CONCLUSION

This result suggests that Z-BUF improves the pulmonary function in this model of severe lung injury and may be an effective tool in attenuating the CPB derived inflammatory process.

SUMMARY

Unfortunately there have been very few prospective randomized studies comparing the clinical outcomes of patients treated with large volume ultrafiltration (14,15). Given the shortage of impressive clinical outcome data and the varying results of mediator removal studies, the application of ultrafiltration as a therapeutic technique is still a controversial topic. A few researchers have suggested that different membrane materials may have significantly different mediator removal potential (16–18). One important future direction for research in this area should include a comprehensive comparison of different membrane materials with regard to their clinical performance.

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Glucose and Outcome After Cardiac Surgery: What are the Issues?

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Hyperglycemia frequently occurs during the conduct of cardiopulmonary bypass (CPB) for cardiac surgery. In addition to the exogenous administration of glucose containing solutions [most notably with dextrose containing cardioplegia as well as variably in the pump prime] (1), the stress response to both surgery and CPB marked by significant increases in circulating catecholamines (epinephrine and norepinephrine) and cortisol (2) results in significant peripheral insulin resistance and marked increases in blood glucose concentrations (3–5). Hyperglycemia, defined arbitrarily as a serum glucose >200 mg/dL occurs in as many as 75% of patients during surgery with patients with pre-existing diabetes mellitus having an even higher incidence (6).

Attenuating this hyperglycemic response to cardiac surgery has proven difficult, with even high insulin doses more often than not failing to return glucose to normal levels during surgery. Part of this failure is reflective of the significant anti-insulin effects of elevated circulating catecholamines and cortisol (7), and partly it is related to the impaired ability of insulin to transport glucose intracellularly under the hypothermia that is frequently used during the normal conduct of cardiac surgery (3). Indeed, Chaney et al. found that not only was normoglycemia difficult to attain during cardiac surgery, but that with large insulin doses administered during surgery, a high incidence of hypoglycemia in the post-bypass period posed a significant risk (8). In addition, excessive insulin can also result in hypokalemia due to its enhancement of potassium transmembrane transport

mechanisms. Although it would seem intuitive that the administration of additional insulin or insulin/glucose solutions to target normoglycemia would be safe and efficacious, the use of these protocols to achieve normoglycemia has not been adequately studied. More recently, some moderate successes have been demonstrated with the use of insulin/glucose infusions to better maintain appropriate serum glucose levels during surgery. Indeed, Carvalho et al. (9) described methodology to essentially lock in the glucose level at a predefined target. Although their study was relatively small (n = 47), it demonstrated clear efficacy compared to previous surgery trials (8) and warrants further large scale evaluation. Using a slightly different approach than previous studies, they described a hyperinsulinemia normoglycemic clamp technique that rather than using insulin administration as a "reaction" to hyperglycemia, purposely administered high doses of insulin so that exogenous glucose would have to be given to prevent hypoglycemia. In doing so, when patients were exposed to the usual periods of stress-induced hyperglycemia, the amount of glucose that was being infused was reduced resulting in optimal glucose control. Importantly, they supplemented potassium by continuous infusion and also monitored glucose levels every 5–10 minutes. Compared to conventionally treated patients, >95% of patients managed by their "clamp" technique achieved normoglycemia.

So with hyperglycemia being common and with most previously studied protocols for hyperglycemia being difficult, if not impossible, to achieve normoglycemia, a number of investigators have examined some of the adverse sequelae associated with hyperglycemia during cardiac surgery. There is emerging clinical and experimental evidence implicating hyperglycemia with various immunomodulatory effects, particularly in those patients with critical illness (10,11). In particular, hyperglycemia has been demonstrated to reduce white blood cell function, most notably macrophages and neutrophils (12). Furthermore, Rassias et al (13) demonstrated that insulin infusions can significantly improve neutrophil function (in diabetic patients) thus reversing some of the hyperglycemia-mediated immunosuppression.

Mediastinitis is a particularly ominous infection that can occur in the post-cardiac surgery period. Although the risk factors for this potentially devastating infection are multiple, hyperglycemia has recently been demonstrated to be associated with a higher incidence of mediastinitis, particularly in patients who are diabetic and/or obese (14,15). As a result, efforts have been targeted at lowering the incidence of hyperglycemia in hopes of decreasing significant mediastinal infection. Although there is some evidence that this may be effective, it has not been studied in sufficiently large populations to be confidently proven. Although perhaps not directly applicable to the issue of infection and cardiac surgery, van den Berghe et al. in a recent study of intensive insulin therapy in intensive care unit patients, demonstrated that not only did aggressive insulin treatment effectively achieve normoglycemia and reduce bloodstream infection by 45%, but it also reduced mortality (8.0% for conventional treatment vs. 4.6% for intensive insulin therapy; $p < 0.04$) (12).

In addition to its immunomodulatory effects, hyperglycemia, because of its osmotic effects, also has an impact on the kidney, acting as a potent osmotic diuretic. However, little work has focused on its potential impact on longer-term renal impairment that has been demonstrated in certain subsets of patients after cardiac surgery (16,17).

With respect to neurologic outcome, a great body of work has demonstrated a relationship between hyperglycemia and worse outcome after a number of different cerebral injuries. Experimentally, there is a wealth of data linking hyperglycemia with adverse cerebral outcome after stroke (18–21). Although this has also been demonstrated clinically for stroke in non-surgical settings (22–24), in cardiac surgery patients, the link between hyperglycemia and adverse neurologic outcome is far less clear (25).

The potential mechanisms for hyperglycemia's association with adverse neurologic outcome are several-fold. Firstly, higher glucose levels lead to a higher degree of substrate availability for the production of lactate during anaerobic metabolism consequent with cerebral ischemia (26–28). The resulting intracellular acidosis then interferes with glycolysis, protein synthesis, hemeostatis, enzyme function, and other critical intracellular process (28–30). In addition, hyperglycemia has been shown to increase the release of excitotoxic amino acids (glutamate and aspartate) during cerebral ischemia (31). The release of these amino acids is a key mediator in the ischemic cascade; the presence of hyperglycemia augments this injurious response (32). Furthermore, there is potentially some evidence suggesting that the presence of hyperglycemia itself may enhance the inflammatory response (33). As it is already known that CPB stimulates a vigorous inflammatory response (34,35), and that inflammation may mediate several adverse outcomes, including cerebral, the additional hyperglycemia-mediated inflammation may cause further injury. Given that cerebral ischemia has the potential to occur during cardiac surgery, this may be one potential mechanism why adverse cerebral outcome would be expected to be linked with hyperglycemia during cardiac surgery.

Thus far, however, most studies have been too small (and consequently underpowered) to demonstrate any meaningful associations between hyperglycemia and adverse cerebral outcome during cardiac surgery. This is particularly true for stroke. Until recently, this was similarly true for cognitive dysfunction where, although thought for a number of years to be related to hyperglycemia, studies had failed to demonstrate any association (25). Most recently, however, our research group reported the results of a study involving patients (n = 709) undergoing CABG with CPB where cognitive function was assessed both pre-and post-op (6 weeks). The incidence of cognitive deficit was compared between those who developed hyperglycemia vs. those who did not. The hyperglycemic patients had a cognitive deficit rate of 40% vs. 29% in the normoglycemic group (OR, 1.85, 95% CI 1.1–3.0; p = 0.0165). The presence of hyperglycemia increased the risk of cognitive dysfunction by as much as 85% (6).

The next logical steps in our understanding of hyperglycemia's (and its therapy) link to outcome is to move forward with well designed, adequately powered interventional studies. Because of repeated failures in hyperglycemia therapy during cardiac surgery, there is little data focusing on whether treating or preventing hyperglycemia (with insulin/glucose infusions) can actually reduce some of this cognitive dysfunction and other neurologic injury. This remains a potentially fruitful avenue for future study.

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Glucose Monitoring on CPB

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Serum glucose levels rise during cardiopulmonary bypass (CPB). This appears to be regardless of temperature during CPB. The cause of this rise is multifactorial but there are two prime areas of cause;

1. increased transformation of glycogen to glucose as a response to stress
2. decreased insulin secretion secondary to surgery, anesthesia and hypothermia.