Clinical Study

Relationships of Adiponectin with Markers of Systemic Inflammation and Insulin Resistance in Infants Undergoing Open Cardiac Surgery

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Received 4 August 2012; Accepted 22 May 2013

1. Introduction

Insulin resistance and systemic inflammation frequently occur in infants undergoing cardiac surgery with cardiopulmonary bypass (CPB). Insulin resistance presenting with increased blood glucose level (hyperglycemia) and decreased sensitivity to insulin increases morbidity and mortality in critically ill patients [1, 2]. Intensive insulin therapy aiming at euglycemia improves their clinical outcome [3–5]. In a recently published study involving patients undergoing cardiac surgery, intraoperative insulin resistance was associated with an increased risk of short-term adverse outcomes [6]. The inflammatory reaction and injury may contribute to the development of postoperative complications [7, 8]. The magnitude and duration of the systemic inflammatory response determine the development of tissue damage, multiorgan failure, or even death [9, 10]. Our previous studies have demonstrated that ameliorating insulin resistance attenuates the systemic inflammatory response in infants undergoing CPB [11].

Adiponectin, a hormone derived from the adipose tissue, has been demonstrated to have insulin-sensitizing and anti-inflammatory properties in obesity and type 2 diabetes mellitus [12]. Recently adiponectin has also been shown to have a reverse correlation with insulin resistance and inflammatory mediators [13]. Studies on the relationship of adiponectin with insulin resistance and inflammatory mediators in infants undergoing cardiac surgery with cardiopulmonary bypass are scarce. The present study was undertaken to investigate the association of adiponectin with the development of insulin...
resistance and kinetic changes of inflammatory mediators in infants undergoing CPB.

2. Materials and Methods

The present study has been approved by the Ethics Committee of Xijing Hospital, The Fourth Military Medical University, and performed according to the World Medical Association Declaration of Helsinki.

2.1. Patients. Patient population: infants aged between 6 months and 3 years undergoing open cardiac surgery with CPB for congenital heart disease were enrolled for the study at our hospital from June 2010 to August 2011. Detailed information was given to the parents preoperatively and their written consent was obtained. None of the infants had a history of diabetes mellitus. Exclusive criteria included preoperative liver and kidney disease or dysfunction, preoperative coagulation disorder, palliative or second operation, and impaired blood glucose levels.

2.2. Measurements of Insulin Resistance. Overnight fasting was advised for all patients on the preoperative day. Insulin resistance was recorded by the individual insulin requirement to maintain euglycemia. Blood glucose was monitored on an hourly basis and insulin infusion rate was adjusted to maintain glucose levels between 4.4 and 8.3 mmol/L. The infusion of insulin is a standard of care and started when the glucose concentration became higher than 8.3 mmol/L. An insulin glycaemic index (insulin × glucose/22.5) was calculated at each time point.

2.3. Determination of Insulin, Adiponectin, IL-6, and TNF-α Levels. Blood samples were taken at 7 time points for each patient as follows: before anesthesia (T1), at the initiation of CPB (T2), at the termination of CPB (T3), 6 h after CPB (T4), 12 h after CPB (T5), 24 h after CPB (T6), and 48 h after CPB (T7). Serum level of adiponectin was determined with a commercial enzyme-linked immunosorbent assay (R&D, Wiesbaden, Germany). Serum insulin levels were measured with an insulin kit (R&D Systems, Abingdon, UK). Plasma
### 3. Results

#### 3.1. Characteristics of the Study Group. Baseline characteristics of the study participants are shown in Table 1. The cardiac surgery included repair of ventricular septal defects in 35 patients, atrial septal defects in 18 patients, and correction of tetralogy of Fallot in 7 patients.

#### 3.2. Kinetics of Insulin Resistance. Blood glucose was monitored on an hourly basis throughout the observation period. All patients required insulin treatment to maintain euglycaemia. Figure 1(a) shows the stable blood glucose levels throughout the observation period. Serum insulin concentrations increased at the termination of CPB, following the course of exogenously applied insulin, and remained stable thereafter (Figure 1(b)). To create a more specific parameter of insulin resistance that combines serum glucose with serum insulin levels, we calculated an insulin glycaemic index (insulin x glucose/22.5) at each time point (Figure 1(c)). The insulin glycaemic index increased during the first 22 hours of the observation period and remained stable thereafter reflecting the kinetics of exogenously applied insulin.

#### 3.3. Kinetics Inflammatory Cytokines. During the observation period inflammatory cytokines rapidly increased with peak concentrations of TNF-α and IL-6 at the 6 h time point (Figures 2(a) and 2(b)). Adiponectin serum levels were repressed throughout the observation period reaching a minimum at the 6 h time point (Figure 3).

#### 3.4. Correlations of Adiponectin with Metabolic Variables at Different Time Points. There was no association between the adiponectin at T3, T5, T6, and T7 time points and glycemic index, TNF-alpha and IL-6 (Table 2). At T4 (6 h after CPB) we found significant inverse correlations of adiponectin with insulin glycaemic index, IL-6, and TNF-α (Figure 4). Correlation of adiponectin with the insulin glycaemic index was $r = -0.465$ ($P < 0.001$) was adiponectin with IL-6, $r = -0.427$ ($P < 0.001$), and adiponectin with TNF-α was $r = -0.447$ ($P < 0.001$).

### 4. Discussion

Several studies have reported that adiponectin has a negative correlation with insulin resistance in chronic diseases such as metabolic syndrome and type 2 diabetes [15, 16]. However, the relationship of adiponectin with insulin resistance and inflammatory mediators in infants undergoing cardiac surgery with cardiopulmonary bypass has not been identified so far. The present study demonstrated the correlation of adiponectin with insulin resistance and the kinetic changes of inflammatory cytokines in infants undergoing CPB. CPB provokes a systemic inflammatory response. This inflammatory reaction may contribute to the development of postoperative complications. The marked increases in the amount of exogenous insulin requirement to maintain euglycaemia as well as circulating insulin levels during CPB surgery suggest the development of insulin resistance. Our study showed significant increase in TNF-α and IL-6 levels after the initiation of CPB and their kinetics at various time points. At the same time, the need of an increased rate of insulin infusion to maintain euglycaemia following the operation suggested the development of insulin resistance. Insulin resistance is

### Table 1: Baseline characteristics and operative data of infants ($n = 60$).

| Characteristic                              | Data          |
|--------------------------------------------|---------------|
| Male gender (%)                            | 36 (60%)      |
| Age (year)                                 | $1.5 \pm 0.4$ |
| Body weight (kg)                           | $5.9 \pm 1.7$ |
| Left ventricular ejection fraction (%)     | $67.4 \pm 8.6$|
| Cardiopulmonary bypass time (min)         | $50.3 \pm 7.9$|
| Cross-clamping time (min)                 | $35.4 \pm 4.3$|
| Cardiopulmonary bypass flow (L/min/m$^2$) | $2.8 \pm 0.4$ |
| Ultrafiltration (mL/kg)                    | $337 \pm 32$  |
| Insulin (μU/mL)                            | $7.8 \pm 1.6$ |
| Blood glucose level (mmol/L)              | $4.6 \pm 0.5$ |
| Tumor necrosis factor-α (pg/mL)           | $32.7 \pm 10.4$|
| Interleukin-6 (pg/mL)                     | $19.9 \pm 15.7$|
| Adiponectin (µg/mL)                       | $9.5 \pm 1.2$ |

Data are presented as the number (%) of patients or mean values ± SD.

### Table 2: Correlations of adiponectin with metabolic variables.

|                      | Adiponectin with the insulin glycaemic index | Adiponectin with IL-6 | Adiponectin with TNF-α |
|----------------------|---------------------------------------------|-----------------------|------------------------|
| T1                   | $-0.415^*$                                   | $-0.397^*$            | $-0.419^*$             |
| T2                   | $-0.408^*$                                   | $-0.384^*$            | $-0.379^*$             |
| T3                   | $-0.354$                                     | $-0.347$              | $-0.364$               |
| T4                   | $-0.465^{**}$                                | $-0.427^{**}$         | $-0.447^{**}$          |
| T5                   | $-0.346$                                     | $-0.352$              | $-0.357$               |
| T6                   | $-0.358$                                     | $-0.371$              | $-0.374$               |
| T7                   | $-0.361$                                     | $-0.375$              | $-0.342$               |

Pearson’s correlation coefficient ($r$) and $P$ values of the corresponding significance test are both presented. (T: time; T1: before anesthesia; T2: initiation of CPB; T3: termination of CPB; T4: 6 h after CPB; T5: 12 h after CPB; T6: 24 h after CPB; T7: 48 h after CPB. *$P < 0.05$ and **$P < 0.001$.)
associated with the inflammatory response, but its molecular basis and physiological significance are not fully understood. Inflammatory mediators such as TNF-α and IL-6 either alone or through synergistic effect could lead to the development of insulin resistance by blocking the signal transduction of insulin, impairing insulin sensitivity, and increasing free fatty acids [17, 18]. Insulin resistance would be more intense as inflammatory mediator levels increase.

Adiponectin has been shown to directly or indirectly affect insulin sensitivity through modulation of insulin signaling and the molecules involved in glucose and lipid metabolism [12]. Adiponectin-deficient mice were shown to be prone to diet-induced obesity and insulin resistance and its reversal by adiponectin treatment [19]. In humans, low adiponectin was more closely associated with insulin resistance than adiposity [20]. In infants undergoing cardiac surgery, IL-6 and TNF-α levels were markedly increased while serum adiponectin levels were moderately decreased. This suggests the inverse relationship of circulating adiponectin levels to IL-6 and TNF-α and insulin resistance in critically ill patients. The repression of adiponectin serum levels in our model and its association with insulin resistance are in agreement with previous reports [13, 21]. Low adiponectin levels were associated with high inflammatory levels and intense insulin resistance. This indicates the role of adiponectin in regulation of glucose metabolism (insulin resistance) and inflammatory mediators.

5. Conclusions
In summary, we have demonstrated the significant inverse association of adiponectin with markers of systemic inflammation and insulin resistance in infants undergoing open cardiac surgery. The better understanding of the association of adiponectin with insulin resistance and systemic inflammation will be of high clinical value as it may have therapeutic implications.

Authors’ Contribution
Yukun Cao and Ting Yang contributed equally to this paper.

Acknowledgment
This work was supported by the Grants from the Translational Medicine Foundation of Xijing Hospital (no. XJZT11Z08).
**Figure 4**: Correlations of adiponectin at T4 (6 h after CPB) with IL-6 (a), TNF-α (b), and insulin glycaemic index (c). Pearson’s correlation coefficient ($r$) and $P$ values of the corresponding significance test are both presented.

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