Featured research

Abstracts and commentaries

Prognostic value of troponin I levels for predicting adverse cardiovascular outcomes in postmenopausal women undergoing cardiac surgery

Stearns JD, Dávila-Román VG, Barzilai B, Thompson RE, Grogan KL, Thomas B, Hogue CW Jr. *Anesth Analg*. 2009;108:719–726.

Adverse cardiac events that follow cardiac surgery are an important source of perioperative morbidity and mortality for women. Troponin I provides a sensitive measure of cardiac injury, but its concentrations after cardiac surgery may vary between the sexes. Our purpose in this study was to evaluate the prognostic value of troponin I concentrations for predicting cardiovascular complications in postmenopausal women undergoing cardiac surgery. The cohort of this study were women enrolled in a previously reported clinical trial evaluating the neuroprotective potential of 17β-estradiol in elderly women. In that study, 175 postmenopausal women not receiving estrogen replacement therapy and scheduled to undergo coronary artery bypass graft (with or without valve surgery) were prospectively randomly allocated to groups to receive 17β-estradiol or placebo in a double-blind manner, beginning the day before surgery and continuing for 5 days postoperatively. Serial 12-lead electrocardiograms were performed and serum troponin I concentrations were measured before surgery, after surgery on arrival of the patient in the intensive care unit, and for the first 4 days after operation. The primary endpoint of the present study was major adverse cardiovascular events (MACE), defined as a Q-wave myocardial infarction, low cardiac output state or death within 30 days of surgery. The diagnosis of Q-wave myocardial infarction was made independently by two physicians blinded to the treatment and patient outcomes, with the final diagnosis requiring consensus. A low cardiac output state was defined as cardiac index <2.0 L/min per m^2 for >8 h, regardless of treatment. Troponin I concentrations on postoperative day 1 were predictive of MACE (area under the receiver operator curve $= 0.862$). A cutoff point for troponin I of >7.6 ng/mL (95% confidence interval 6.4 to 10.8) provided the optimal sensitivity and specificity for identifying patients at risk for MACE. The negative predictive value of a troponin I concentration for identifying a patient with a composite cardiovascular outcome was high (96%) and the positive predictive value moderate (40%). Postoperative troponin I concentrations were not different between women receiving perioperative 17β-estradiol treatment and those receiving placebo, and the frequency of MACE was not influenced by 17β-estradiol treatment. We conclude that, in postmenopausal women, increased troponin I concentrations on postoperative day 1 are predictive of MACE. Monitoring of perioperative troponin I concentrations might provide a means for stratifying patients at risk for adverse cardiovascular events.

Commentary

A small increase in troponin concentration may occur in clinically stable populations, and is frequently observed after successful percutaneous coronary intervention (PCI) or bypass surgery.

With the new universal definition of myocardial infarction, routine dosage of troponin I after revascularization procedures could result in an overdiagnosis of myocardial infarction. A recent American Heart Association/American College of Cardiology statement defined an increase of troponin I greater than 3 times the 99th percentile after PCI as ''periprocedural myocardial infarction''. In patients with stable coronary disease, troponin increases significantly after PCI in 31% of patients and is independently and significantly associated with an increase in major adverse cardiac events at 1 and 18 months [1]. Conversely, in a more recent study [2], such an increase occurred in 23.4% of patients who underwent PCI, but was not associated with a greater rate of adverse cardiac events at 1 year. The investigators concluded that the definition of myocardial infarction may be too strict, and that measurement of troponin I after PCI is of questionable use. A meta-analysis of 20 studies involving 15 581 patients undergoing PCI [3] led its authors to conclude that an increase in troponin I is significantly associated with increased mortality and non-fatal myocardial infarction.

In this study by Stearns et al in postmenopausal women, increased postoperative troponin I concentrations were, again, predictive of major adverse cardiac events.

It may be concluded that monitoring of periprocedural troponin I in patients undergoing percutaneous or surgical coronary revascularization is helpful in stratifying those at risk, and in predicting adverse events.

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Mario Marzilli

Impaired insulin signaling accelerates cardiac mitochondrial dysfunction after myocardial infarction

Sena S, Hu P, Zhang D, Wang X, et al. *J Mol Cell Cardiol*. 2009 Feb 26 [Epub ahead of print].

Diabetes increases mortality and accelerates left ventricular dysfunction after myocardial infarction. This study sought to determine the impact of impaired myocardial insulin signaling, in the absence of diabetes, on the development of dysfunction after myocardial infarction. Mice with cardiomyocyte-restricted knockout of the insulin receptor (CIRKO) and wildtype (WT) mice were subjected to proximal left coronary artery ligation (MI) (groups CIRKO-MI and WT-MI, respectively) and followed for 14 days. Despite equivalent infarct size, mortality was increased in CIRKO-MI mice compared with WT-MI mice (68% compared with 40%, respectively). In surviving mice, left ventricular ejection fraction and d*P*/d*t* were reduced by >40% in CIRKO-MI animals compared with those in WT-MI mice. Relative to shams, isometric developed tension in left ventricular papillary muscles increased in WT-MI mice, but not in CIRKO-MI mice. Time to peak tension and relaxation were prolonged in CIRKO-MI mice compared with WT-MI animals, suggesting impaired, load-independent myocardial contractile function. To elucidate mechanisms for impaired left ventricular contractility, mitochondrial function was examined in permeabilized cardiac fibers. Whereas maximal ADP-stimulated mitochondrial rates of O_2 consumption (V_{ADP}) with palmitoyl carnitine as substrate were unchanged in WT-MI mice relative to sham-operated animals, V_{ADP} was significantly reduced in CIRKO-MI mice (13.17 ± 0.94 compared with 9.14 ± 0.88 nmol O_2/min per mg dry weight; $P < 0.05$). Relative to those in WT-MI, in CIRKO-MI the levels of expression of glucose transporter 4 (GLUT4), peroxisome proliferator activated receptor-alpha (PPARα), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2), the fatty acid oxidation genes, *MCAD*, *LCAD*, *CPT2*, and the electron transfer flavoprotein, ETFDH, were repressed. Thus reduced insulin action in cardiac myocytes accelerates after myocardial infarction left ventricular dysfunction, in part because of a rapid decline in mitochondrial fatty acid oxidative capacity, combined with limited glucose transport capacity that may reduce substrate utilization and availability.

Commentary

Diabetes increases the risk of cardiovascular disease, with diabetic individuals having a two- to fourfold greater risk of death from myocardial infarction than non-diabetic individuals [1,2]. Multiple abnormalities associated with diabetes mellitus – such as hyperglycemia, hyperlipidemia, and insulin resistance – have been postulated to contribute to adverse outcomes in diabetes following myocardial ischemia [3]. However, the specific contribution of impaired myocardial insulin action *per se* in the response of the heart to myocardial ischemia is incompletely understood. Sena et al sought to determine the impact of impaired myocardial insulin signaling, in the absence of diabetes, on the development of left ventricular dysfunction after myocardial infarction.

To examine the role of altered cardiomyocyte insulin signaling in the adaptation to myocardial infarction, independently of confounding systemic factors, the authors subjected CIRKO mice and wildtype mice to proximal left coronary artery ligation (myocardial infarction) and followed them up for 14 days. The goal was to assess potential mechanisms of left ventricular dysfunction during the period of greatest risk. Echocardiographic data, mitochondrial respiration, and gene expression data collected 14 days after infarction in both groups showed that, despite equivalent infarct size, mortality was increased in CIRKO mice compared with wildtype mice, whereas, in surviving mice, left ventricular ejection fraction and d*P*/d*t* were reduced by more than 40% in the CIRKO group.

To elucidate the mechanisms for the accelerated left ventricular dysfunction in CIRKO mice, the authors examined mitochondrial function by determining oxygen consumption in cardiac fibers that were exposed to fatty acid. They found that, whereas the maximal ADP-stimulated mitochondrial rate of consumption of O_2 (V_{ADP}) with a fatty acid substrate was unchanged in wildtype mice relative to sham-operated animals, it was significantly reduced in cardiac fibers of infarcted CIRKO mice. They also found that accelerated left ventricular dysfunction in CIRKO mice after myocardial infarction was associated with the rapid decline in mitochondrial function, and that this decline in mitochondrial function paralleled a specific reduction in the expression of the transcriptional regulator PPARα, a key regulator of fatty acid metabolism, an additional reduction in expression of genes the products of which determine

mitochondrial β-oxidation capacity, and a decrease in levels expression of the gene for GLUT4 (an important mediator of glucose uptake). These findings indicate that insulin signaling might play an important part in sustaining left ventricular metabolic capacity post myocardial infarction.

This study has some limitations. CIRKO mice have total deletion of insulin signaling, rather than insulin resistance. It is therefore possible that, under such conditions, the absence, not only of insulin-dependent metabolic pathways, but also of insulin signaling – particularly the absence of pro-survival mechanisms mediated by insulin signaling [4] – could have contributed to the accelerated rate of left ventricular dysfunction. Genetic deletion of insulin signaling is obviously more drastic than the more partial degrees of cardiac insulin resistance that might occur in individuals with insulin resistance or diabetes. Although this study provides an indication of some major metabolic and functional consequences of defects in insulin signaling, additional work in models with partial impairment in myocardial insulin action will be required to determine the consequences of lesser degrees of insulin resistance on the myocardial adaptations that occur after myocardial infarction.

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Danielle Feuvray

Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies

Whitlock G, Lewington S, Sherliker P, et al, for the Prospective Studies Collaboration. *Lancet*. 2007;373:1083–1096.

The main associations of body-mass index (BMI) with overall and cause-specific mortality can best be assessed by long-term prospective follow-up of large numbers of people. The Prospective Studies Collaboration aimed to investigate these associations by sharing data from many studies. Collaborative analyses were undertaken of baseline BMI versus mortality in 57 prospective studies with 894 576 participants (mean recruitment age 46 [SD 11] years; mean BMI 25 [SD 4] kg/m^2; 541 452 men), 61% in western Europe and North America. The median recruitment year was 1979 (interquartile range 1975–1985). The analyses were adjusted for age, sex, smoking status, and study. To limit reverse causality, the first 5 years of follow-up were excluded, leaving 66 552 deaths of known cause during a mean of 8 (SD 6) further years of follow-up (mean age at death 67 [SD 10] years): 30 416 vascular; 2070 diabetic, renal, or hepatic; 22 592 neoplastic; 3770 respiratory; 7704 other. In both sexes, mortality was lowest at BMI about 22.5–25 kg/m^2. Above this range, positive associations were recorded for several specific causes and inverse associations for none, the absolute excess risks for greater BMI and smoking were roughly additive, and each 5 kg/m^2 greater BMI was, on average, associated with about 30% greater overall mortality (hazard ratio per 5 kg/m^2 1.29, 95% confidence interval [CI] 1.27 to 1.32): 40% for vascular mortality (hazard ratio 1.41, 95% CI 1.37 to 1.45); 60–120% for diabetic (hazard ratio 2.16, 95% CI 1.89 to 2.46), renal (hazard ratio 1.59, 95% CI 1.27 to 1.99), and hepatic (hazard ratio 1.82, 95% CI 1.59 to 2.09) mortality; 10% for neoplastic mortality (hazard ratio 1.10, 95% CI 1.06 to 1.15]); 20% for respiratory (hazard ratio 1.20, 95% CI 1.07 to 1.34) and all other mortality (hazard ratio 1.20, 95% CI 1.16 to 1.25). Below the range 22.5–25 kg/m^2, BMI was associated inversely with overall mortality, mainly because of strong inverse associations with respiratory disease and lung cancer. These inverse associations were much stronger for smokers than for non-smokers, despite cigarette consumption per smoker varying little with BMI. Although other anthropometric measures (eg, waist circumference, waist-to-hip ratio) could well add extra information to BMI, and BMI to them, BMI is in itself a strong predictor of overall mortality both above and below the apparent optimum of about 22.5–25 kg/m^2. The progressive excess mortality above this range is mainly attributable to vascular disease and is probably largely causal. At 30–35 kg/m^2, median survival is reduced by 2–4 years; at 40–45 kg/m^2, it is reduced by 8–10 years (which is comparable to the effects of smoking). The definite excess mortality below 22.5 kg/m^2 is mainly attributable to smoking-related diseases, and is not fully explained.

Commentary

This Herculean analysis leaves little room for doubt. It is best to have a BMI around 22.5–25 kg/m^2. Either

side of this narrow range, mortality increases. However above 25 kg/m^2 this increase follows a log-linear relationship and is therefore most obvious for BMI values greater than 30 kg/m^2. In fact, it seems it is safer to be slightly above the ideal range (BMI 27.5–30 kg/m^2) than below it (18.5–22.5 kg/m^2).

The power of this study lies in its size and in its design. Events were collected prospectively, but 16 000 deaths occurring within 5 years of first enrolment were excluded to remove bias from reverse causality – established disease affecting baseline BMI, rather than BMI affecting occurrence of subsequent disease. Potential participants with overt pre-existing heart or cerebrovascular disease were not enrolled. Despite the exclusion of the first 5 years of follow-up, the study still included 6.5 million person-years of observation during which 72 749 deaths were identified. Approximately 60% of these deaths occurred in patients aged 35–69 years, reflecting the demographics of the populations recruited to the constituent studies. The average duration of follow-up beyond the 5th year was 8 years. The sheer number of events allowed separate analyses of death by cause. The positive correlation between BMI above 22.5 kg/m^2 and death was seen most clearly for ischemic heart disease, stroke, other vascular diseases, diabetes-related death, and deaths related to non neoplastic kidney and liver disease. The determination of cause of death varied by constituent study, but was most commonly by death certificate.

Finally, the excess mortality seen in individuals weighing less than the ideal BMI was primarily related to respiratory disease, and this was most marked in smokers. It is possible that this was the result of pre-existing chronic respiratory disease with a natural history that exceeded the arbitrary 5 year cutoff, and thus the result of reverse causality.

The main difficulty in translating this powerful study into changes in practice is knowing which component of the excess mortality seen with BMI >25 kg/m^2 is a direct result of BMI and which is the result of established risk factors that are associated with BMI. The authors demonstrate a clear positive correlation between low-density lipoprotein (LDL) cholesterol and systolic and diastolic blood pressure and BMI, and clear negative correlation between high-density lipoprotein (HDL) cholesterol and BMI. Thus the authors estimate that much, if not all, the increased cardiovascular mortality can be explained by these risk factors, up to a BMI of approximately 30 kg/m^2. Beyond this, mortality increases more steeply than blood pressure, LDL cholesterol or LDL:HDL ratio. Thus the excess mortality must be explained by other factors, such as insulin resistance, which were not systematically assessed. The other problem is that, although some of the constituent studies performed more sophisticated analyses of fat distribution and lean body mass, these were not performed sufficiently frequently to be included in the analyses. It is possible, therefore, that individuals with similar BMI values may have different risks according to the presence and distribution of fat. There was no analysis of ''normal weight obesity'', although most participants were from Western countries. The lack of these refinements makes it difficult to translate the findings of the study to an individual patient, although the findings send a very clear message regarding population risk and the increasing prevalence of obesity (BMI >30 kg/m^2) in most countries.

The clear and unambiguous findings of this study suggest that it is best to have a BMI of 22.5–25 kg/m^2 – a target that is very difficult to achieve for most overweight and obese individuals. They provide some reassurance that, up to a BMI of 30 kg/m^2, risk seems largely to accrue through established risk factors that are more easily modified than BMI itself. Beyond a BMI of 30 kg/m^2, risk increases sharply, and it is even more unclear how this risk can be reduced independently of tackling BMI directly.

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