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.

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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/m²), 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 = (Cv – Ca) x (FBF x [101 – hematocrit/100]), where Cv and Ca 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),

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body mass index (26.1 ± 0.5 kg/m² vs. 24.4 ± 0.6 kg/m²), 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.

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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.

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.

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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.