

## Commentary

# Systemic inflammatory response to cardiac surgery: does female sex really protect?

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See *Research*, page 343

### Abstract

Sex hormones have important interactions with the immune system and modulate the inflammatory response. In this regard, oestrogen inhibits the transcription of proinflammatory cytokines and confers tissue protection in experimental models. On the basis of this evidence, Trotter *et al.* in this issue of *Critical Care* addressed the question of whether, in children, female sex would protect against the deleterious effects of cardiac operations with cardiopulmonary bypass by providing a favourable anti-inflammatory cytokine balance. The observations made in that study suggest sex-related immunomodulation and organ protection during cardiac surgery in the paediatric population. Prospective trials conducted in large series, including sex hormone determination in neonates, infants and children with congenital cardiac defects, are necessary to test this hypothesis. The verification of sex-related intraoperative organ protection would provide new opportunities for preventing the uncontrolled systemic inflammatory response that may occur during cardiac surgery.

**Keywords** cardiac surgery, children, cytokines, sex, inflammation, outcome

In a report published in this issue of *Critical Care*, Trotter *et al.* (page 343) draw attention to the possibility that sex might play a role in modulation of the systemic inflammatory response to cardiac surgery [1]. In that study, girls indeed had higher preoperative and postoperative levels of the natural anti-inflammatory cytokine IL-10, and exhibited lower postoperative morbidity than did boys. Could it be assumed then that female sex, because of the influence of oestrogen, protects against systemic inflammation? This question merits further investigation, the outcome of which could have implications for the timing of corrective cardiac surgery in children.

### Cardiac surgery and the systemic inflammatory response

The exact mechanisms that initiate and control the systemic inflammatory reaction associated with cardiac surgery have not yet been fully elucidated. It is generally accepted, however, that contact between blood and the foreign surfaces of the extracorporeal circulation circuit, and

ischaemia of almost all tissues followed by their reperfusion trigger a cascade of inflammatory events that may finally result in cell damage and cell death [2,3]. Cytokines are central in this scenario. They are synthesized by circulating leucocytes, resident macrophages, and endothelial and parenchymatous cells of various organs, and they play an important role in the initiation and termination of the systemic inflammatory response (Table 1). Proinflammatory cytokines such as IL-1 $\beta$  and tumour necrosis factor- $\alpha$  are representative of the first category of cytokines. IL-10 (the natural anti-inflammatory, macrophage-deactivating cytokine) controls and terminates inflammation, whereas IL-6 (the main regulator of the acute-phase reaction) possesses both proinflammatory and anti-inflammatory properties [4].

### Links between inflammation and the neuroendocrine system

Cytokines are not exclusively inflammatory mediators, and play important roles in the regulation of interactions between

**Table 1****The role of cytokines in the initiation and termination of the systemic inflammatory response**

Cytokine	Properties
IL-1 $\beta$	Proinflammatory
Tumor necrosis factor- $\alpha$	Proinflammatory
IL-10	Anti-inflammatory
IL-6	Both proinflammatory and anti-inflammatory

the nervous, endocrine and immune systems. In this regard, IL-10 enhances corticotropin-releasing factor and adrenocorticotrophic hormone, and is therefore believed to regulate activity of the hypothalamo-pituitary axis [5]. Conversely, cytokine production is modulated by steroid and sex hormones [6,7], and an increasing body of evidence suggests that oestrogen and progesterone participate in modulation of the secretion of proinflammatory and anti-inflammatory cytokines [7].

**Does female sex protect against systemic inflammation?**

In their report, Trotter *et al.* [1] raise the question of whether sex, by influencing perioperative cytokine production, modifies the systemic inflammatory response to cardiac surgery and, consequently, postoperative morbidity in infants and children. An interesting observation of the study is that, in the series presented, girls had higher levels of IL-10 before and during the intervention than boys. Although this was associated with less postoperative morbidity, it was not associated with higher levels of progesterone.

That study is limited by the lack of homogeneity of the patient cohort in terms of age, ranging from infancy to adolescence, and preoperative clinical condition, including various cyanotic and noncyanotic heart diseases. However, it draws attention to the possibility that individual factors such as sex could play a role in modulation of the systemic inflammatory response to cardiac surgery. This hypothesis is supported by previous experimental and clinical observations, in which oestrogen was shown to provide protective effects in sepsis-like models. In this regard, 17 $\beta$ -oestradiol and a selective oestrogen receptor modulator administered to rats subjected to splanchnic artery occlusion followed by reperfusion led to reduced tissue injury [8]. One mechanism by which oestrogen could provide organ protection in this model is by reduction in endothelial damage induced by tumour necrosis factor- $\alpha$ . Indeed, oestrogen receptors  $\alpha$  and  $\beta$  mediate inhibition of the activity of nuclear factor- $\kappa$ B (a transcription factor of several proinflammatory cytokines) and prevent apoptosis of cultured cardiomyocytes [9,10]. Furthermore, oestrogen could also inhibit chemotaxis of stimulated monocytes [11].

Although the results of those experimental studies point toward a protective effect of female sex in clinical situations that involve acute systemic inflammation, the data emerging from clinical trials are conflicting. In adults, female sex is reported to be associated with both decreased or increased morbidity and mortality after sepsis [12,13], burn trauma [14] and cardiac surgery [15]. In our own paediatric experience the incidence of multiple organ failure after cardiac surgery did not differ between girls and boys [16]. However, Nichols *et al.* [17] listed male sex as among the predictors of acute respiratory failure after bone marrow transplantation in children. If male sex really does have a negative influence on outcome in critically ill children, as suggested by Nichol *et al.* [17] and Trotter *et al.* [1], then the question arises of why and how this is the case. Indeed, because plasma concentrations of oestradiol are similar in prepubertal girls and boys [18], it is unlikely that this hormone could mediate protective effects in this age group. However, this does not exclude the possibility that other sex hormones, such as testosterone and follitrophin, plasma levels of which are higher and lower in boys and girls, respectively, could modulate the systemic inflammatory response in the paediatric population.

**Conclusion**

The study of Trotter *et al.* [1] should stimulate further investigation into this important issue. Such an endeavour, however, would require the enrolment of a large homogeneous cohort of patients in whom cytokine balance, sex hormone levels and outcome could be related to each other and between patients. Ideally, different age groups should be considered in order to identify those who are at low or high risk. Because oestradiol levels are higher during the neonatal period than later in infancy [18], one could address the question of whether neonates who require cardiac surgery profit by their very particular hormonal environment. If this were the case, then it would be a serious argument in favour of corrective cardiac surgery during the neonatal period rather than in later infancy or childhood.

**Competing interests**

None declared.

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