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Microvascular Dysfunction in Diabetic Patients after Cardioplegic Arrest and Cardiopulmonary Bypass

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Abstract

Purpose of the Review—The purpose of current review is to describe the changes of microvascular function in diabetic patients after cardioplegic (CP) arrest and cardiopulmonary bypass (CPB) and cardiac surgery.

Recent findings—Cardiac surgery, especially that involving CP and CPB, is associated with significant changes in vascular reactivity of coronary/peripheral microcirculation, vascular permeability, gene/protein expression, and programmed cell death, as well as with increased morbidity and mortality after surgical procedures. In particular, these changes are more profound in patients with poorly controlled diabetes.

Summary—Since alterations in vasomotor regulation are critical aspects of mortality and morbidity of CP/CPB, a better understanding of diabetic regulation of microvascular function may lead to improve post-operative outcomes of diabetic patients after CP/CPB and cardiac surgery.

Keywords

Diabetes Mellitus; Microvascular Dysfunction; Cardioplegia; Cardiopulmonary Bypass; Cardiac Surgery

INTRODUCTION

Diabetes mellitus is an established risk factor for the development of coronary artery disease (CAD) and for morbidity after cardiac surgery. In diabetic patients, CAD is more prevalent compared to non-diabetic patients, but also is more extensive, involves multiple vessels, and is rapidly progressive. Patients with diabetes represent a significant proportion of the patient population requiring myocardial revascularization. In this diabetic population with more severe CAD, coronary artery bypass grafting (CABG) is associated with increased rates of perioperative complications and mortality as compared to non-diabetic patients. Diabetes has been well established as an independent risk factor for increased early and late mortality in patients treated with CABG.(1–3) In addition to decreased survival, patients with diabetes

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Conflicts of Interest

There are no conflicts of interest.

have been shown to have increased rates of sternal wound infection and mediastinitis, as well as saphenous vein harvest site infections. (4–7) Diabetes has also been associated with increased rates of renal and neurologic complications as well as prolonged, postoperative Intensive Care Unit stays.(8) Diabetes also increases the risk of renal failure and stroke with valve surgery. (9, 10) Postoperative myocardial dysfunction also appears to be exacerbated by diabetes as it is an independent predictor of postoperative low cardiac output syndrome. (11, 12) Finally, once patients with diabetes have been discharged from the hospital, evidence suggests that this group of patients is at high-risk for readmission. Thus, diabetics present a challenging patient population for cardiac surgeons. In these patients, severe, multivessel coronary disease often necessitates surgical revascularization, which in the diabetic population is associated with increased morbidity and mortality.

Despite advances in myocardial protection strategies and CPB circuits and techniques, CP/CPB is associated with postoperative vasomotor dysfunction which can lead to organ malperfusion.(13–19) Specifically, previous work has demonstrated, in large animal models and in patients, CP/CPB-induced dysfunction in the coronary, pulmonary, cerebral and skeletal microcirculation.(20–28) The microcirculation, which consists of vessels with an internal diameter of less than 200 μm, is the primary site of resistance in the vasculature and of paramount importance in governing tissue blood flow. (13, 29)Disturbances in this system secondary to CP/CPB result in impaired myogenic tone and responses to vasoconstrictors. (13, 30) Clinically, this can manifest as systemic hypotension, and myocardial dysfunction secondary to impaired coronary perfusion.(31)Recent studies demonstrate that these alterations are more pronounced in patient with poorly controlled diabetes.(26, 32–36) These effects often necessitate the use of vasopressors, such as phenylephrine to maintain adequate blood pressure. The molecular mechanisms underlying the control of microvascular constriction and vasodilatation in the normal physiologic setting and clinically after CP/CPB remain to be elucidated, and investigation is further complicated by variation in regulatory mechanisms in different vascular beds. (13, 29) Given the microcirculation's critical role in tissue perfusion, understanding the mechanisms that regulate this system is essential. Over past one decade, details of metabolic/diabetic regulation of microvascular function during CP/CPB and cardiac surgery have been extensively studied by our lab and others. Here, we highlight recent work, focusing on the effects of diabetes-on vasomotor/endothelial function, gene/protein expression, vascular permeability and programmed cell death in the setting of CP/CPB and cardiac surgery.

Vasomotor Dysfunction in Diabetic Patients after CP/CPB and Cardiac Surgery

CP/CPB is widely recognized to induce systemic inflammatory response, resulting in multiple organ/tissue damage.(37, 38) CP/CPB elicits multi-factorial microvascular dysfunction that varies according to affected organ/tissue bed, with reduced microvascular resistance in peripheral microcirculation, and increased propensity to spasm in the cardiac, pulmonary, mesenteric and cerebral microvascular beds.(13, 30, 39–41) For example, CP/CPB impairs myogenic contractile responses of human coronary and peripheral arterioles to phenylephrine, endothelin-1 and thromboxane-A-2 (TXA-2). (26, 27, 29, 31,

42) Inhibition of PKC-α reduced phenylephrine induced vasoconstriction in coronary and skeletal microvessels, whereas activation of PKC-α-augmented phenylephrine induced responses.(29) ET-A receptors are predominantly localized in the human coronary microcirculation, whereas ET-B receptors seem to be less abundant.(27, 31) CP/CPB has no effects on ET-1-related gene/protein expression. The contractile response to ET-1 is in part through the activation of ET-A receptors and PKC-α. (27, 31)Patients with poorly controlled diabetes demonstrate a decreased contractile response to ET-1 in human peripheral microvasculature as compared with non-diabetics.(26) These results provide novel mechanisms of ET-1-induced contraction in vasomotor dysfunction in diabetic patients. In contrast, TXA-2-induced coronary arterial constriction is via TP receptors and PLC, but not PKC-α. (42)These changes may be in part responsible for the decrease in arteriolar tone, and accompanying hypotension sometimes observed after cardiac operations utilizing CP/CPB.

On the other hand, CP/CPB enhances serotonin (5–HT)-induced vasoconstriction in human coronary arterioles.(28, 43, 44) CP/CPB enhances contractile response of arterioles to 5-HT may be due to the stimulated prostaglandin release (likely TXA-2) secondary to induction of COX-2 expression. (28, 43) Further study shows that 5HT-induced vascular dysfunction after CP/CPB may be mediated by increased expression of 5HT-1B receptor and subsequent phospholipase A2 (PLA-2) activation in myocardial coronary smooth muscle.(44) These findings may have implications regarding the cause of coronary spasm during acute myocardial ischemia. Verma and colleague also reported that diabetic coronary microvessels respond to CP/CPB with greater ET-1-mediated vasoconstriction and diminished nitric oxide-mediated vasodilatation; and 3) these effects are attenuated by ET antagonism. (35) These findings suggest that the use of ET-1 receptor antagonists might be a novel strategy for improving the resistance of the diabetic heart to CP/CPB.

Microvascular Endothelial Dysfunction in Diabetic Patients after CP/CPB and Cardiac Surgery

Numerous studies have confirmed that CP/CPB causes microvascular endothelial dysfunction in multiple organ/tissue vessels and variety of animal models.(13–15, 22, 23, 33, 34, 39, 40, 45) The in-vivo findings have correlated closely with in-vitro alterations in vascular function after CP/CPB. Uncontrolled diabetes is associated with endothelium-dependent and -independent vascular dysfunction of coronary and peripheral arterioles. The relaxation responses of coronary and peripheral arterioles to endothelium-dependent ADP, bradykinin, Substance P were significantly impaired in poorly controlled diabetes as compared to that of well-controlled diabetes or non-diabetes. (33, 34) In addition, uncontrolled diabetes worsens the recovery of coronary and peripheral arteriolar endothelial function after CP/CPB.(33, 34) These alterations are associated with an increased expression/activation of PKC-α and protein kinase C-β and enhanced oxidative/nitrosative stress. CP/CPB also causes microvascular endothelial dysfunction associated with and likely in part due to impaired function of SK_{Ca} and IK_{Ca} channels in the animal and human coronary circulation, suggesting that novel mechanisms of vascular endothelial dysfunction after cardiac surgery.(46–48) In single cell recording, diabetes reduces endothelial SK_{Ca}/

IK_{Ca} currents, and endothelial hyperpolarization.(36) But diabetes or CP/CPB fails to affect the total gene/protein expression of SK_{Ca} and IK_{Ca} of the coronary and peripheral arteries suggesting that this effect is post-translational.(46, 47)

Altered Gene/Protein Expression of Growth Factors and Their Related Genes in Diabetic Patients after Cardiac Surgery

The CP/CPB-induced gene/protein expression of growth factors and there related gene has been found in animal and humans.(49–52) In pig model of CPB, a study shows that VEGF protein and its flk-1 receptor gene expressions are selectively increased and the potent VEGF-induced vascular responses are enhanced in the coronary microcirculation after blood cardioplegia.(53) In the human study, compared with pre-CPB, post-CPB, myocardial tissues revealed 851 upregulated and 480 downregulated genes in the diabetic group, compared with 480 upregulated and 626 downregulated genes in the nondiabetic group. There were 18 genes that were upregulated in diabetic and nondiabetic patients (including inflammatory/transcription activators FOS, CYR 61, and IL-6, apoptotic gene NR4A1, stress gene DUSP1, and glucose-transporter gene SLC2A3). However, 28 genes showed such marked upregulation in the diabetic group exclusively (including inflammatory/transcription activators MYC, IL8, IL-1_, growth factor vascular endothelial growth factor, amphiregulin, and glucose metabolism-involved gene insulin receptor substrate 1), and 27 genes in the nondiabetic group only, including glycogen-binding subunit PPP1R3C. These results have important implications for the design of tailored myocardial protection and operative strategies for diabetic patients undergoing CP/CPB.(50)

The serum levels of VEGF and hepatocyte growth factors were significantly elevated in diabetic patients when compared with non-diabetic patients before versus 6 hours post-CP/CPB.(51) In addition, significantly elevated mRNA expression of hypoxia-inducible factor-1a, cyclic adenosine monophosphate response element binding protein, and E1A binding protein p300 was observed 4 days post-CP/CPB exclusively in patients with diabetes. The differential profile of gene and protein expression of growth factors and their related genes in patients with or without diabetes could be associated with increased edema and weight gain in patients with diabetes after CP/CPB. Length of hospitalization (10 vs 6 days) and weight gain were significantly greater for diabetic patients compared with non-diabetic patients. (32, 51) Taken together, the resulting increase in microvascular permeability and increased tissue-organ edema contributes to an increased length of stay and worsened outcomes in patients with poorly controlled diabetes after cardiac surgery.(32)

Down-regulation of Endothelial Adherens-Junction Protein after CP/CPB in Diabetic Patients

However, the molecular mechanism underlying CP/CPB-enhanced peripheral vascular permeability and tissue edema merits further investigation. Protein tyrosine phosphorylation plays a critical role in numerous vascular processes including vasomotor regulation and the regulation of vascular permeability mediated through adherens junctions and other endothelial cell-cell contacts.(15, 32, 54) Adherens junctions are cellular contacts that are

formed by transmembrane and intracellular proteins. They are organized in clusters at cell-cell contacts and connect through their cytoplasmic domain with a complex arrangement of transmembrane proteins known as cadherins. Cadherins are single chain transmembrane proteins that interact with other related proteins (β-catenin, plakoglobin, and p120) to promote linkage to the actin cytoskeleton. In vascular endothelium, the major cadherin, VE-cadherin, is bonded to catenins and the actin cytoskeleton.(32, 55–60) They tend to be dynamic and highly regulated by oxygen-derived free radicals, and cytokines, such as VEGF.(61, 62) Bacterial lipopolysaccharide (LPS) is known to disrupt endothelial barrier function, in part by protein tyrosine kinase activation.(63) Hence, systemic organ dysfunction during sepsis may in part be due to an altered state of cell-cell junctions. When adherens junctions are stabilized, VE-cadherin loses tyrosine phosphorylation and binds with plakoglobin and actin, while β-catenin is reduced in the adhesion complex with VE-cadherin.(64) Poorly controlled diabetes down-regulates endothelial adherens-junction protein activation/expression/localization in the setting of CP/CPB.(32) CP/CPB increased phosphorylation of VE cadherin and decreased β and γ catenins in patients undergoing CABG surgery. This is consistent with previous studies in pigs, where we found that CP/CPB results in the increase of phosphorylation of VE cadherin and degradation of β and γ catenins in pig myocardium.(15, 54) These findings indicate that CP/CPB has an important effect in endothelial cadherin assembly and integrity of human coronary endothelium. The increased tyrosine phosphorylation and deterioration of VE-cadherin indicates the damage of the cell-cell endothelial junctions in the diabetic vessels undergoing CP/CPB and cardiac surgery. These alterations may lead to the increase in vascular permeability and endothelial dysfunction and affect outcomes in diabetic patients after cardiac surgery.(32)

Increased Myocardial Programmed Cell Death in Diabetic Patients after CP/CPB and Cardiac Surgery

Despite optimal current surgical myocardial protection, CP/CPB is still associated with programmed cell deaths, such as apoptosis.(16, 17, 19, 65–68) CP/CPB induces both programmed cell death and survival signaling via the caspase-dependent and intrinsic pathways in human myocardium and endothelial cells. (69–71) In particular, uncontrolled diabetes mellitus is associated with increases in myocardial apoptosis and expression of key apoptosis mediators at baseline and in the setting of CP/CPB.(72, 73) Moreover, compared with non-diabetics, diabetic myocardium demonstrated attenuation of the cardioprotective STAT3 pathway after CP/CPB and cardiac surgery.(74) Identification of this mechanism offers a possible target for therapeutic modulation.

Diabetic hearts have lower basal urocortin levels that fail to increase after cardioplegic arrest, which is associated with increased apoptosis and postsurgical cardiac dysfunction. (75)

Heart surgery was also associated with a robust increase in autophagic flux indicated by depletion of LC3-I, LC3-II, Beclin-1, and autophagy 5-12; the magnitude of change for each of these factors correlated significantly with changes in the flux marker p62. (76) In

addition, changes in p62 correlated directly with cross-clamp time and inversely with the mortality and morbidity risk scores. Human heart responds to cardioplegic ischemia by activating HIR2, a pathway that can be compromised by comorbid conditions. Amplifying HIR2 during cardiac surgery could mitigate the operative risk in vulnerable patients and would represent an entirely new approach to intraoperative myocardial protection.(77) Perioperative ischemia/reperfusion significantly upregulated 11 (13.1%) and downregulated 3 (3.6%) of 84 ATGs. Specifically, there were increases in the autophagy machinery components ATG4A, ATG4C, and ATG4D; tumor necrosis factor–related apoptosis-inducing ligand, MAPK8 and BCL2L1; and chaperone-mediated autophagy activity with increased heat shock protein (HSP) A8, HSP90AA1, and a-synuclein. Autophagy activity was confirmed through observations of higher LC3-I levels and an increase in the LC3-II/LC3-I ratio. Autophagy activation coincided with increased AMPK activation and decreased protein levels of the mammalian target of rapamycin, the latter a key negative regulator of autophagy.(76) Activation of signal transducer and activator of transcription 5 (STAT5) in left ventricular (LV) myocardium at early reperfusion is associated with such protection. Autophagy, i.e., removal of dysfunctional cellular components through lysosomes, has been proposed as one mechanism of cardioprotection STAT5-phosphorylation was greater at early reperfusion only with RIPC. STAT3- and ERK1/2-phosphorylation.(78) Protection through RIPC in patients undergoing CABG surgery does not appear to be associated with enhanced autophagy in LV myocardium at early reperfusion.

CHALLENGES and FUTURE DIRECTION

The cellular mechanisms responsible for diabetic and CP/CPB dysregulation myogenic tone and endothelial function are far from clear. Future work may focus on: 1) The effects of well-controlled and poorly controlled DM on CP/CPB-induced changes in coronary and peripheral microvascular myogenic tone and contraction and associated signaling;2) The effects of glucose control on smooth muscle α-adrenergic and vasopressin-induced microvascular signaling and altered calcium handling will be determined after CP/CPB in the coronary and peripheral microcirculation; 3) The effect of tight perioperative control of glucose (target glucose <130 mg/dl) vs. less aggressive regimen (glucose <200 mg/dl) on altered vascular function and markers of inflammation and cardiac and other clinical outcomes in diabetic and non-diabetic patients; 4) The differential effects of gender and aging on myogenic and α-adrenergic pathway in the microvasculature of well-controlled and poorly controlled diabetic and age-matched non-diabetic patients. To achieving these goals, multiple approaches should be employed, such as, in-vitro microvascular imaging, molecular signaling, microarray, and proteomic techniques.

CONCLUSION

Diabetes is associated with vascular dysfunction in all tissues, including the microvasculature. Thus, a better understanding of mechanisms that regulates microvascular tone during and after cardiac surgery may provide the basis for the development of new methods to decrease the detrimental effects of CP/CPB. Since CP/CPB is used in most cardiac operations and diabetic patients have a greater incidence of death and complications after heart surgery, the clinical applications will be directed toward improving microvascular

preservation and reducing the untoward effects of extracorporeal circulation on altered vasomotor regulation and subsequent organ injury.

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Bullet Point

1. Diabetes is associated with endothelium-dependent and -independent microvascular dysfunction of coronary and peripheral arterioles.
2. Diabetes worsens the recovery of coronary and peripheral arteriolar function after cardioplegic arrest and CPB
3. Diabetic altered myogenic tone in human microvasculature after CP/CPB and cardiac surgery.
4. Diabetes down-regulates endothelial adherens-junction protein activation/expression/localization in the setting of CP/CPB
5. Diabetes mellitus is associated with increases in myocardial apoptosis and expression of key apoptosis mediators at baseline and in the setting of CP/CPB and cardiac surgery