HOW TO MANAGE PERFUSION IN THE PRESENCE OF CO-MORBIDITIES: THE PERFUSION SITUATION IN DIABETES

S.Pervez Ahmad Uzma Mazahir Atta ur Rehman Noreen Baig

At first sight, it may be difficult to envision how a chronic disease that is affecting the body on a molecular level may influence the acute management of extracorporeal circulation employed to perform cardiac surgery. The settings for cardiopulmonary bypass are practically the same as those in patients without diabetes, the steps to be taken and the drugs to be given are also similar (with the possible exception of the dose of insulin applied to control blood glucose). Yet, the outcome of patients with diabetes undergoing cardiac surgery is significantly worse.[1,2] One of the key questions with respect to perfusion in this context is whether and how changes in the management of cardiopulmonary bypass can affect outcome in these patients. It is no secret that patients with diabetes usually present with significantly more co-morbidities increasing perioperative risk. Thus, it may be hypothesized that the standard application of cardiopulmonary bypass in patients with diabetes may be adequate and paying specific attention to perfusion may be of minor importance. Indeed, based on the currently available information, it will be difficult to fully reject this hypothesis. However, there is growing evidence[2-7] that minor modifications in the management protocols of cardiopulmonary bypass (specifically maintaining euglycemia during and after cardiopulmonary bypass) may have a major impact on outcome. For a complete understanding of this suggestion, it is necessary to review some basic principles of the diabetic pathophysiology.

There are two types of diabetes; type 1, where insulin production is impaired and type 2, where the effect of insulin on the end organ is impaired (also referred to as insulin resistance). There are also several variants and mixtures of the two types of diabetes which will not be considered in this basic overview.

* *Address for correspondence:*
Department of Clinical Perfusion,
National Institute of Cardiovascular Diseases
Karachi.

From a practical standpoint it is important to realize that patients with type 1 diabetes may be adequately treated by insulin replacement, while this therapeutic option does not really exist for type 2 diabetes. Here the pancreas is already generating elevated levels of insulin. While further insulin addition is the therapy of choice (or stimulation of the pancreas to secrete more), the underlying problem (i.e. insulin resistance) is usually not treated. The long-term detrimental effects of diabetes are generally based on the long-term exposure of end organ tissue to high concentrations of serum glucose and/or the presence of insulin resistance. The diabetic long-term sequelae include renal failure, diabetic retinopathy, coronary artery disease, and diabetic neuropathy. While the list goes on and on, the key effect with respect to perfusion is the development of diabetic microangiopathy, potentially resulting in poor end organ perfusion during cardiopulmonary bypass.[8] Thus, the perfusionist may be faced with normal "macro-perfusion" (i.e. his pump flow may be adequate as calculated for the patient, and he may not notice anything unusual), yet, end organ perfusion may be inadequate resulting in complications such as renal failure or neurological complications. Efforts to address these potential differences by altering perfusion strategy (e.g., from a non-pulsatile to a pulsatile flow) have yielded inconclusive results.[9,10] Thus, the impact of diabetes on "micro-perfusion" during cardiopulmonary bypass has to be taken into account, but it also has to be realized that very little can be done in the acute setting to overcome this perfusion difficulty.

Interestingly, one of the effects of diabetes on the cellular, level appears to be a promising candidate as therapeutic target for the perfusionist. There is growing evidence that the short-term treatment of dysregulated glucose homeostasis may affect outcome.[2-7] This is critical information for both cardiac surgeon and perfusionist because no other procedure interferes so acutely and greatly

with the patient's glucose homeostasis than cardiac surgery with extracorporeal circulation.

During cardiac surgery, every patient develops some degree of insulin resistance.[11] It is a common notion that this insulin resistance is due to the stress-induced release of cortisol and other stress hormones such as epinephrine. These hormones stimulate gluconeogensis in the liver, activate glycogenolysis of most cells and inhibit insulin action. The result is hyperglycemia. These mechanisms are independent of the presence of diabetes, but they aggravate a pre-existing state of insulin resistance.[11] Therefore, even non-diabetic patients demonstrate various degrees of hyperglycemia during and after cardiac surgery, but the peak glucose levels are generally higher when a patient suffers from diabetes.

The evidence that post operative hyperglycemia is associated with poor outcome comes mainly from diabetic patients.[3,4] The Portland group[3] demonstrated that the degree of post operative hyperglycemia in patients with diabetes mellitus undergoing cardiac surgery is independently correlated with operative mortality and morbidity. This finding is consistent with the pathophysiological conception that diabetes mellitus aggravates perioperative insulin resistance, suggesting that the patients with the most severe insulin resistance are at -the greatest risk. If insulin resistance is involved in this mechanism, it appears reasonable to assume that hyperglycemia is also a risk factor in non-diabetic patients. Indeed, van den Berghe et al.[5] demonstrated in a landmark study at the beginning of the millennium that establishing euglycemia in intensive care patients (the majority of patients were non-diabetics) after any type of surgery (65% cardiac) significantly reduces morbidity and mortality, most dramatically in patients requiring extended intensive care units stays.[5] In addition to this, it has been demonstrated in a retrospective databank analysis that the peak glucose level during cardiopulmonary bypass is an independent predictor of mortality in both diabetic and non-diabetic patients undergoing cardiac surgery.[2] Thus, insulin resistance appears to be involved in the mechanisms of these detrimental effects, which in turn appears to be independent of the presence or absence of diabetes.

While the evidence that insulin resistance and/or perioperative hyperglycemia negatively affect outcome in cardiac surgery is growing, the evidence that treating hyperglycemia improves outcome is still wanting. The van den Berghe trial[5] as mentioned above makes a strong argument in this direction, but an etiologic link between insulin resistance and/or hyperglycemia and poor outcome has not been fully established. A first important step was recently taken through a prospective randomized study by the Lazar group in Boston.[4] The investigators demonstrated a short and long-term survival benefit for diabetic patients receiving a mixture of glucose-insulin-potassium to establish euglycemia after cardiac surgery.[12] However, we still do not know whether aggressive management of euglycemia already during CPB is also capable of affecting outcome. Such studies have not yet been performed. In the meantime, it appears advisable to aggressively establish euglycemia during and after CPB by applying insulin (even in higher doses) or withholding glucose infusions. Even if hyperglycemia cannot be avoided by applying insulin, some of the negative side effects of hyperglycemia (e.g. increased leucocyte adherence to the endothelium) may be counteracted by increasing the levels of circulating insulin.[13] Irrespective of the remaining inconsistencies, a recent evidence-based review of the practice of cardiopulmonary bypass recommends the establishment of euglycemia during cardiopulmonary bypass for all patients and rates the evidence as class 1, level B.[14] Even if it may turn out that this minor modification in CPB management does not have the desired effect, it appears extremely unlikely that the maintenance of euglycemia or the application of even extreme dosages of insulin is detrimental.[11] However, if the results of the van den Berghe-trial[5] translate to the specific management of patients undergoing cardiac surgery, the impact of this minor modification may be staggering.

Maintaining euglycemia during and after CPB is a simple but powerful tool to reduce morbidity and mortality in patients undergoing cardiac surgery. This conclusion appears to be true for both diabetic and non-diabetic situations. Diabetes mellitus affects the perfusion condition during CPB in other ways, but there is currently no specific management strategy available that has been documented to reduce risk.

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