

LETTERS TO THE EDITOR

Cytokines and Acute Cardiac Rejection—the Unfulfilled Promise?

The interesting report of Fyfe et al. (1) on coronary sinus sampling of cytokines after heart transplantation is based on the hypothesis that if cytokines were being actively produced within the graft, there should be a significant difference between cytokine concentration measured from the coronary sinus and that obtained during simultaneous sampling from the superior vena cava. The current theory on the sequence of immune recognition of a foreign antigen, its presentation to the T lymphocyte receptor and subsequent activation of lymphocytes proposes a process driven by various cytokines stimulating the invasion of cytotoxic T cells into the graft and the inflammatory changes seen on endomyocardial biopsy (2,3). We and others (4,5) have previously reported a temporal relation between the sequences of elevated soluble interleukin-2 receptor levels and subsequent significant cardiac allograft rejection spanning a number of days. We suggest that the peak levels of immune activators may either predate the histologic changes or relate to the early development of rejection. It is therefore not surprising that Fyfe et al. (1) were unable to demonstrate any direct correlation between concurrent cytokine levels and biopsy grade.

Their secondary hypothesis regarding the measurement of cytokine concentration in the coronary sinus or superior vena cava or the difference between these two concentrations and its correlation with the severity of rejection on myocardial biopsy may be similarly flawed. Furthermore, the investigators give no breakdown of the various rejection grades obtained. Were higher levels noted in the higher rejection grades? This would be hard to interpret given the small sample size.

Fyfe et al. give no indication of how they deemed cytokine activity to be “baseline” when they compared cytokine concentrations measured during the absence of rejection with those measured during an episode of rejection in each patient. There is a striking augmentation of cytokine release after acute tissue injury due to a surgical procedure, as well as after bacterial and viral infection (4,6); if blood specimens are taken during this time, the sampling will be invalidated and the levels of cytokines potentially very high. The harvesting of endomyocardial biopsy tissue as part of a routine surveillance endomyocardial biopsy that shows acute rejection may not reflect the level of cytokine activation that may have been present well before the detection of an abnormality on routine surveillance endomyocardial biopsy. The peak levels of various immune markers may well predate the histologic changes or relate to the early development of rejection and could therefore explain the poor relation between simultaneous interleukin-2 receptor levels and allograft rejection (2,4). The rejection process itself may have been present for some time before biopsy, when cytokine activation may have been at its highest; at the time of taking the blood samples the rejection process may even be in a state of resolution, or cytokine production in a state of exhaustion. The histologic changes seen at the time of acute rejection, although specific, probably are a relatively late reflection of immune activation.

The recent development of various immune specific monoclonal antibodies (7,8) provides great help in the interpretation of the role of cytokines and offers exciting alternatives to the current immunosuppressive armamentary for the treatment of significant rejection.

The approach of Fyfe et al. (1) potentially creates unjustified prejudice against these agents, and we suggest that the utility of cytokine monitoring in solid organ transplantation requires serial collection of samples, with detailed reference to the level of immunosuppression, tissue injury and so forth, taking place in the weeks preceding sampling to best interpret levels.

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References


Reply

The points raised by Jennison et al. are interesting and I think adequately covered in our discussion. Our hypothesis that coronary sinus cytokine levels represent a cardiac source are subject to the caveats mentioned in our report and not by Jennison et al.: 1) penetration from the interstitial space; 2) coronary blood flow (known to be increased in heart transplant patients both at baseline and especially during rejection [1]); and 3) clearance of the cytokine from the serum. Interleukin-2 (IL-2) receptors, which appear to be the major focus of the letter of Jennison et al., have a relatively long half-life in serum, which may make it impossible to detect differences between the coronary sinus and superior vena cava. In our cases, as explained in the Discussion, IL-2 receptor levels were artificially elevated by antithymocyte preparations, which may have obscured any potential differences.

The suggestion of Jennison et al. that cytokine release predates rejection is shown in our Figure 7. Similar profiles were seen for interleukin-4 and tumor necrosis factor-alpha. What length of time should we allow to elapse before we consider a particular cytokine release to be associated with a specific rejection episode? Only careful collection of multiple samples over time will allow this question to be answered. We cannot ethically justify performing this...
procedure on our patients for purely scientific reasons outside the context of indicated biopsies.

All rejection episodes were International Society in Heart and Lung Transplantation grade 3A and greater, and baseline was considered grade 0 to 1. Blood samples were not taken during surgery and there was no evidence of active viral infection at the time of cytokine measurement. Active infection was an exclusion criterion for inclusion of data into the study.

We believe that our study does not prejudice the further development of monoclonal antibodies, mainly because Jennison et al. misunderstood the aim of our study. This was an observational study to examine which cytokines are being released and only secondarily to correlate these cytokines with rejection. The study does not have the power to address the latter question. We should have stated that there is no obvious relation between a particular cytokine and rejection; this does not imply that a relation does not exist. In fact, our Figure 7 suggests that a relation may well exist. We believe that documenting that a number of cytokines other than IL-2 receptor (Ref. 3 to 8 of Jennison et al.) are being released from the cardiac allograft (and not from some unknown peripheral site) provides exciting new potential therapeutic options.

PULMONARY EMBOLISM AFTER CARDIAC SURGERY

I was impressed by the unusually high incidence of pulmonary embolism after cardiac operations in the report by Josa and associates (1). Their retrospective data led logically to the conclusion that the incidence of pulmonary embolism in the patients undergoing coronary artery bypass grafting (3.9%) is higher than that (3%) reported by Kakkar et al. (2) in a prospective study of patients undergoing general surgical operations. However, I feel uncomfortable with their conclusion because we recently reported different results (3) on the same issue.

In our report (3), we reviewed the clinical records of 4,393 patients who underwent cardiac surgery requiring cardiopulmonary bypass at a large university hospital between January 1984 and December 1988. Of these, only 13 patients developed venous thromboembolism postoperatively. There were eight cases of deep vein thrombosis and five of pulmonary embolism. Three of the patients with pulmonary embolism underwent coronary artery bypass grafting and two had aortic valve replacement. Pulmonary embolism accounted for the death of one patient. Follow-up data were available in all patients and averaged 38 ± 5.6 months (range 2 to 72). Actuarial survival at 5 years was 92% after a cardiac operation (Fig. 1).

Our observations agree with their proposed risk factors of prolonged immobility, obesity and previous deep vein thrombosis. However, the incidence of venous thromboembolism after open heart surgery was 0.3% in our series (3). The increasing use of intravenous and oral anticoagulant agents before open heart surgery and the routine use of platelet suppressant therapy may offer possible explanations for the observed low occurrence of postoperative pulmonary embolism in this subset of patients. Based on our experience, it appears that the 3.9% incidence of pulmonary embolism among cardiac surgical patients is extremely high.

In many cases of pulmonary embolism occurring after general surgical operations, deep vein thrombosis is the most common source for dislodgment of a clot in the pulmonary circuit. It is unclear why the incidence of deep vein thrombosis is very low in pulmonary embolism cases in the series of Josa and associates (1). This discrepancy requires explanation.

Limitations of retrospective studies on this complex issue emphasize the need for a randomized prospective study to investigate the true incidence of venous thromboembolic complications after cardiac surgery.

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References

Reply
Canver’s letter raises two important issues: the incidence of deep vein thrombosis and pulmonary embolism after cardiac surgery. With respect to the first, it was not the aim of our study to determine the incidence of deep vein thrombosis in patients undergoing cardiac surgery. Although deep vein thrombosis precedes pulmonary embolism, it is usually asymptomatic and can be detected only by