in diabetic animals leads to increased capillary density before myocardial infarction. Despite poor prognostic in the long-term, all these results suggest that diabetes mellitus and consequently hyperglycemia may indeed play a cardioprotective role against myocardial infarction in the short term.

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Key words: Conditioned hyperglycemia; Diabetes mellitus; Myocardial infarction; Cardioprotection; Survival factors

Core tip: Hyperglycemia or diabetes triggers a conditioned state that may protect the heart against ischemic injury and associated detrimental effects. These beneficial effects are present in short term diabetes and/or moderate hyperglycemia. The increase in glucose availability, the preferred energy substrate of the heart in stress condition, is likely to be one of the main cardioprotector mechanisms of hyperglycemia. However, other cardioprotective mechanisms seem to be involved, such as the release of cellular survival factors, ions preventing overload and angiogenesis. A fuller understanding of the mechanisms underlying conditioned hyperglycemia is then critical for the development of effective therapeutic strategies against ischemic heart disease.

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CONDITIONED HYPERGLYCEMIA AND MYOCARDIAL INFARCTION

Diabetes type 1 is a chronic disease characterized by hy-
perglycemia resulting from genetic and environmental factors. Complications of cardiac function are a leading cause of morbidity and mortality in type 1 diabetic patients. Diabetes induces cardiac dysfunction or diabetic cardiomyopathy, regardless of the presence or absence of vascular disease, coronary artery disease, arteriosclerosis and myocardial infarction.

In hospital environments, glucose and insulin administration are induced in coronary artery bypass grafting patients. This therapy protects the myocardium and inhibits ischemia-induced adenosine monophosphate-activated protein kinase activation. However, intraoperative insulin resistance is associated with increased risk of complications, regardless of the patient’s diabetic state.

The increase in mortality in diabetic patients after myocardial infarction remains controversial. Intensive glucose control is widely used in patients with diabetes mellitus and stress-induced hyperglycemia. In this review study, we found that this strategy increases the risk of hypoglycemia, and dangerously increases catecholamine levels with hemodynamic response. Such significant changes may culminate in serious or even fatal cardiovascular events.

Elevated admission glucose levels are common in patients with myocardial infarction and are strongly associated with increased mortality. Mortality of hyperglycemic patients was lower in the 1985 to 2008 period when compared to normoglycemic patients. Efforts to establish optimal treatment for these patients remain warranted.

Accumulated evidence in clinical studies on diabetic cardiomyopathy suggests increased myocardial infarction and mortality in diabetic patients; however, experimental data regarding the increased resistance of diabetic animals to ischemic injury are quite controversial.

Conversely, chronic hyperglycemia is associated with increased incidence of long-term cardiovascular complications, although its effect on acute hyperglycemic response and mortality after acute myocardial infarction remains unclear.

One review study suggests that the diabetic heart may be more, equally, or even less susceptible to ischemia-reperfusion injury (novel cardioprotective strategy for the diabetic heart). Our review study, however, aims at demonstrating the role of conditioned hyperglycemia as a protective mechanism of the heart after ischemic injury and in the preservation of cardiac function.

**CELLULAR SURVIVAL FACTORS: CELL DEATH AND ANGIOGENESIS**

Several studies have suggested that cardiomyocyte loss in ischemic cardiomyopathy may occur either by necrosis or by apoptosis, without significant inflammatory response. This loss has been found to contribute to the decline of the left ventricular function in humans. Indeed, experimental studies have shown that the chronic treatment of isolated cardiomyocytes with a high glucose content medium increased the rate of cell death. In contrast, exposure to short periods of a high glucose medium or diabetes has been found to protect the heart against a variety of pathological insults, including ischemia, hypoxia, and calcium overload. Several mechanisms have been proposed to explain the cardio-protective role of high glucose exposure, such as up-regulation of antiapoptotic factor Bel-2, inactivation of proapoptotic factor Bad, and activation of prosurvival factors.

To investigate the mechanisms behind improved cardiac function (accompanied by a reduction in lesion area) in diabetic rats (30 d of hyperglycemia) undergoing myocardial infarction (15 d), we evaluated the gene expression regulating cardiac cellular survival factors: Bax, Fas, Bel-2 e p53. In fact, gene expression was increased in diabetic animals after myocardial infarction, suggesting that the pro and anti apoptotic pathways can be activated simultaneously in this condition; this hypothesis was further strengthened by increased caspase-3 activity. These findings suggest an increased cell turnover acting to preserve cardiac function and reduce tissue injury.

Cell survival factors can be activated by increased Bel-2, as the up-regulation of Bel-2 in some cells prevents excessive accumulation of calcium by mitochondria, thus favoring cell survival. In this tissue, although calcium overload may be induced by ischemia, the association with hyperglycemia appears to reduce the activity of the Na+/Ca2+ exchanger.

Lending support to these findings, a study showed a reduction in protein expression of the Na+/Ca2+ exchanger in diabetic infarcted hearts, which might contribute to mitochondrial disruption and contracture, inducing structural damage. In fact, the improvement in cardiac function in diabetic infarcted rats may be associated with the protective effect of Bel-2, which abolishes the damage caused by the accumulation of calcium in the heart of diabetic rats.

Cytosolic Ca2+ overload during ischemia may be due to Ca2+ entry by reverse-mode of Na+/Ca2+ exchanger (NCX) secondary to the rise in Na+ concentration. During ischemia, the anaerobic metabolism increases proton generation, which is extruded from the cell by Na+/H+ exchanger (NHE), resulting in increased cytosolic Na+ concentration. This activates the reverse-mode of NCX exchanger, which in turn promotes an increase in Ca2+ concentration in the cardiomyocyte. Research has suggested that Na+/H+ exchange activity is decreased in diabetic hearts. Therefore, Ca2+ accumulation in the diabetic is lower than in the non-diabetic ischemic heart.

Several factors are related to cell survival: hypoxia inducible factor-1α (HIF-1α) is a transcription factor expressed in response to a decreased partial pressure of oxygen, and it is able to activate genes involved in angiogenesis, such as vascular endothelial growth factor (VEGF). As a result of diabetic hyperglycemia, these survival factors were increased in diabetic animals before and after myocardial infarction.

Interestingly, the expression of VEGF was also elevated before myocardial infarction in diabetic animals,
and results were similar to the observed in interleukin 8 (IL-8) gene, i.e., chemokine regulating neutrophil influx and activation with angiogenic propriety\(^{(29-31)}\). IL-8 plays an important role in the recruitment of granulocytes in the infarcted myocardium, increasing cell adhesion (integrin) and activating the signaling pathways of cell survival mitogen-activated protein kinase and protein kinase C (PKC), which contribute to angiogenesis\(^{(32)}\). Ooie et al\(^{(33)}\) have found that administration of streptozotocin for 12 wk in rats leads to increased tolerance to ischemic injury in an isolated heart model. These researchers also observed the translocation of protein kinase C-\(\varepsilon\) (PKC-\(\varepsilon\)) from the cytosol to the sarcolemal membrane, where the protein is activated. PKC-\(\varepsilon\) is a K\(_{ATP}\) channel opener in both the sarcolemal and mitochondrial membrane\(^{(34)}\). Opening mitochondrial K\(_{ATP}\) channel during ischemia stabilizes mitochondrial potential, reduces mitochondrial Ca\(^{2+}\) overload, prevents ATP depletion, and the generation of reactive oxygen species\(^{(34,35)}\).

Mitochondrial permeability transition pore (MPTP) is a downstream of PKC-\(\varepsilon\)\(^{(36)}\), which indicates that PKC interacts with MPTP, leading to phosphorylation of MPTP, and inhibits Ca\(^{2+}\) induced MPTP opening. Opening MPTP allows water and solutes to enter the mitochondria, increasing matrix volume and rupturing of the outer mitochondrial membrane, which results in the release of intermembrane cytochrome c, which can trigger apoptosis (Figure 1).

In this scenario, since hyperglycemia results in an increase of survival factors and induces angiogenesis, this may be interpreted as responses to repeated insults which eventually determine an ischemic conditioning in diabetic rats. These responses are strongly associated with improved left ventricle (LV) function observed after ischemic injury, suggesting the presence of a physiological mechanism of protection against heart damage.

**ROLE OF INFLAMMATORY CYTOKINES ON CARDIAC FUNCTION**

Cardiac repair after myocardial infarction is dependent on the activation of tumor necrosis factor alpha (TNF-\(\alpha\)), IL-1\(\beta\) and IL-6 cytokines, which results in leukocyte recruitment to the infarcted area\(^{(37)}\). In consequence, the immune imbalance between pro-inflammatory and anti-inflammatory properties can be modified in favor of more or less inflammatory factors, depending on the time course of the progression of heart failure. In this regard, changes in the concentration of TNF-\(\alpha\) may have different effects on all the cell types involved in cardiac injury and repair, and in the suppression of cardiac contractility\(^{(38)}\) to improve cardiomyocyte apoptosis\(^{(39)}\).

In fact, Malfitano et al\(^{(41)}\) have found a reduction of TNF-\(\alpha\) in diabetic rats after myocardial infarction. The signaling of IL-1\(\beta\) is crucial for the activation of inflammatory and fibrogenic pathways in the healing of myocardial infarction, and it may play a role in the pathogenesis of post-infarction remodeling\(^{(40)}\). Moreover, the induction of members of the IL-6 family leads to a rapid recruitment of mononuclear cells and cardiomyocyte ischemic myocardium\(^{(41)}\), thus indicating that the concentration of...
IL-6 was increased only in infarcted rats, but remained unchanged in diabetic animals after ischemic injury.

These three pro-inflammatory cytokines are not only associated with the inflammatory response, but are also involved in heart failure, cardiomyopathy and LV remodeling, suggesting that the reduction of inflammatory factors may be one of the mechanisms responsible for improved heart function observed in this group. These findings corroborate a previous study of our group, in which it was demonstrated that hyperglycemia in mice and in cell culture is capable of suppressing the expression of pro-inflammatory mediators by apoptosis of neutrophils and lymphocytes. In fact, a high proportion of apoptotic lymphocytes in diabetic states strengthen the hypothesis that immune function is impaired in patients with poorly controlled diabetes.

GLUCOSE METABOLISM IN CELL SURVIVAL

Another result which is in line with our findings is the increased expression of glucose transporter type-1 (GLUT-1) in diabetic rats after myocardial infarction. Indeed, previous studies have shown that the supply of glucose, with the regulation of GLUT-1, plays a critical role in cardioprotective response to myocardial ischemia, with increased glucose supply during the acute ischemia and progression to heart failure.

This is a result of increased availability and use of glucose, the preferred energy substrate of the heart in times of stress. Thus, the current clinical practice of tightly controlling blood glucose in patients having cardiac events may be detrimental to the heart in the acute setting.

Much of the ATP generated by anaerobic glycolysis is consumed for the maintenance of ion gradient thought membranes. Part of the ATP generated is hydrolyzed by reverse mode of the mitochondrial F1F0-ATPase, which uses the energy to generate mitochondrial membrane potential (ΔΨ) (Figure 1).

CONCLUSION

Finally, the increase in survival pathways such as Bcl2, PKC-ε, Akt and in capillary density may effectively contribute to the reduction of ischemic injury and cardiac fibrosis (modulation of cardiac fibroblasts) in diabetic animals. This might be the key to a better heart function, as the increased GLUT-1 expression plays an important role in increasing glucose uptake in ischemic conditions. The clinical importance of the deficiency of glucose in the treatment of heart failure is not necessarily highlighted when blood glucose control is the pursued goal of treatment. In the DIGAMI II study reported on 1253 diabetic patients with acute myocardial infarction allocated to three treatment arms including acute insulin-glucose infusion followed by insulin-based long-term glucose control (group 1), insulin-glucose infusion followed by standard glucose control (group 2), and routine metabolic management according to local practice (group 3) that neither all-cause mortality nor morbidity (stroke and non-fatal reinfarctions) differed between the three groups.

The compensatory mechanism associated with the positive balance of regulatory genes related to program cell survival, reduction of inflammatory cytokines, and increased glucose use as energy substrate. Taken together, they promote greater plasticity and improved cellular resistance to ischemic injury in short term, suggesting an ischemic conditioning in hyperglycemia. These findings should be translated into more effective patient care strategies following ischemic events. Therefore, future studies should be conducted to further elucidate the mechanisms underlying conditioned hyperglycemia in cardioprotection after ischemia.

Possible cardioprotector mechanisms of conditioned hyperglycemia or diabetes against ischemia and reperfusion injuries. Hyperglycemia seems to be cardioprotective due to the increased glucose provision to heart during stress. In the ischemia condition much of the ATP generated by glycolysis is breakdown by reverse mode of the mitochondrial F1F0-ATPase, which uses the energy to maintain mitochondrial potential (ΔΨ). Diabetic heart accumulates less Ca2+ due the inhibition NCX and NHE exchange activities. PKC-ε activity increases in diabetes, activating mitochondrial KATP channel and closing MPTP in the mitochondrial outer membrane. These effects reduce calcium overload, increasing ATP production and decreasing cytochrome C from mitochondria during ischemia. Hyperglycemia increases anti apoptotic Bcl-2 protein and reduces caspase-3 activity. The contents of HIF-1α mRNA and protein increase in diabetic heart. HIF-1α target genes which in turn improve cellular oxygenation (VEGF) and glucose metabolism (GLUT-1).

REFERENCES

1. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, Farzadfar F, Stevens GA, Lim SS, Riley LM, Ezzati M. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. Lancet 2011; 377: 568-577 [PMID: 21295844 DOI: 10.1016/S0140-6736(10)62036-3]

2. Bertoni AG, Tsai A, Kasper EK, Brancati FL. Diabetes and idiopathic cardiomyopathy: a nationwide case-control study. Diabetes Care 2003; 26: 2791-2795 [PMID: 14514581]

3. Qi D, Rodrigues B. Glucocorticoids produce whole body insulin resistance with changes in cardiac metabolism. Am J Physiol Endocrinol Metab 2007; 292: E654-E667 [PMID: 17077342]

4. An D, Rodrigues B. Role of changes in cardiac metabolism in development of diabetic cardiomyopathy. Am J Physiol Heart Circ Physiol 2006; 291: H1489-H1506 [PMID: 16751299]

5. Carvalho G, Pelletier P, Albacker T, Lachapelle K, Joanisse DR, Hatzakorzian R, Lattermann R, Sato H, Marette A, Schricker T. Cardioprotective effects of glucose and insulin administration while maintaining normoglycemia (GIN therapy) in patients undergoing coronary artery bypass grafting. J Clin Endocrinol Metab 2011; 96: 1469-1477 [PMID: 21346060 DOI: 10.1210/jc.2010-1934]

6. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T,
Schricker T. The association of preoperative glycemic control, intraoperative insulin sensitivity, and outcomes after cardiac surgery. J Clin Endocrinol Metab 2010; 95: 4338-4344 [PMID: 20650106 DOI: 10.1210/jc.2010-0135]

7 Rana OA, Byrne CD, Greaves K. Intensive glucose control and hypoglycaemia: a new cardiovascular risk factor? Heart 2014; 100: 21-27 [PMID: 23697655]

8 Deckers JW, van Domburg RT, Akkerhuis M, Nauta ST. Relation of admission glucose levels, short- and long-term (20-year) mortality after acute myocardial infarction. Am J Cardiol 2013; 112: 1306-1310 [PMID: 23866731 DOI: 10.1016/j.amjcard.2013.06.007]

9 Ravingerová T, Neckár J, Kolar F. Ischemic tolerance of rat hearts in acute and chronic phases of experimental diabetes. Mol Cell Biochem 2003; 249: 167-174 [PMID: 12956412]

10 Cao JJ, Hudson M, Jankowski M, Whitehouse F, Weaver RS, Rayfield EJ, Chesebro JH. Mechanisms determining the diabetic heart: too sweet for its own good? Circ Res 2010; 278: 1156-1165 [PMID: 2046798 DO1: 10.1093/circres/hkf035]

11 Bafy G, Miyashita T, Williamson JR, Reed JC. Apoptosis induced by withdrawal of interleukin-3 (IL-3) from an IL-3-dependent hematopoietic cell line is associated with reprogramming of intracellular calcium and is blocked by enforced Bcl-2 oncoprotein production. J Biol Chem 1993; 268: 6511-6519 [PMID: 8454620]

12 Feuvray D, Lopaschuk GD. Controversies on the sensitivity of the diabetic heart to ischemic injury: the sensitivity of the diabetic heart to ischemic injury is decreased. Cardiovasc Res 1997; 34: 113-120 [PMID: 9217880]

13 Rodrigues B, Rosa KT, Medeiros A, Schaan BD, Brum PC, De Angelis K, Irigoyen MC. Hyperglycemia can delay left ventricular dysfunction but not autonomic damage after myocardial infarction in rodents. Cardiovasc Diabetol 2011; 10: 26 [PMID: 21470409 DOI: 10.1186/1475-2840-10-26]

14 Murphy E, Perlman M, London RE, Steenbergen C. Amiloride delays the ischemia-induced rise in cytosolic free calcium. Circ Res 1991; 68: 1250-1258 [PMID: 1902148]

15 Murphy E, Steenbergen C. Mechanisms underlying acute protection from cardiac ischemia-reperfusion injury. Physiol Rev 2008; 88: 581-609 [PMID: 18391174 DOI: 10.1152/physrev.00024.2007]

16 Paulson D. The diabetic heart is more sensitive to ischemic injury. Cardiovasc Res 1997; 34: 104-112 [PMID: 9217879 DOI: 10.1016/S0008-6363(97)00018-7]

17 Semenza GL. Hypoxia-inducible factor 1 and the molecular physiology of oxygen homeostasis. J Lab Clin Med 1998; 131: 207-214 [PMID: 9523843 DOI: 10.1016/S0022-2143(98)90091-9]

18 Koch AE, Polverini PJ, Kuncel SL, Harlow LA, DiPietro LA, Elnner VM, Elnner SG, Strieter RM. Interleukin-8 as a macrophage-derived mediator of angiogenesis. Science 1992; 258: 1798-1801 [PMID: 1281554 DOI: 10.1126/science.1281554]

19 Mukaida N. Interleukin-8: an expanding universe beyond neutrophil chemotaxis and activation. Int J Hematol 2000; 72: 391-398 [PMID: 11197203]

20 Zeilhofer HU, Schorr W. Role of interleukin-8 in neutrophil signaling. Curr Opin Hematol 2000; 7: 178-182 [PMID: 10786656 DOI: 10.1097/00002251-200005000-00009]

21 Takami T, Merrick V, Petruzelli L. Signaling pathways involved in IL-8-dependent activation of adhesion through Mac-1. J Immunol 2002; 168: 4559-4566 [PMID: 11971003]

22 Ootie T, Takahashi N, Narula N, Ooie T, Kojima M, Shinohara T, Shigematsu S, Hara M, Yoshimatsu H, Saikawa T. Ischemia-induced translocation of protein kinase C-epsilon mediates cardioprotection in the streptozotocin-induced diabetic rat. Circ J 2003; 67: 955-961 [PMID: 14578604 DOI: 10.1253/circj.67.955]

23 Wang Y, Ashraf M. Role of protein kinase C in mitochondrial KATP channel-mediated protection against Ca2+ overload injury in rat myocardium. Circ Res 1999; 84: 1156-1165 [PMID: 10470940 DOI: 10.1161/01.RES.84.10.1156]

24 Xu M, Wang Y, Ayub A, Ashraf M. Mitochondrial K(ATP) channel activation reduces anoxic injury by restoring mitochondrial membrane potential. Am J Physiol Heart Circ Physiol 2001; 281: H1295-H1303 [PMID: 11514300]

25 Baines CP, Song CX, Zhang YF, Wang GW, Zhang J, Wang OL, Guo Y, Bolli R, Cardwell EM, Ping P. Protein kinase Cpsilon interacts with and inhibits the permeability transition pore in cardiac mitochondria. Circ Res 2005; 92: 873-880 [PMID: 15663490 DOI: 10.1161/01.RES.80.10.1156]

26 Frangogiannis NG. The immune system and cardiac repair. Pharmacol Res 2008; 58: 88-111 [PMID: 18620057 DOI: 10.1016/j.phrs.2008.06.007]

27 Yokoyama T, Vaca L, Rossen RD, Durante W, Hazarika P, Mann DL. Cellular basis for the negative inotropic effects of tumor necrosis factor-alpha in the adult mammalian heart. J Malignant cells and their relationship with the diabetic heart.
39 Engel D, Peshock R, Armstrong RC, Sivasubramanian N, Mann DL. Cardiac myocyte apoptosis provokes adverse cardiac remodeling in transgenic mice with targeted TNF overexpression. *Am J Physiol Heart Circ Physiol* 2004; 287: H1303-H1311 [PMID: 15317679 DOI: 10.1152/ajpheart.00053.2004]

40 Bujak M, Dobaczewski M, Chatila K, Mendoza LH, Li N, Reddy A, Frangogiannis NG. Interleukin-1 receptor type I signaling critically regulates infarct healing and cardiac remodeling. *Am J Pathol* 2008; 173: 57-67 [PMID: 18535174 DOI: 10.2353/ajpath.2008.070974]

41 Gwechenberger M, Mendoza LH, Youker KA, Frangogiannis NG, Smith CW, Michael LH, Entman ML. Cardiac myocytes produce interleukin-6 in culture and in viable border zone of reperfused infarctions. *Circulation* 1999; 99: 546-551 [PMID: 9927402 DOI: 10.1161/01.CIR.99.4.546]

42 Pithon-Curi TC, De Melo MP, Curi R. Glucose and glutamine utilization by rat lymphocytes, monocytes and neutrophils in culture: a comparative study. *Cell Biochem Funct* 2004; 22: 321-326 [PMID: 15338472 DOI: 10.1002/cbf.1109]

43 Alba-Loureiro TC, Munhoz CD, Martins JO, Cerchiaro GA, Scavone C, Curi R, Sannomiya P. Neutrophil function and metabolism in individuals with diabetes mellitus. *Braz J Med Biol Res* 2007; 40: 1037-1044 [PMID: 17665039 DOI: 10.1590/S0100-879X2006005000143]

44 King LM, Opie LH. Glucose and glycogen utilisation in myocardial ischaemia—changes in metabolism and consequences for the myocyte. *Mol Cell Biochem* 1998; 180: 3-26 [PMID: 9546626 DOI: 10.1016/A:100678019309]

45 Cave AC, Ingwall JS, Friedrich J, Liao R, Sause KW, Apstein CS, Eberli FR. ATP synthesis during low-flow ischemia: influence of increased glycolytic substrate. *Circulation* 2000; 101: 2090-2096 [PMID: 10790352 DOI: 10.1161/01.CIR.101.17.2090]

46 Rosenblatt-Velin N, Montessuit C, Papaioannou I, Terrand J, Lerch R. Postinfarction heart failure in rats is associated with upregulation of GLUT-1 and downregulation of genes of fatty acid metabolism. *Cardiovasc Res* 2001; 52: 407-416 [PMID: 11738057 DOI: 10.1016/S0008-6363(01)00393-5]

47 Chu LM, Osipov RM, Robich MP, Feng J, Oyamada S, Bianchi C, Sellke FW. Is hyperglycemia bad for the heart during acute ischemia? *J Thorac Cardiovasc Surg* 2010; 140: 1345-1352 [PMID: 20542299 DOI: 10.1016/j.jtcs.2010.05.009]

48 Di Lisa F, Blank PS, Colonna R, Gambassi G, Silverman HS, Stern MD, Hansford RG. Mitochondrial membrane potential in single living adult rat cardiac myocytes exposed to anoxia or metabolic inhibition. *J Physiol* 1995; 486 (Pt 1): 1-13 [PMID: 7562625]
