Although prospective, our study reports a single-center experience in a small and highly selected patient cohort with a remarkably low-risk profile and a very short time-to-treatment. There is a conflicting evidence about the prognostic significance of prodromal angina associated with pPCI, because someone found a better outcome (7), while others not (8,9). We documented that the additional infarct size reduction associated with prodromal angina translated into better long-term ejection fraction, which could positively affect prognosis in an appropriately sized patient cohort. Differences in patient selection and study protocols (retrospective vs. prospective), as well as inconsistency of the prodromal angina definition, could also explain conflicting results.

In conclusion, in our study, prodromal angina leads to a smaller infarct size most likely through ischemic preconditioning. This might represent a clinical "marker" of myocardial viability. Larger prospective trials are needed to demonstrate whether this observation translates into a better outcome in patients receiving pPCI.

Filippo Ottani, MD
Mario Galli, MD
Santino Zerboni, MD
***Marcello Galvani, MD**

*Fondazione Cardiologica "M.Z. Sacco"
P.zza F.lli Ruffini, 6
47100 Forlì, Italy
E-mail: ottanif@omf.dsnet.it

doi:10.1016/j.jacc.2005.02.033

REFERENCES

1. Ottani F, Galvani M, Ferrini D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. Circulation 1995;91:291–7.
2. Kloner RA, Shook T, Antman EM, et al. Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. Circulation 1998;97:1042–5.
3. Andreotti F, Pasceri V, Hackett DR, Davies GJ, Haider AW, Maseri A. Preinfarction angina as a predictor of more rapid coronary thrombolysis in patients with acute myocardial infarction. N Engl J Med 1996;334:7–12.
4. Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct size. Arch Intern Med 1985; 145:1877–81.
5. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW. Advantages and application of the centerline method for characterizing regional ventricular function. Circulation 1986;74: 293–305.
6. Hata K, Whittaker P, Kloner RA, Przyklenk K. Brief antecedent ischemia attenuates platelet-mediated thrombosis in damaged and stenotic canine coronary arteries: role of adenosine. Circulation 1998; 97:692–702.
7. Ishihara M, Inoue I, Kawagoe T, et al. Effect of prodromal angina pectoris on altering the relation between time to reperfusion and outcomes after a first anterior wall acute myocardial infarction. Am J Cardiol 2003;91:128–32.
8. Zahn R, Schiele R, Schneider S, et al. Effect of preinfarction angina pectoris on outcome in patients with acute myocardial infarction treated with primary angioplasty (results from the Myocardial Infarction registry. Am J Cardiol 2001;87:1–6.
9. Tomoda H, Aoki N. Comparison of protective effects of preinfarction angina pectoris in acute myocardial infarction treated by thrombolysis versus by primary coronary angioplasty with stenting. Am J Cardiol 1999;84:621–5.

Gender Differences in Endothelial Tissue-Type Plasminogen Activator Release in Middle-Aged Adults

To the Editor: Between the ages of 45 and 65 years, the incidence of myocardial infarction is three times higher in men compared with women. In addition, the prevalence of thrombotic stroke is ~50% greater in men than women (1). The mechanisms behind this gender difference in atherothrombotic events remain unclear. Impaired endothelial regulation of fibrinolysis, specifically reduced capacity to release tissue-type plasminogen activator (t-PA), has been linked directly to increased atheromatous plaque burden and increased coronary atherothrombosis (2,3). Endothelial t-PA release is the predominant physiologic mechanism governing endogenous fibrinolysis. Currently, it is unknown if a gender difference in endothelial t-PA release exists. If so, this may contribute to the gender-related disparity in the prevalence and incidence of atherothrombotic events in middle-aged adults. We tested the hypothesis that the capacity of the endothelium to release t-PA is greater in middle-aged women compared with men.

Sixty-six healthy sedentary adult humans ages 45 to 65 years were studied: 30 men (58 ± 1 year) and 36 women (58 ± 1 year). All subjects were nonobese (body mass index ≤30 kg/m^2), normotensive (blood pressure <140/90 mm Hg), nonsmokers, nonmedicated, and free of overt cardiovascular, metabolic, and hematologic disease, which were assessed by medical history, resting and exercise electrocardiograms, and fasting blood chemistries. The women were at least one year postmenopausal (range 1 to 32 years) and had never taken or had discontinued use of hormone replacement therapy at least one year before the start of the study. Before participation, the subjects provided written informed consent according to the guidelines of the University of Colorado at Boulder.

Endothelial release of t-PA antigen and plasminogen activator inhibitor (PAI)-1 antigen in response to bradykinin and sodium nitroprusside was determined using an isolated forearm model. Net release or uptake rates were calculated as follows: net release = $(C_V - C_A) \times (FBF \times [101 - \text{hematocrit}/100])$, where C_V and C_A represent the concentration in the vein and artery, respectively, and FBF represents forearm blood flow. The total amount of t-PA antigen released across the forearm in response to bradykinin was calculated as the area under each curve above baseline using a trapezoidal model. Bradykinin was infused intra-arterially at 12.5, 25, and 50 ng/100 ml tissue/min and sodium nitroprusside at 1, 2, and 4 μg/100 ml tissue/min for 5 min at each dose. To avoid an order effect, the sequence of drug administration was randomized. Plasma concentrations of t-PA and PAI-1 antigen were determined by enzyme immunoassay.

Differences in subject baseline characteristics and area under the curve data were determined by unpaired *t* test. Group differences in FBF and endothelial t-PA and PAI-1 release to bradykinin and sodium nitroprusside were determined by repeated measures analysis of variance. The relationships among the variables of interest were assessed by means of Pearson's correlation coefficient and linear regression analysis. Data are reported as mean ± SEM. Statistical significance was set at $p < 0.05$.

Although none of the subjects was obese, the men demonstrated higher (all $p < 0.05$) body mass (81.8 ± 1.5 kg vs. 65.4 ± 1.6 kg),

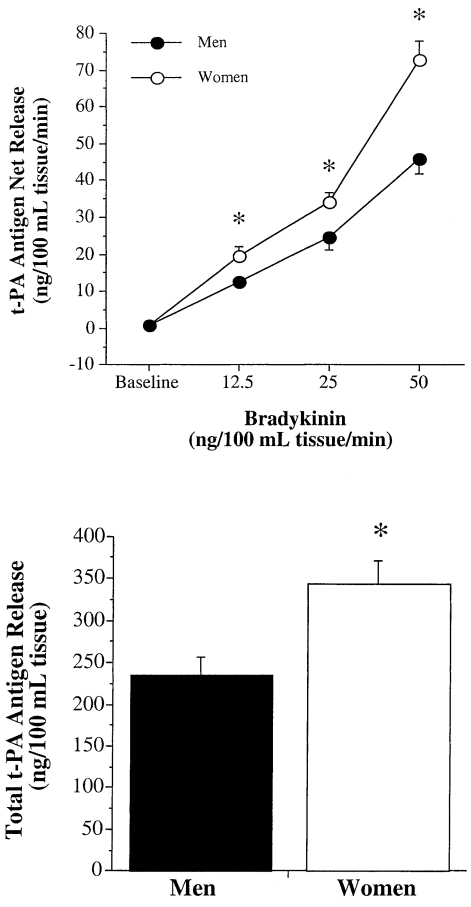

Figure 1. Net release rate and total amount of tissue-type plasminogen activator (t-PA) antigen released (area under the curve) across the forearm in response to bradykinin in men and women. Values are mean ± SEM. *$p < 0.05$ vs. men.

body mass index (26.1 ± 0.5 kg/m^2 vs. 24.4 ± 0.6 kg/m^2), and waist circumference (94.1 ± 1.7 cm vs. 83.2 ± 2.1 cm), whereas the women had a higher percentage of body fat (35.7 ± 1.1% vs. 25.8 ± 0.5%). The FBF responses to bradykinin and sodium nitroprusside were modestly (~15%) but significantly higher in the men.

Basal net release of t-PA antigen was not significantly different between the groups. In response to bradykinin, net release of t-PA antigen increased in a dose-dependent fashion in both groups; however, the response was significantly greater in the women (from 0.9 ± 0.6 ng/100 ml tissue/min to 72.6 ± 5.3 ng/100 ml tissue/min) compared with the men (0.9 ± 0.6 ng/100 ml tissue/min to 45.7 ± 3.3 ng/100 ml tissue/min). As a result, the total amount of t-PA antigen released (area under the curve) was 46% higher ($p < 0.01$) in the women than the men (344 ± 27 ng/100 ml tissue vs. 235 ± 20 ng/100 ml of tissue) (Fig. 1). Sodium nitroprusside elicited no significant changes in endothelial t-PA antigen release in either group. The effects of bradykinin and sodium nitroprusside on the net release of PAI-1 antigen were minimal and not significantly different between groups. No significant correlation was found between any anthropometric or metabolic variable and t-PA release in either group.

The primary new finding of the present investigation is that endothelial release of t-PA occurs in a gender-specific fashion in healthy middle-aged adults. Indeed, the rate and total amount of t-PA released from the endothelium were ~50% higher in middle-aged women compared with men. Our findings demonstrate a major gender-related difference in an important endogenous defense mechanism against thrombosis.

The reasons for the overwhelming gender disparity in cardiovascular disease rates in middle-aged adults are unclear. Scrutiny of epidemiologic data indicates no significant gender-related differences in the incidence and prevalence of traditional cardiovascular disease risk factors in middle-aged adults (1). To the best of our knowledge, this study is the first to demonstrate gender-specific differences in the capacity of the endothelium to release t-PA in middle-aged adults. Endothelial release of t-PA is the crucial step in the prevention of clot propagation and plays a central role in maintaining vascular patency. Importantly, diminished t-PA release is associated with atherosclerotic disease and clinical cardiovascular events (2–5). Given the lack of appreciable gender discrepancy in other important risk factors, the observed difference in endothelial t-PA release may be a function of intrinsic genetic phenotypes between men and women. Indeed, there is evidence linking specific genetic expression profiles with gender differences in arterial stiffness (6). We are currently exploring potential gender-related differences in polymorphisms associated with t-PA release.

Although the men demonstrated greater vasodilator capacity than the women, we do not believe that the difference (~15%) is physiologically or clinically remarkable. What the FBF responses clearly indicate is that the noted gender difference in t-PA release was not a blood flow-related phenomenon. Despite higher FBF responses to bradykinin, the men exhibited lower endothelial release of t-PA than women. More importantly, when viewed collectively the divergent vasomotor and fibrinolytic responses highlight the complexities of gender-related differences in vascular function that, in turn, impact disease development.

In conclusion, the results of the present study identify a marked difference in the capacity of the endothelium to acutely release t-PA between middle-aged men and women. Endothelial fibrinolytic function may be an important physiologic mechanism underlying the profound gender-related difference in the incidence and prevalence of atherothrombotic events in middle-aged adults.

***Brian L. Stauffer, MD**
Greta L. Hoetzer, PhD
Gary P. Van Guilder, MS
Derek T. Smith, PhD
Christopher A. DeSouza, PhD

*Integrative Vascular Biology Laboratory
University of Colorado
354 UCB
Boulder, CO 80309
E-mail: brian.stauffer@colorado.edu

doi:10.1016/j.jacc.2005.02.025

Please note: this work was supported by grants NIH HL06830, DK62061, and 2 MO1-RR00051.

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics—2004 update. Dallas, TX: American Heart Association, 2003.
2. Newby DE, Wright RA, Labinjoh C, et al. Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking: a mechanism

for arterial thrombosis and myocardial infarction. Circulation 1999;99:1411–5.
3. Newby DE, McLeod AL, Uren NG, et al. Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis. Circulation 2001;103:1936–41.
4. Carmeliet P, Schoonjans L, Kieckens L, et al. Physiological consequences of loss of plasminogen activator gene function in mice. Nature 1994;368:419–24.
5. Christie PD, Edelberg JM, Picard MH, et al. A murine model of myocardial microvascular thrombosis. J Clin Invest 1999;104:533–9.
6. Durier S, Fassot C, Laurent S, et al. Physiological genomics of human arteries: quantitative relationship between gene expression and arterial stiffness. Circulation 2003;108:1845–51.

Letters to the Editor

Is There an Optimal Hematocrit Value for Cardiac Patients?

The significance of anemia in congestive heart failure (CHF) has only recently received attention, as evidenced by two state-of-the-art papers published over the last several months (1,2). Anemia is more common in CHF than could be accounted for by age or the degree of renal dysfunction (2). Moderate to severe anemia can contribute to the development or worsening of CHF. Conversely, CHF can lead to moderate anemia (2). Recent reports have largely resolved the question: Is anemia a cause or a consequence of CHF? (3). Erythropoietin, which has a long history in the management of anemia complicating chronic renal failure, is being used for treatment of anemia in CHF (4–6).

Besides the potential risks of worsening hypertension and increased thrombosis as pointed out by Felker et al. (1), anemia correction in CHF may have other adverse effects. High hematocrit has been reported to be associated with a higher rate of Q-wave myocardial infarction (MI) after coronary artery bypass grafting (7). That a high hematocrit value was associated with an increased risk for MI has actually been known for a long time (8). As a matter of fact, George Burch (9–14), who wrote extensively on the subject since the early 1960s, advocated bloodletting in patients with coronary artery disease with a high hematocrit value (13,14). It might be appropriate to quote what Burch wrote in 1979 (14):

> "It is well known that a high hematocrit is associated with high viscosity and that a highly viscous fluid requires more work of the pump to circulate it than does a less viscous liquid. Furthermore, the flow of highly viscous fluid is reduced, even with all else being equal. Nevertheless, physicians fail to bleed patients with active coronary disease and myocardial ischemia, whose hematocrit is high and whose blood viscosity is increased. It has been shown that bloodletting in patients with ischemic heart disease definitely improved the clinical state of these patients when their hematocrit was reduced to average normal levels."

Therefore, as Felker et al. (1) cautioned, one must balance the risk of correcting the anemia in CHF against the risks of such treatment. What the optimal hematocrit value should be for patients with coronary artery disease or CHF has to await the results of controlled studies on a large number of patients.

***Tsung O. Cheng, MD, FACC**

*George Washington University
Medical Center
Washington, DC 20037
E-mail: tcheng@mfa.gwu.edu

doi:10.1016/j.jacc.2005.02.024

REFERENCES

1. Felker GM, Adams KF Jr., Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol 2004;44:959–66.
2. Coats AJS. Anaemia and heart failure. Heart 2004;90:977–9.
3. Wisniacki N, Aimson P, Lye M. Is anemia a cause or a consequence of heart failure in the elderly? Heart 2001;85 Suppl I:P4.
4. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erhythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–44.
5. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001;37:1775–80.
6. Mancini DM, Katz SD, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003;107:294–9.
7. Spiess BD, Ley C, Body SC, et al. Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. J Thorac Cardiovasc Surg 1998;116:460–7.
8. Cheng TO. High hematocrit value is a risk factor for myocardial infarction. J Thorac Cardiovasc Surg 1999;117:199–200.
9. Burch GE, DePasquale NP. Hematocrit, blood viscosity and myocardial infarction. Am J Med 1962;32:161–3.
10. Burch GE, DePasquale NP. The hematocrit in patients with myocardial infarction. JAMA 1962;180:62–3.
11. Burch GE, DePasquale NP. Hematocrit, viscosity and coronary blood flow. Dis Chest 1965;48:225–32.
12. Burch GE. Erythrocytosis and ischemic heart disease. Am Heart J 1961;62:139–40.
13. Burch GE, DePasquale NP. Phlebotomy: use in patients with erythrocytosis and ischemic heart disease. Arch Intern Med 1963;111:687–95.
14. Burch GE. Of bloodletting. Am Heart J 1979;98:666.

Further Aspects of Anemia, Heart Failure, and Erythropoietin

A routine laboratory hemoglobin measurement reflects "hemoglobin concentration." This approximates the total-body circulating hemoglobin (TBH) to plasma volume (PV) ratio, but provides no absolute quantitative information about either TBH or PV. Anemia arises when the TBH:PV ratio falls. This occurs with either decreased TBH or increased PV. This distinction is important: in a recent study, 46% of anemic patients with heart failure had a normal total red cell volume, with anemia attributable to excess PV (1).

In their review, Felker et al. (2) raise several issues concerning anemia and heart failure that warrant further consideration. They adopt the term "true anemia" to describe a decrease in TBH (2). This begs the question: is a reduced hemoglobin concentration any *truer* if it arises from decreased TBH rather than increased PV? Undoubtedly not, and the term "true anemia" should probably be avoided as it is imprecise. Felker et al. also indicate that "anemia results in decreased oxygen-carrying capacity" (2). Again, this statement is imprecise. It is a decrease in TBH that results in decreased oxygen-carrying capacity.