

BRACHIAL ARTERY FLOW-MEDIATED DILATATION IN WOMEN WITH RHEUMATOID ARTHRITIS*

Pedro Teixeira Castro¹, Carlos Antônio Barbosa Montenegro², Antonio Carlos Pires Carvalho³, Jorge Fonte de Rezende Filho⁴, Washington Bianchi⁵, Dante Valdetaro Bianchi⁶, Sandra Pereira Leite⁷

Abstract **OBJECTIVE:** To evaluate the endothelial function in patients with rheumatoid arthritis by means of brachial artery flow-mediated vasodilation. **MATERIALS AND METHODS:** Sixty-eight patients, 32 with rheumatoid arthritis and 36 in the control group, underwent brachial artery flow-mediated dilatation (B-mode ultrasound for evaluating cardiovascular risk). Afterwards, the correlation among brachial artery flow-mediated vasodilation, C-reactive protein, and disease duration in patients with rheumatoid arthritis was evaluated. **RESULTS:** The brachial artery flow-mediated dilatation of the brachial artery in rheumatoid arthritis corresponded to $5.6 \pm 9.69\%$, and in the control group, to $23.24 \pm 5.65\%$, with a statistically significant difference ($p < 0.00001$). C-reactive protein result was 4.8 ± 9.1 mg/l. The correlation among age, brachial artery flow-mediated dilatation, and C-reactive protein in patients with rheumatoid arthritis has not shown a statistically significant result. **CONCLUSION:** Women with rheumatoid arthritis present a significant endothelial dysfunction when compared with normal women.

Keywords: Rheumatoid arthritis; Endothelial dysfunction; Brachial artery flow-mediated dilatation.

Resumo *Dilatação fluxo-mediada da artéria braquial em mulheres com artrite reumatóide.*

OBJETIVO: Avaliar a função endotelial em pacientes com artrite reumatóide, pela dilatação fluxo-mediada da artéria braquial. **MATERIAIS E MÉTODOS:** Sessenta e oito pacientes, sendo 32 com artrite reumatóide e 36 do grupo controle, foram avaliadas pela dilatação fluxo-mediada da artéria braquial (método ultra-sonográfico, no modo B, de avaliação de risco cardiovascular). Em um segundo tempo, foi avaliada a correlação entre a dilatação fluxo-mediada da artéria braquial, a proteína C reativa e o tempo de doença em pacientes com artrite reumatóide. **RESULTADOS:** A dilatação fluxo-mediada da artéria braquial na artrite reumatóide foi igual a $5,6 \pm 9,69\%$ e no grupo controle foi igual a $23,24 \pm 5,65\%$, diferença estatisticamente significativa ($p < 0,00001$). A proteína C-reativa teve resultado de $4,8 \pm 9,1$ mg/l. A correlação entre a idade, a dilatação fluxo-mediada da artéria braquial e a proteína C reativa nas pacientes com artrite reumatóide não mostrou resultado estatisticamente significativa. **CONCLUSÃO:** Mulheres com artrite reumatóide apresentam importante disfunção endotelial quando comparadas com mulheres normais.

Unitermos: Artrite reumatóide; Disfunção endotelial; Dilatação fluxo-mediada da artéria braquial.

* Study developed at Clínica de Ultra-sonografia Botafogo, in conjunction with the 39th Infirmary of Santa Casa da Misericórdia do Rio de Janeiro and Departamento de Radiologia da Faculdade de Medicina da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.

1. Fellow Master Degree, Teaching Assistant, Faculdade de Medicina da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.

2. Titular Member of Academia Nacional de Medicina (National Academy of Medicine), Director for Clínica de Ultra-sonografia Botafogo, Rio de Janeiro, RJ, Brazil.

3. Adjunct Doctor Professor, Department of Radiology, Adjunct Coordinator for the Program of Post-Graduation in Radiology, Faculdade de Medicina da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.

4. Private Docent, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP, Adjunct Professor of Obstetrics, Faculdade de Medicina da Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil.

5. Fellow Master Degree in Clinical Medicine, Faculdade de Medicina da Universidade Federal do Rio de Janeiro (UFRJ), Head for the 39th Infirmary of Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

6. MD, Physician, the 39th Infirmary of Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

7. MD, Radiologist, Clínica de Ultra-sonografia Botafogo, Rio de Janeiro, RJ, Brazil.

Mailing address: Dr. Pedro Teixeira Castro, Rua Voluntários da Pátria, 445/806, Botafogo, Rio de Janeiro, RJ, Brazil, 22270-903. E-mail: pedrotcastro@gmail.com

INTRODUCTION

Rheumatoid arthritis is associated with high cardiovascular morbimortality. Observational studies demonstrate a three to 18-year decrease in life expectancy⁽¹⁾ in female patients with rheumatoid arthritis, with cardiovascular diseases accounting for 50% of mortality in these patients⁽²⁾. With a higher incidence in women (2–5/1)⁽³⁾, the relative risk of acute myocardial infarct in female patients with rheumatoid arthritis is 2.0⁽⁴⁾.

Cardiovascular diseases in rheumatoid arthritis are associated with systemic inflammation and endothelial lesion. Traditionally, sedentarism, high body mass index

and dyslipidemia are some cardiovascular risk factors, however they do not fully explain the increase in cardiovascular diseases incidence⁽⁵⁾. The silent onset of cardiovascular diseases occurs on arterial walls and progresses through well-known mechanisms including endothelial dysfunction, inflammation, plaque formation and vascular remodeling, later atherosclerotic plaque rupture, and thrombosis⁽⁶⁾.

Endothelial dysfunction plays an important role in the formation of cardiovascular diseases⁽⁷⁾ and contributes for the atheroma plaque rupture that accounts for 70% of acute myocardial infarcts in asymptomatic patients⁽⁸⁾.

The present study was aimed at evaluating the endothelium-dependent function by means of brachial artery flow-mediated dilatation (FMD) in women with rheuma-

Received September 3, 2006. Accepted after revision February 21, 2007.

toid arthritis, comparing them with normal women.

Firstly described in 1992, FMD evaluates the endothelial function with basis on the production of nitric-oxide released by the endothelium after ischemic stimulus. This stimulus will cause nitric oxide release and arterial dilatation that may be measured by means of ultrasound⁽⁹⁾.

Later in the present study, we have compared the endothelial function with other method for evaluating inflammation and cardiovascular risk usually utilized in the clinical practice, the C-reactive protein test. FMD was correlated with C-reactive protein, age and duration of the disease in patients with rheumatoid arthritis.

MATERIALS AND METHODS

Sixty-eight patients (32 with rheumatoid arthritis and 36 in a control group) were examined. Because of the great FMD variation in results described in the literature⁽¹⁰⁾, 36 patients (control group) have been included for correlation of endothelial function in these two groups. The control group has included 36 women in the age range between 20 and 49 years. All of the patients in this group were normotense, non-tobacco users, non-diabetic, were at menacme, with total cholesterol levels ≤ 200 mg/dl, and with no familiar history of vascular diseases.

Between March and August/2004, 32 patients diagnosed with rheumatoid arthritis by the Rheumatology Ambulatory at the 39th Infirmary of Santa Casa da Misericórdia do Rio de Janeiro were invited to participate in this study.

Only five patients were male. Considering that FMD results are influenced by the sex of the patient⁽¹¹⁾, the authors decided to exclude the male patients, limiting the study to the female patients. The remaining 27 female patients with rheumatoid arthritis were selected according to the Sociedade Brasileira de Reumatologia (Brazilian Society of Rheumatology) criteria⁽¹²⁾ for the diagnosis of rheumatoid arthritis. With ages between 26 and 71 years, the patients were non-tobacco users and did not present other autoimmune diseases.

Some of the patients were affected by other comorbidities, but this was not taken

into consideration in the present study, because the objective was to evaluate the inflammatory status of rheumatoid arthritis. Besides, it is already known that rheumatoid arthritis typically courses with these diseases. Disease intensity, clinical condition and antirheumatic drug use were not evaluated. FMD is highly influenced by the patient's sex, height and muscular mass, but not by the age⁽¹¹⁾.

For analyzing the significance of the endothelial function evaluation in these patients, C-reactive protein and FMD were separately compared. All of the patients were simultaneously submitted to FMD and C-reactive protein test.

All of the patients have agreed to participate in the present study that was approved by the Committee for Ethics in Research of our Institution.

FMD was performed according to the already described technique^(13,14), with the patient in dorsal decubitus, after rest, in a calm and controlled-temperature environment. Medicines and food ingestion was not restricted, considering that the objective of the study was to evaluate the patients in their daily habits. The identification of

the right brachial artery was made with the aid of color Doppler, at 2 to 5 cm above the cubital fold. A Toshiba Nemium equipment with a 14 MHz, high resolution, B-mode, linear transducer was utilized. The brachial artery diameter is measured by calculating the distance between the proximal and distal (DI) intima at diastole. Ischemia is induced with pneumatic compression of the brachial artery for five minutes, and the artery measurement is repeated between 60 and 90 seconds after interruption of the compression (D2), in the diastole period, with the aid of pulsatile Doppler. The endothelium-dependent function is defined by the formula:

$$(D2 - D1)/D1 \times 100 \quad (\text{Figures 1 and 2}).$$

The higher is the numeric value of the study, the better is the endothelial function. The present study has opted for not numerically comparing the FMD with other studies. This is an operator- and equipment-dependent method; besides, the numerical analysis is subject to errors.

For routine evaluation of the disease, C-reactive protein was tested after 12-hour fasting, with positive and quantitative re-

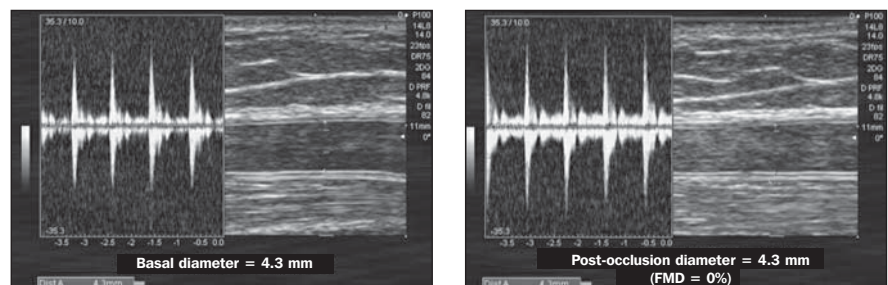


Figure 1. FMD in a patient with rheumatoid arthritis: basal diameter = 4.3 mm; post-occlusion = 4.3 mm; FMD = 0%, showing poor endothelial function, because nitric-oxide production has not occurred after induction (occlusion).

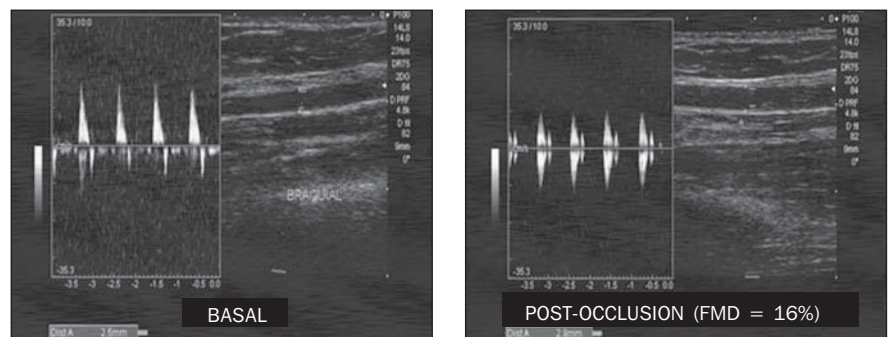


Figure 2. FMD in a patient with a good endothelial function: basal diameter = 2.5 mm; after occlusion = 2.9 mm. FMD = 16%.

sults, in centesimal values above 0.01mg/dl. For this purpose, the APTEC kit (Selectra-Merck; Darmstadt, Germany) was utilized — with 0.01 mg/dl sensitivity; RV = 0.0–1.0 mg/dl; intrassay CV = 2.9% and interassay CV = 2.9%.

Results were recorded on average (\pm standard deviation). The difference between parameter for both groups was evaluated by the Chi-square test. Calculations and statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 11.0.0 (SPSS, Inc.; Chicago, IL, USA). The difference was considered as statistically significant when $p < 0.005$.

RESULTS

Mean ages varied significantly between groups. It is important to note that the control group was formed by women at menopause, considering that menopause is a risk factor for cardiovascular disease. Ages in the control group ranged between 22 and 42 (mean = 28.9 \pm 7.1) years. In the rheumatoid arthritis, the ages ranged between 26 and 76 (mean = 49.9 \pm 12.9) years. In this group, ages were significantly ($p < 0.000$) higher than in the control group (Graph 1).

The control group FMD was 23.24 (\pm 5.65)%, while in the rheumatoid arthritis was 5.65 (\pm 9.69)%, with a statistically significant difference ($p < 0.000$) (Graph 2).

Five patients failed to demonstrate vasodilation, with FMD equal or less than zero. Four of these patients were less than 50 years old, demonstrating that the FMD difference between the groups was not affected by the ages, as per Graph 3 ($p = 0.001$).

The C-reactive protein test result was 4.8 (\pm 9.1) mg/l and disease duration of 6.2 (\pm 6.5) years. Correlation of age, FMD, C-reactive protein and disease duration did not show any significant result.

DISCUSSION

The present study demonstrates that patients with rheumatoid arthritis present endothelial dysfunction, and FMD does not correlate with C-reactive protein, patient's age and disease duration.

Early stages of atherosclerosis are usually found in immunological and inflammatory diseases where cardiovascular complications resulting from the formation and rupture of atherosclerotic plaques represent a relevant cause of morbimortality⁽¹⁵⁾.

Endothelial dysfunction is the earliest event in the atheromatous lesions formation, and its evaluation is a promising tool for estimating coronary prognosis, especially in patients with chronic inflammation, considering that a persistent dysfunction is a reason for an obscure prognosis⁽¹⁶⁾.

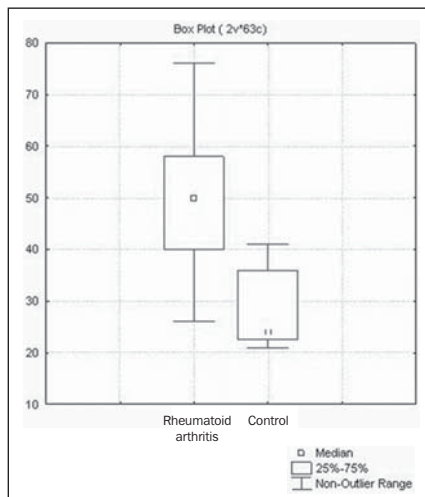
Although an ideal method for diagnosing endothelial dysfunction has not been

established yet, there are evidences that FMD allows an adequate evaluation of the endothelial behavior and reflects the coronary endothelial function and behavior⁽¹⁷⁾.

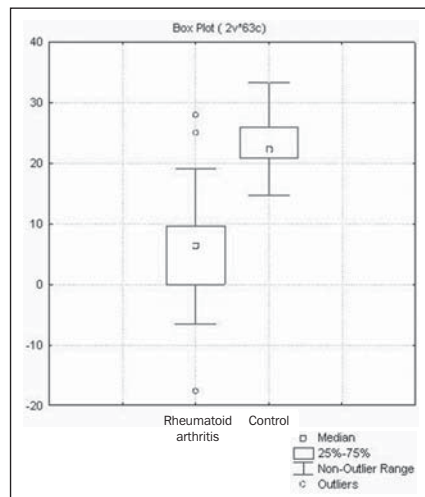
Age does not affect the endothelial function evaluation with FMD, so the significant difference in the groups age analysis does not affect the data interpretation of age groups. This is corroborated by the difference between patients with less than 50 of age and those in the control group⁽¹¹⁾.

Like the present study, other studies have found a significant endothelial dysfunction in patients with autoimmune diseases by means of FMD. The presence of systemic inflammation predisposes to atherosclerosis, affecting the endothelial function and decreasing the production of nitric oxide by the endothelium. This decrease in the nitric oxide production leads to a smaller arterial dilatation upon induced ischemia. In a study evaluating the infliximab therapy in 11 patients with rheumatoid arthritis, once the inflammation decreased, there was an improvement in the FMD⁽¹⁸⁾.

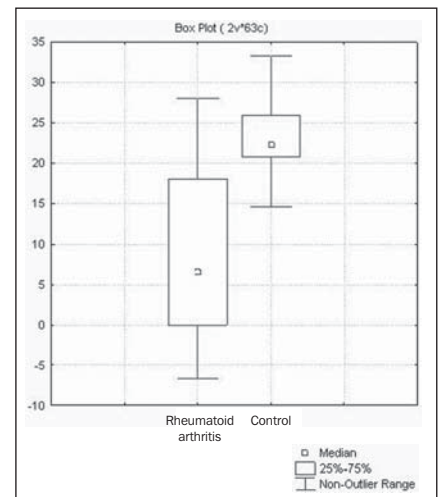
In patients treated for rheumatoid arthritis, FMD was related to the HLA-DRB1 (human leukocyte antigen histocompatibility gene) and not to the clinical condition of the patients⁽¹⁹⁾. In a comparison of FMD results in patients with rheumatoid arthritis with control paired by age and sex, patients with low levels of disease activity have demonstrated a significant decrease in



Graph 1. Age of patients (median \pm standard deviation) in the group with rheumatoid arthritis and in the control group.



Graph 2. FMD in the control and rheumatoid arthritis groups.



Graph 3. FMD difference between control and rheumatoid arthritis groups, both with less-than-50-year-old patients.

the endothelial function⁽²⁰⁾; however, one study has not found differences between patients with rheumatoid arthritis and control group⁽¹⁴⁾.

FMD and C-reactive protein present correlation in healthy individuals and in those with cardiovascular risk factors.

An investigation evaluating seven cardiovascular risk markers in 2,113 subjects has demonstrated inverse correlation between FMD and C-reactive protein (the higher is the C-reactive protein level, the lower is the nitric oxide production – FMD)⁽²¹⁾.

In a study evaluating the endothelium-dependent function in healthy subjects, the C-reactive protein level has presented a correlation with the FMD, but has not presented a closed relation between both methods in the evaluation of an inflammatory process in patients at low cardiovascular risk⁽²²⁾.

In patients with coronary pathology, there was correlation between FMD and C-reactive protein in the ²³⁾.

The most surprising data is the non-correlation between FMD and C-reactive protein. The present study demonstrates that, even in patients treated for rheumatoid arthritis and with normal levels of C-reactive protein, there is presence of systemic inflammation. The persistent and silent, systemic inflammation exposes a clinically managed patient to cardiovascular risk.

Nitrate-mediated endothelium-independent vasodilation was not utilized. Sometimes, this control method is utilized to affirm that the decrease in arterial dilatation is a result from the endothelial dysfunction, and not an arterial smooth muscle dysfunction.

With disparate results between C-reactive protein and FMD, we have concluded that there is endothelial dysfunction in women with rheumatoid arthritis, and that the C-reactive protein level does not provide an adequate evaluation of the cardiovascular risk in these patients.

Quyyumi⁽²⁴⁾ affirms that systemic inflammation markers like FMD, carotid

media/intimal complex and pulse-wave analysis arise as methods for evaluating the atherosclerosis risk. He recommends the inclusion of these methods, including the biochemical ones, in randomized studies for screening and diagnosis of cardiovascular risk. Considering that a high level of systemic inflammation affects the endothelial function, inflammation markers like FMD may provide a better evaluation of the cardiovascular risk in patients with rheumatoid arthritis.

FMD is a promising method for evaluation of inflammation⁽²⁵⁾ in the clinical practice, and may be extended to patients with rheumatoid arthritis for direct measurement of vascular physiopathology and preventive therapeutic response.

REFERENCES

- Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how “high-grade” systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003;108:2957–2963.
- DeMaria AN. Relative risk of cardiovascular events in patients with rheumatoid arthritis. *Am J Cardiol* 2002;89(6A):33D–38D.
- Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet* 2001;358:903–911.
- Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303–1307.
- Wang L, Feng G. Rheumatoid arthritis increases the risk of coronary heart disease via vascular endothelial injuries. *Med Hypotheses* 2004;63:442–445.
- Cohn JN. Introduction to surrogate markers. *Circulation* 2004;109(25 Suppl 1):IV-20–21.
- Bugiardini R, Manfrini O, Pizzi C, Fontana F, Morgagni G. Endothelial function predicts future development of coronary artery disease: a study of women with chest pain and normal coronary angiograms. *Circulation* 2004;109:2518–2523.
- Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* 2003;108:1664–1672.
- Raitakari OT, Celermajer DS. Flow-mediated dilatation. *Br J Clin Pharmacol* 2000;50:397–404.
- Bots ML, Westerink J, Rabelink TJ, de Koning EJ. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurements on the FMD response. *Eur Heart J* 2005;26:363–368.
- Schroeder S, Enderle MD, Baumbach A, et al. Influence of vessel size, age and body mass index on the flow-mediated dilatation (FMD%) of the brachial artery. *Int J Cardiol* 2000;76:219–225.
- Laurindo IMM, Pinheiro GRC, Ximenes AC, et al. Consenso brasileiro para o diagnóstico e tratamento de artrite reumatóide. *Rev Bras Reumatol* 2002;42:355–361.
- Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39:257–265.
- Kuscu NK, Kurhan Z, Yildirim Y, Tavli T, Koyuncu F. Detection of endothelial dysfunction in preeclamptic patients by using color Doppler sonography. *Arch Gynecol Obstet* 2003;268:113–116.
- Van Doornum S, McColl G, Jenkins A, Green DJ, Wicks IP. Screening for atherosclerosis in patients with rheumatoid arthritis: comparison of two in vivo tests of vascular function. *Arthritis Rheum* 2003;48:72–80.
- Verma S, Wang CH, Lonn E, et al. Cross-sectional evaluation of brachial artery flow-mediated vasodilation and C-reactive protein in healthy individuals. *Eur Heart J* 2004;25:1754–1760.
- Widlansky ME, Gokce N, Keaney JF, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003;42:1149–1160.
- Hurlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002;106:2184–2187.
- Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porrúa C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)* 2003;82:407–413.
- Vaudo G, Marchesi S, Gerli R, et al. Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. *Ann Rheum Dis* 2004;63:31–35.
- Kathiresan S, Gona P, Larson MG, et al. Cross-sectional relations of multiple biomarkers from distinct biological pathways to brachial artery endothelial function. *Circulation* 2006;113:938–945.
- Williams IL, Chowienczyk PJ, Wheatcroft SB, et al. Effect of fat distribution on endothelial-dependent and endothelial-independent vasodilatation in healthy humans. *Diabetes Obes Metab* 2006;8:296–301.
- Kang SM, Chung N, Kim JY, et al. Relation of vasodilator response of the brachial artery to inflammatory markers in patients with coronary artery disease. *Echocardiography* 2002;19:661–667.
- Quyyumi AA. Inflamed joints and stiff arteries: is rheumatoid arthritis a cardiovascular risk factor? *Circulation* 2006;114:1137–1139.
- Faulx MD, Wright AT, Hoit BD. Detection of endothelial dysfunction with brachial artery ultrasound scanning. *Am Heart J* 2003;145:943–951.