [39] Sitia S, Tomasoni L, Cicala S, Delfino L, Atzeni F, Sarzi-Puttini P, De Gennaro Colonna V, Turiel M. Effects of long-term disease-modifying antirheumatic drugs on endothelial function in patients with early rheumatoid arthritis. *Eur J Echocardiogr* 2008; 9:166.
- [40] Mäki-Petäjä KM, Booth AD, Hall FC, Wallace SM, Brown J, McEniery CM, Wilkinson IB. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. *J Am Coll Cardiol* 2007; 50: 852-8.