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Obesity, insulin resistance, and the metabolic syndrome: determinants of endothelial dysfunction in Whites and Blacks

Lteif AA, Han K, Mather KJ. *Circulation*. 2005;112:32–38.

Insulin resistance is strongly associated with obesity and other components of the metabolic syndrome (MS). The relative importance of these components in the determination of endothelial function is unknown. Furthermore, there is conflicting evidence about whether ethnic differences exist in the relative importance of these components in regard to other cardiovascular outcomes. We evaluated the contributions of insulin resistance, obesity, and the other components of the MS to impaired endothelial function. The relationships of the MS components (as defined according to the National Cholesterol Education Program) and insulin resistance (estimated using the homeostasis model) with endothelium-dependent vasodilatation were examined in 42 white and 55 black individuals. Endothelium-dependent vasodilatation was assessed as the increment in leg blood flow (measured by thermodilution) after exposure to methacholine chloride. Waist circumference, glucose, blood pressure, and insulin resistance distributions did not differ between ethnic groups; in our sample the black individuals had greater high-density lipoprotein cholesterol (1.31 compared with 1.09 mmol/L; $P < 0.001$) and lower triglyceride concentrations (1.01 compared with 1.37 mmol/L; $P < 0.005$) than white individuals. In the absence of the MS, black individuals exhibited reduced endothelium-dependent vasodilatation compared with white individuals ($P < 0.005$), and both groups demonstrated significantly worse endothelial function when the MS was present (maximal increase in leg blood flow: black individuals $107 \pm 9\%$ MS absent, $53 \pm 16\%$ MS present; white individuals $163 \pm 16\%$ MS present, $54 \pm 18\%$ MS absent; $P < 0.007$, MS absent compared with present; $P = \text{NS}$ for interaction of ethnicity and MS). Multivariable regression analysis

examining relationships of endothelial function with the five MS components (analyzed as continuous variables) revealed independent relationships only with waist circumference ($P < 0.01$) and systolic blood pressure (SBP, $P < 0.02$). Waist circumference was no longer independently associated after insulin resistance had been added to the modeling ($P < 0.02$ for log of homeostasis model index of insulin resistance; $P < 0.02$ for SBP). Ethnicity still exerted an independent effect on endothelial function after the above components had been accounted for ($P < 0.04$ for an additional effect of ethnic status on endothelial function), with an ethnic difference in the effect of insulin resistance on endothelial function ($P < 0.046$ for interaction of ethnicity and log of homeostasis model index of insulin resistance). These findings suggest that insulin resistance and SBP are the principal determinants of endothelial dysfunction in the MS and that there are ethnic differences in the relative importance of these factors. These differences may imply different benefits from treatments targeting blood pressure or insulin resistance in different ethnic groups.

Commentary

Obesity and metabolic syndrome are associated with impaired endothelium-dependent vasodilatation. Insulin has a specific and physiological action to vasodilate skeletal muscle vasculature in humans; this action appears to be important both for the maintenance of vascular tone and the modulation of uptake of substrates. Insulin resistance has been reported to be associated with both defective insulin-mediated and endothelium-dependent vasodilatation; these findings suggest the possibility that the endothelium may also exhibit resistance to the action of insulin in modulating the endothelium-derived nitric oxide system. Obesity and the metabolic syndrome are associated with impaired endothelium-dependent vasodilatation. Insulin resistance is considered to be the pathogenic link between the components of

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metabolic syndrome and endothelial dysfunction. This suggests that, in clinical practice, it would be important to measure insulin resistance in the metabolic syndrome state. Little information is available about ethnic differences between the presence of insulin resistance and cardiovascular outcomes. This study investigated the contribution of clinical variables associated with metabolic syndrome to the development of endothelial dysfunction. The study population included 42 white and 55 black individuals. At baseline, high-density lipoprotein cholesterol concentrations were higher and triglyceride concentrations were lower among black individuals; there were no statistical differences in insulin, glucose, or insulin resistance between the two groups. The endothelium-dependent vasodilatation was impaired in black individuals compared with their white counterparts, and both demonstrated a worse endothelial function in the presence of metabolic syndrome. The addition of the homeostasis model index (to calculate insulin resistance) removed the independent contribution of waist circumference in the determination of endothelial dysfunction, suggesting that, in obesity, the effects are mediated by insulin resistance.

Mario Marzilli

Impaired coronary blood flow in patients with metabolic syndrome: documented by Thrombolysis in Myocardial Infarction (TIMI) frame count method

Turhan H, Erbay AR, Yasar AS, Bicer A, Sasmaz H, Yetkin E. *Am Heart J*. 2004;148:789–794.

Endothelium plays an important part in regulating coronary vascular tone. In addition, several of the cardiovascular risk factors that are associated with the metabolic syndrome have been reported to be associated with endothelial dysfunction. In the present study we aimed to evaluate the coronary blood flow in patients with metabolic syndrome by means of the Thrombolysis in Myocardial Infarction (TIMI) frame count. Forty-two patients with metabolic syndrome (group I) and 42 control individuals without the syndrome (group II) were included in the study. All had angiographically proven normal coronary arteries. Diagnosis of metabolic syndrome was based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines published in 2001. Coronary flow rates of all participants were documented by TIMI frame count. TIMI frame counts for each of the major epicardial coronary arteries were found to be significantly greater in patients with metabolic syndrome than in controls

(corrected TIMI frame count for left anterior descending coronary artery: 35 ± 7 compared with 25 ± 7 , respectively; left circumflex coronary artery: 32 ± 9 compared with 25 ± 7 , respectively; right coronary artery: 31 ± 9 compared with 24 ± 5 , respectively; $P < 0.001$ for all). Statistically significant independent relationships were found between TIMI frame count and body mass index ($R^2 = 0.480$, $P < 0.009$), waist circumference ($R^2 = 0.551$, $P < 0.001$), and triglyceride concentration ($R^2 = 0.434$, $P < 0.036$). We have shown for the first time that patients with metabolic syndrome and angiographically normal coronary arteries have greater TIMI frame counts for all three coronary vessels, indicating impaired coronary blood flow, compared with control individuals without metabolic syndrome.

Commentary

Patients with metabolic syndrome and typical angina pectoris (group I) have been compared with control individuals without metabolic syndrome and atypical chest pain (group II). The study shows for the first time that patients with metabolic syndrome and angiographically normal coronary arteries have greater TIMI frame counts for all three coronary vessels, indicating impaired coronary blood flow, compared with control individuals without metabolic syndrome. Given the absence of epicardial obstructions, greater TIMI frame counts are likely to reflect a microvascular dysfunction. Because of the important role of endothelium in the control of coronary blood flow (by regulating coronary vascular resistance) and because of the association of the insulin resistance with endothelial dysfunction, metabolic syndrome and impaired coronary blood flow could be ascribed, at least in part, to an absolute or relative deficiency in the action of insulin on the vessel wall. Furthermore, the significant positive correlations between mean TIMI frame count and body mass index, waist circumference, triglyceride concentration (the most frequent components of metabolic syndrome in group I), and fasting plasma glucose is intriguing. Body mass index and central fat distribution are inversely related to the endothelium-dependent vasodilatation. The increased concentrations of free fatty acid, resulting from increased lipolysis, indirectly increase the release of vasoconstrictor substances (such as endothelin-1), have a direct effect on the endothelial nitric oxide system, and may also induce the formation of reactive oxygen species that could quench nitric oxide and thus result in decreased nitric oxidation at the level of vascular smooth muscle.

Mario Mazilli

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Postconditioning the human heart

Patrick Staat, Gilles Rioufol, Christophe Piot, et al. *Circulation*. 2005;112:2143–2148

In animal models, brief periods of ischemia performed just at the time of reperfusion can reduce infarct size, a phenomenon called postconditioning. In this prospective, randomized, controlled, multicenter study, we investigated whether postconditioning may protect the human heart during coronary angioplasty for acute myocardial infarction.

Thirty patients, submitted to coronary angioplasty for ongoing acute myocardial infarction, contributed to the study. Patients were randomly assigned to either a control or a postconditioning group. After reperfusion by direct stenting, control individuals underwent no further intervention, whereas postconditioning was performed within 1 min of reflow by four episodes of 1 min of inflation and 1 min of deflation of the angioplasty balloon. Infarct size was assessed by measuring total creatine kinase release over 72 h. Area at risk and collateral blood flow were estimated on left ventricular and coronary angiograms. No adverse events occurred in the postconditioning group. Determinants of infarct size, including ischemia time, size of the area at risk, and collateral flow, were comparable between the two groups. Area under the curve of creatine kinase release was significantly reduced in the postconditioning group, averaging $208\,984 \pm 26\,576$ arbitrary units, compared with $326\,095 \pm 48\,779$ in control individuals – a 36% reduction in infarct size. Blush grade, a marker of myocardial reperfusion, was significantly increased in postconditioned compared with control individuals: 2.44 ± 0.17 and 1.95 ± 0.27 , respectively ($P < 0.05$).

These findings suggest that postconditioning by coronary angioplasty protects the human heart during acute myocardial infarction.

Commentary

Many have heard of ischemic preconditioning but, I suspect, fewer of ischemic postconditioning. Ischemic preconditioning was described, about two decades ago, as a way of protecting the heart against infarction by subjecting it to prior, repeated, short episodes of ischemia. In contrast, ischemic postconditioning was described only as recently as 2003 [1]. As the name suggests, it describes a method of reducing infarction by subjecting the heart to repeated short episodes of ischemia after the event. In other words, interrupting the reperfusion that follows the prolonged period of ischemia that causes infarction. Those with long memories will realize that this is really a modified form of reperfusion. Studies many years ago showed an attenuation of injury by curtailing reperfusion,

especially the reactive hyperemic phase that occurs immediately after ischemia. This has caused some to question whether postconditioning really is a new phenomenon, or merely ‘old wine in new bottle’ [2]; I would tend to agree with the wine analogy. Nonetheless, the new bottle is attractive and has done an excellent job at promoting the old wine. Consequently, the field of reperfusion injury has become revitalised. One manifestation of its vitality is the above manuscript.

Staat and his fellow collaborators with Ovize have been quick off the mark in performing a small ‘proof of principle’ study in the setting of primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI). The attraction of postconditioning, in contrast to preconditioning, is that it can be applied after occlusion of the infarct-related artery. There is therefore no longer the need to predict this arbitrary event. Furthermore, primary percutaneous coronary intervention is an increasingly common mode of reperfusion that allows postconditioning with relative ease.

Patients with STEMI resulting from occlusion of either the left anterior descending or right coronary artery, and in whom direct stenting restored at least Thrombolysis In Myocardial Infarction grade 2 flow, were allocated randomly to groups to undergo either unhampered reperfusion (control) or 60 s of reperfusion followed by four 60-s episodes of intracoronary balloon inflation to prevent antegrade flow (postconditioned). Each of these inflations was separated by four periods of 60 s of balloon deflation, or interspersed reperfusion. Compared with the 14 controls, the 16 postconditioned patients had significant reductions in creatine kinase-derived infarction size and improved myocardial blush grade measured at minute 8 of reperfusion in both groups.

There are several minor criticisms that can be levelled at this study. The main concern is that this is a chance finding attributable to small group size and possible differences between the groups. However, Staat et al went to appreciable lengths to ensure that the main determinants of infarct size – duration of ischemia, myocardial risk volume, and depth of ischemia, or collateral flow – were adequately matched. However, the techniques used to measure these determinants were not contemporary. Other possible criticisms are that the principal endpoints of injury, creatine kinase release and blush grade, can be influenced by the postconditioning process, independent of a true reduction in infarct size. For example, blush grade was determined at minute 8 after balloon deflation; this equated to 8 min of reperfusion in the control group and only 4 min in the postconditioned group. Thus the postconditioned risk zone could have been inadequately reperfused and relatively hyperemic. Similarly, the postconditioning process

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could conceivably alter the dynamics of creatine kinase release or reduce infarction at the expense of increased apoptosis.

Despite a number of possible minor criticisms, this is an important study that, if verified in a larger cohort, could alter the practice of primary percutaneous coronary intervention for STEMI, to the benefit of very many patients. The authors should be congratulated for their foresight and efficiency.

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Michael Marber
