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Acute Postoperative Frailty

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We read with great interest the article by Dr Wolfe concerning the influence of surgical stress on muscle mass in the elderly. The author underlines that the catabolic response to stress is of even greater concern in the elderly, because of the limited muscle mass of many older people before injury and operation.¹ Wolfe also suggests that hormonal therapy together with nutritional supplementation and exercise can represent a possible strategy to prevent the catabolic response and improve physical function after operation.

We agree with the author. But some additional issues need to be addressed. A major focus of research in clinical geriatrics is frailty syndrome, a clinical entity characterized by a vicious cycle in which sarcopenia plays a central role.² Hormonal dysregulation (decline in anabolic hormones and increase in catabolic hormones) and inflammation (increased levels of inflammatory cytokines), often through a synergistic interaction, are important pathways to frailty.^{2,3} Several authors have proposed that frailty becomes clinically evident at the time of acute stress.²

Major surgical stresses, such as coronary artery bypass grafting with cardiopulmonary bypass, are examples of such triggers and are followed by an acute inflammatory response and hormonal changes that have been related to hemodynamic and metabolic effects. We recently investigated alterations in anabolic and catabolic hormones occurring after coronary artery bypass grafting in older patients⁴ in 19 patients (12 men and 7 women) aged 70.1 ± 6.1 years (age range 62 to 80 years) with coronary artery disease who underwent cardiac operation. Cortisol, dehydroepiandrosterone, luteinizing hormone, estradiol, total testosterone, sex hormone-binding globulin, and insulin-like growth factor-1 were measured the day before, on the day of the procedure, and 1, 2, 3, and 4 days after operation. We found a substantial decrease in serum insulin-like growth factor-1 levels along with increased levels of cortisol, dehydroepiandrosterone, and estradiol in both men and women. A dramatic drop in serum testosterone levels (< 200 ng/dL, considered a cut-off for hypogonadism) was also observed in older men after operation.⁵ Reduction in anabolic hormones such as testosterone and insulin-like growth factor-1 can be explained and can also contribute to an increase in inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor- α , IL-1 β , a chain of events that can lead to sarcopenia after operation.^{2,3} In addition, inflammation plays an important role in muscle catabolism.² All these findings support the intriguing notion proposed by Wolfe

suggesting that administering an anabolic hormone before, during, and immediately after operation can actually reduce postoperative complications.

Testosterone is a good candidate for replacement therapy in older men having an operation because, in addition to its anabolic effects on skeletal muscle, well described by Ferrando and colleagues,⁶ it can negatively modulate inflammatory cytokines.⁷ Our group recently found an important inverse association between serum testosterone and IL-6 soluble receptor in an older male population, which was independent of potential confounders. The presence of soluble IL-6 receptor expands the repertoire of cells that respond to IL-6 signaling, enhancing the biologic activity of IL-6.⁸ Guler and coauthors⁹ studied 25 adult men who received a coronary stent. Testosterone enanthate (IM once a week for 3 weeks) considerably attenuated the increment in C reactive protein and IL-6 that commonly occurs after the stenting procedure. In accordance, testosterone enanthate (100 mg/week) in 27 hypogonadal men for 1 month substantially reduced circulating levels of the other two important inflammatory cytokines (tumor necrosis factor- α and IL-1 β) and increased IL-10 levels (an antiinflammatory cytokine).⁷

In conclusion, surgical stresses are followed by increased inflammation and hormonal dysregulation. In the elderly, this stress is superimposed on the already altered hormonal milieu and preexisting mild proinflammatory state and sarcopenia.^{10,11} We are grateful to Dr Wolfe for emphasizing the importance of this topic in the older population. The premises are good. The time for a randomized clinical trial to test this hypothesis has arrived.

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