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Original Research Article

Short-term response of metabolic hormones to coronary artery bypass surgery

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ABSTRACT

Purpose: To explore the response pattern of plasma adipokine and ghrelin levels to coronary artery bypass graft (CABG) surgery in patients with (on-pump) and without (off-pump) cardiopulmonary bypass (CPB).

Material/methods: Sixteen consecutive patients (age: 62 ± 10 years, male: 10) with obstructive coronary artery disease (CAD) who underwent elective CABG surgery with CPB and intraoperative GIK infusion were selected for on-pump group and 19 CAD patients (age: 63 ± 10 years, male: 16) were included in the off-pump group. Blood samples were taken before, during and after surgery. Intraoperative samples were withdrawn simultaneously for peripheral vein and sinus coronarius (SC). Plasma adipokine concentrations were measured by ELISA, those of ghrelin by RIA kits.

Results: In response to surgical intervention there was an early, transient fall in plasma levels of adiponectin ($p < 0.0001$) and resistin ($p = 0.002$) followed by an increase to approach their initial values. Plasma ghrelin also increased ($p = 0.045$), this increase, however, was confined to the period of GIK supported CPB. Plasma insulin ($p = 0.003$) and resistin ($p = 0.009$) was significantly higher in the peripheral vein than in SC. The perioperative hormone profile of patients without CPB (off-pump) proved to be comparable to that of on-pump patients in spite of the insulin administration and greater oxidative and inflammatory stress.

Conclusions: Adipose tissue-derived factors appear to mediate the metabolic and vascular changes that occur in patients with CABG surgery. Epicardial adipose tissue is unlikely to have major contribution to the development of CAD as adipokines are not elevated in SC independent of the mode of intervention.

1. Introduction

Coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB) has been shown to be frequently associated with postoperative complications, including systemic inflammatory response syndrome [1,2], myocardial depression, hemodynamic instability [3] and cerebral dysfunction [4]. The major features of the inflammatory reaction are activation of the complement cascade [5], leukocytes [6] adhesion molecules [2], release of proinflammatory cytokines [7] and generation of oxygen free radicals [8]. The underlying pathologies of obstructive coronary artery disease (CAD) that progress to artheriosclerosis are low-grade, chronic inflammation, oxidative stress, endothelial dysfunction and insulin resistance [9,10]. During CABG with CPB all these processes are profoundly amplified and multiorgan dysfunction may occur [1,11]. To attenuate the untoward pathophysiological and clinical consequences of CPB, CABG operations have been increasingly applied without CPB (off-pump).

Abdominal adipose tissue-derived adipokines, cytokines and chemokines have been proposed to be implicated in development of CAD as they stimulate chemotaxis, inflammation, smooth muscle cell proliferation and activate key mediators of atherogenesis [12–15]. Recent studies have shown that epicardial adipose tissue may serve as a paracrine source of harmful inflammatory adipokines, that impair endothelial function and insulin sensitivity

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[16–19]. In this regard, it is to be stressed, that excessive insulin resistance seen in patients with CABG could be overcome by exogenous insulin administration, and tight glycemic control improved perioperative outcomes and decreased recurrent ischemic events [20–22]. In fact, insulin added to the cardioplegic solution had anti-inflammatory, anti-oxidant and anti-thrombogenic influences, optimized myocardial metabolism, improved endothelial and left ventricular function, and ensured early graft patency [23–26].

As adipose tissue-derived factors have been claimed to be involved in inducing and/or mediating the metabolic and vascular dysfunction of CAD, this study was undertaken: (1) to determine plasma levels of metabolic hormones in CABG patients during surgery while receiving CPB and insulin infusion to maintain euglycemia, (2) to compare the plasma levels of these hormones (leptin, adiponectin, resistin, ghrelin) in the peripheral vein and sinus coronarius in an attempt to reveal the possible paracrine/vasocrine contribution of epicardial adipose tissue, and (3) to evaluate the response patterns of hormone levels to the two types of surgical intervention (on-pump vs off-pump).

2. Material and methods

2.1. Patients and surgical procedures

Two groups of consecutive patients undergoing primary CABG surgery with (on-pump) and without (off-pump) CPB were included in the study. The clinical characteristics of the patients and their routine preoperative laboratory data measured 1 day before surgery are given in Table 1. The coronary artery disease (CAD) characteristics of the two groups are given in Table 2. According to our protocol, the patients with CPB received glucose–insulin–potassium infusion (GIK) at a rate of 5.2 g/h glucose, 9.4 U/h regular insulin and 3 mequiv./h potassium. The infusion was administered from the time of anesthetic induction, and was administered until the end of operation. In total 22.7 U insulin was given during a period of 102 min. Blood glucose and plasma potassium levels were monitored every hour, and the rate of infusion was adjusted to maintain glucose levels between 5 mmol/l and 10 mmol/l (90 mg/dl and 180 mg/dl, respectively).

Anesthesia was induced by giving midasolame, fentanyl and pancuronium bromide, and maintained by 1 vol% isoflurane inhalation. Standard surgical revascularization was performed by using arteria mammaria interna and vena saphena as grafts for anastomoses. CPB was done with a roller pump (COBE Century) and a membrane oxygenator (Medos Hilite 7000). Prior to CPB sodium heparin was given in a dose of 300 U/kg to maintain an activated clotting time of about 400 s; the effect of heparin was completely reversed after termination of CPB with protamine sulphate. Myocardial protection was provided with 500–900 ml standard cardioplegic solution supplemented with systemic (35 °C) and topical hypothermia (cold saline lavage at 4 °C). The mean cross clamp and CPB times were 39 ± 13 min and 66 ± 18 min, respectively. Euroscore, assessing the surgical risk of the patients was 5 ± 2 [27]. The clinical and laboratory data of patients who underwent off-pump operation were mostly comparable to patients receiving CPB, although the higher hsCRP and plasma creatinine may indicate more severe disease in the off-pump group (Table 1).

Blood samples were drawn for hormone measurements from peripheral vein before and twice during surgery, and on postoperative days 1 and 5. Simultaneously with samplings from peripheral vein, blood was obtained intraoperatively from the SC prior to placement of the first graft and after completing the last graft.

Table 1
Clinical characteristics and routine laboratory parameters of patients undergoing coronary artery bypass graft surgery with (on-pump) and without (off-pump) cardiopulmonary bypass.

Variable	On-pump ($n = 16$)	Off-pump ($n = 19$)	p-Value
Age (years)	62 ± 10	63 ± 10	0.734
Male, n (%)	10 (63)	16 (84)	0.143
Diabetes mellitus, n (%)	6 (37)	4 (21)	0.283
Oral antidiabetics, n (%)	1 (6)	1 (5)	0.900
Insulin, n (%)	5 (31)	3 (16)	0.278
Smoking, n (%)	3 (19)	4 (21)	0.865
Hypertension, n (%)	16 (100)	17 (90)	0.181
Body mass index (kg/m^2)	30.50 ± 4.58	28.15 ± 4.18	0.123
LDL-cholesterol (mmol/l)	2.38 ± 0.77	2.11 ± 0.88	0.389
Fibrinogen (g/l)	4.34 ± 0.98	4.33 ± 1.36	0.984
hsCRP (mg/l)	5.06 ± 6.38	14.40 ± 15.58	0.034
Leukocytes (G/l)	6.01 ± 1.87	7.40 ± 2.32	0.082
Neutrophil granulocytes (%)	61.63 ± 6.86	59.11 ± 14.51	0.530
Homocysteine (μmol/l)	22.08 ± 12.77	13.26 ± 3.97	0.115
Creatinine (μmol/l)	79.56 ± 24.63	100.06 ± 15.81	0.006
EF (%)	55.5 ± 5.9	58.9 ± 10.8	0.263
Temperature (°C)	35.4 ± 0.4	35.2 ± 1.0	0.382
Euroscore	5 ± 2	4 ± 2	0.846
CPB time (min)	66 ± 18	–	–
Complications			
Pericardial fluid (%)	1 (6)	0 (0)	0.269
Hydrothorax (%)	12 (75)	3 (16)	0.001
Anemia (%)	8 (50)	12 (63)	0.433
Fever (%)	3 (19)	3 (16)	0.817
Atrial fibrillation (%)	4 (25)	6 (32)	0.668
Medical treatment			
Nitrate (%)	5 (31)	6 (32)	0.983
Statin (%)	10 (63)	18 (95)	0.212
ACE-I (%)	10 (63)	16 (84)	0.817
Beta blocker (%)	13 (81)	13 (68)	0.387
Aspirin (%)	4 (25)	13 (68)	0.067

ACE-I, angiotensin converting enzyme-inhibitor; EF, ejection fraction; hsCRP, high sensitivity C-reactive protein; CPB, cardiopulmonary bypass.

After surgery the patients were transferred to the Intensive Care Unit, where vital parameters and fluid balance were monitored and inotropic and respiratory support was provided as it was needed. Postoperative complications included pericardial fluid accumulation (1 vs 0), hydrothorax (12 vs 3), anemia with transfusion (8 vs 12), fever (3 vs 3) and atrial fibrillation (4 vs 6) in the on-pump and off-pump patients, respectively.

2.2. Laboratory measurements

Routine biochemical parameters were measured by standard laboratory methods. Plasma insulin, leptin, adiponectin and resistin concentrations were measured with ELISA, while ghrelin was analyzed with RIA using commercially available kits (Mediagnost, Reutlingen, Germany). The coefficient of variation was <5% within assays, and <15% between assays for all hormone measurements. Age-, gender-, and BMI matched healthy subjects served as controls for the hormone parameters studied. Homeostasis model assessment (HOMA-IR), an estimate of insulin resistance, was calculated according to the formula: insulin x glucose/22.5 [28].

2.3. Statistical analysis

All statistical analyses were performed with SPSS, version 11.5 (SPSS Inc. Chicago, IL, USA). Normality of data was evaluated by the Kolmogorov–Smirnov test. Variables are presented as mean ± SD. Changes in hormone levels during the perioperative period were analyzed using repeated-measures ANOVA or paired t-test as appropriate.