Review

The diabetic heart is more sensitive to ischemic injury

Dennis J. Paulson *

Department of Physiology, Midwestern University, 555 31st Street, Downers Grove, IL 60515, USA

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Abstract

Clinical studies have suggested that the diabetic heart is more sensitive to ischemic injury than the non-diabetic heart. However, results from a number of experimental studies using animal models of diabetes reported no change, increased or decreased sensitivity to ischemia. The purpose of this review is to discuss the possible explanations for this apparent discrepancy. Analysis of the conflicting literature on this subject reveals a pattern which suggests that the disparity of experimental findings stems from differences in the duration and severity of the diabetic state, the ischemic flow rate and whether fatty acids are provided as an exogenous substrate. It appears that short-term or mild diabetes is associated with decreased sensitivity to zero-flow ischemic injury. However, as the duration or severity of diabetes increases, this beneficial effect disappears. The diabetic heart also appears to be more vulnerable to injury during low-flow ischemia and when elevated fatty acids are present.

Keywords: Diabetes; Myocardial ischemia; Reperfusion; Contractile function

1. Clinical studies

Coronary artery disease is a major complication of diabetes mellitus, representing the cause of death in more than half of all patients with this disease [1]. This relationship is true in both insulin-dependent (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The presence of diabetes dramatically reduces survival after myocardial infarction, both in the hospital and over the long term [2–7]. The long-term mortality rate (3–5 years) after acute myocardial infarction has been reported to be 2–3 times higher in individuals with diabetes compared with non-diabetics [8–13]. Patients with diabetes are more likely to have angiographically confirmed silent coronary artery disease with active myocardial ischemia than non-diabetics [14–18]. This detrimental effect of diabetes on the heart is most pronounced in young diabetics [3,4] and women. Women, who typically have a lower risk of developing coronary artery disease, lose this advantage when they become diabetic [13,19–21]. Diabetic women are more vulnerable to re-infarction and death after myocardial infarction than are diabetic men, even though they may exhibit less left ventricular dysfunction [22]. The mortality rate of diabetic patients after coronary artery bypass grafting is about twice that of non-diabetic patients during both the early and late phases after the operation [22]. Diabetic patients are more prone to develop ventricular tachyarrhythmias and high-degree atrioventricular block [23–26]. Using myocardial enzyme release or QRS score to estimate infarct size, diabetic patients were found to have infarct sizes similar to or even smaller than those of non-diabetics, but twice the mortality [27–29].

Evidence suggests that there is a significant association between the degree of metabolic control, as indicated by levels of glycosylated hemoglobin and hyperlipidemia, and the prevalence of cardiovascular disease [30–38]. Hypertension is also a major predictor of cardiovascular disease in diabetes [39]. In fact, it has been shown that the coexistence of diabetes and hypertension increases the risk of left ventricular hypertrophy and cardiac failure more than either disease alone [40–44].
2. Experimental studies

Despite the overwhelming clinical data indicating that the diabetic heart is more sensitive to ischemic injury, a controversy has arisen concerning the sensitivity of the ischemic heart from experimental animal models of diabetes. The diabetic heart isolated from experimental animal models of diabetes will fail faster than control hearts when exposed to hypoxia or a reduction in coronary flow [45–48]. However, studies on the response of the diabetic heart subjected to a period of ischemia followed by reperfusion have produced inconsistent results. Some studies have shown that the diabetic heart is less sensitive to ischemic injury (Table 1), while others have indicated that the diabetic heart is more sensitive (Table 2). Others have found no differences in the vulnerability of the diabetic heart to ischemia and reperfusion relative to non-diabetics (Table 3). Even studies from the same laboratory have produced conflicting results [49–52]. The explanation for these varied results is not certain; but after reviewing the literature, it appears that there are some common characteristics of the studies that have shown the diabetic heart to be less sensitive to ischemia. These characteristics are different from those found in the studies that have shown the diabetic heart to be more sensitive to ischemia. It appears that the sensitivity of the diabetic heart to ischemia is determined by the duration and severity of the diabetic state, the degree of ischemia, and/or the levels of exogenous fatty acids.

2.1. Less sensitive to ischemic injury

Tani and Neely [53] were the first to find evidence that the diabetic heart exposed to zero-flow ischemia exhibited enhanced recovery of cardiac contractile function with reperfusion as compared to hearts from non-diabetic rats. A number of subsequent studies from different laboratories have provided evidence that the diabetic heart is less sensitive to ischemic injury [49,50,54–60]. In all of these studies, streptozotocin (STZ) was used to induce a model of IDDM. The duration of diabetes was 6 weeks or less and a model of global zero-flow ischemia was produced in isolated perfused hearts with only glucose or glucose plus pyruvate as exogenous substrates. There was one study which assessed infarct size of NIDDM rats subjected to in vivo zero-flow regional ischemia which found smaller infarcts in NIDDM rats relative to aged-matched non-diabetic [57].

Several mechanisms have been proposed to explain why diabetic hearts were less sensitive to ischemic injury than control hearts in these studies. For example, the degree of intracellular acidity and how the cell handles this acidosis may explain why diabetic hearts exhibit improved functional recovery from zero-flow ischemia relative to non-diabetic hearts [54]. During ischemia, H⁺ accumulate due, in part, to enhanced glycolytic flux. One mechanism to rid the cell of this excess H⁺ is the Na⁺/H⁺ exchanger. With reperfusion, the activation of this exchanger would result in massive entry of Na⁺ into the cardiac myocyte. The increase in levels of intracellular Na⁺ would reduce with the gradient for the reverse mode of the Na⁺/Ca²⁺ exchanger which may lead to Ca²⁺ overload and irreversible injury. The diabetic heart reportedly has decreased activity of both the Na⁺/H⁺ and Na⁺/Ca²⁺ exchangers. Thus, during zero-flow ischemia followed by reperfusion, the diabetic heart may accumulate less sodium and calcium, which should ultimately improve the recovery of contractile function [54,55,61,62].

Other mechanisms also could account for enhanced recovery of the diabetic heart from zero-flow ischemia with reperfusion relative to control hearts. Increased myocardial content of the free-radical-scavenging enzymes, catalase and glutathione reductase, with diabetes may be a factor [63–65]. It has been suggested that the prolonged

Table 1

Studies indicating that the diabetic heart is less sensitive to ischemic injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Model, dose (mg/kg)</th>
<th>Duration of diabetes</th>
<th>Ischemic substrates (mM)</th>
<th>Ischemic flow and duration</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tani and Neely [53]</td>
<td>rat-STZ, 60</td>
<td>2 days</td>
<td>11 glucose, 5 pyruvate</td>
<td>zero flow, 30 to 60 min</td>
<td>HR and PSP</td>
</tr>
<tr>
<td>Khandoudi et al. [54,55]</td>
<td>rat-STZ, 40</td>
<td>3–4 wk</td>
<td>11 glucose</td>
<td>zero flow, 30 min</td>
<td>CO, HR and PSP</td>
</tr>
<tr>
<td>Kusama et al. [60]</td>
<td>rat-STZ, 65</td>
<td>3 wk</td>
<td>11 glucose, 5 pyruvate</td>
<td>regional zero flow, 5 and 10 min</td>
<td>arrhythmias</td>
</tr>
<tr>
<td>Tosaki et al. [58,59]</td>
<td>rat-STZ, 65</td>
<td>2 wk</td>
<td>10 glucose</td>
<td>zero flow, 30 min</td>
<td>arrhythmias</td>
</tr>
<tr>
<td>Gamble and Lopaschuk [49]</td>
<td>rat-STZ, 55</td>
<td>6 wk</td>
<td>11 glucose</td>
<td>30 min zero flow</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Lopaschuk [50]</td>
<td>rat-STZ, 60</td>
<td>6 wk</td>
<td>11 glucose</td>
<td>zero flow, 25 min</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Liu et al. [57]</td>
<td>neonatal NIDDM, rat-STZ, 90</td>
<td>11–12 mth</td>
<td>in vivo substrates</td>
<td>regional zero flow, 30 and 45 min</td>
<td>infarct size</td>
</tr>
<tr>
<td>Tilton et al. [56]</td>
<td>rabbits-alloxan, 125</td>
<td>6 mth</td>
<td>8 glucose; 3 pyruvate</td>
<td>zero flow, 40 min</td>
<td>LVP</td>
</tr>
</tbody>
</table>

HR = heart rate; PSP = peak systolic pressure; CO = cardiac output; LVP = left ventricular pressure.
ventricular action potential of the diabetic heart under normoxic and ischemic conditions may decrease the susceptibility to reperfusion arrhythmias [58,60]. However, other studies showed that hypoxia in isolated cardiac diabetic myocytes does not elicit a prolongation of the action potential, but rather a shortening occurs in diabetic as well as control myocytes [66]. It has been proposed that alterations in ATP-sensitive K+ channels with diabetes may contribute to the shortening of the action potential shortening in response to hypoxia [67], which would be expected to result in an enhanced susceptibility to arrhythmias.

### 2.2. More sensitive to ischemic injury

In contrast to the above studies, a number of other investigators found evidence that the diabetic heart was more sensitive to ischemic reperfusion injury (Table 2). These studies had a number of factors in common. First of

<table>
<thead>
<tr>
<th>Study</th>
<th>Model, dose (mg/kg)</th>
<th>Duration of diabetes</th>
<th>Ischemic substrates (mM)</th>
<th>Ischemic model</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearse et al. [47]</td>
<td>rat-STZ, 70</td>
<td>1 wk</td>
<td>11 glucose</td>
<td>anoxia, 30 min</td>
<td>aortic flow</td>
</tr>
<tr>
<td>Mihchizuki et al. [78]</td>
<td>rat-STZ, 50</td>
<td>1 wk</td>
<td>11 glucose</td>
<td>low flow: 52 ml/min, 10 min</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Hekimian et al. [73]</td>
<td>rat-alloxan, 45</td>
<td>3 wk</td>
<td>11 glucose; 0.1 palmitate</td>
<td>zero flow</td>
<td>arrhythmias</td>
</tr>
<tr>
<td>Tosaki et al. [58,59]</td>
<td>rat-STZ, 65</td>
<td>8 wk</td>
<td>10 glucose</td>
<td>zero flow, 30 min</td>
<td>LVP</td>
</tr>
<tr>
<td>Paulson et al. [51]</td>
<td>rat-STZ, 60</td>
<td>8 wk</td>
<td>11 glucose</td>
<td>low flow: 1.0 ml/min, 75 min</td>
<td>CO, PSP</td>
</tr>
<tr>
<td>Heijins et al. [110]</td>
<td>rat-STZ, 50</td>
<td>7 wk</td>
<td>11 glucose</td>
<td>zero flow, 45 min</td>
<td>LVP</td>
</tr>
<tr>
<td>Higuchi et al. [79–81]</td>
<td>rat-STZ, 60</td>
<td>8–12 days</td>
<td>11 glucose</td>
<td>low flow: 1 ml/min, 60 min</td>
<td>LVP</td>
</tr>
<tr>
<td>Shimab-ukuro et al. [82]</td>
<td>rat-STZ, 60 mg/kg</td>
<td>8–14 wk</td>
<td>11 glucose</td>
<td>low flow: 1 ml/min, 10 min</td>
<td>LVP</td>
</tr>
<tr>
<td>Broderick et al. [72]</td>
<td>spontaneous ly diabetic BB Wistar</td>
<td>12 wk</td>
<td>30 glucose, 1.2 palmitate</td>
<td>low flow: 0.5 ml/min, 60 min</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Pieper [74]</td>
<td>rat-STZ, 100</td>
<td>48 h</td>
<td>5.5 glucose</td>
<td>zero flow, 20 min</td>
<td>LVP</td>
</tr>
<tr>
<td>Lopaschuk et al. [50]</td>
<td>rat-STZ, 60</td>
<td>6 wk</td>
<td>11 glucose, 1.2 palmitate</td>
<td>zero flow, 25 min</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Forrat et al. [70]</td>
<td>dog-STZ, 30</td>
<td>11 wk</td>
<td>in vivo substrates</td>
<td>regional in vivo, 2 h</td>
<td>infarct size</td>
</tr>
<tr>
<td>Bakth et al. [68]</td>
<td>dog-alloxan serial low doses</td>
<td>1 yr</td>
<td>In vivo substrates</td>
<td>regional in vivo</td>
<td>arrhythmias</td>
</tr>
<tr>
<td>Haider et al. [69]</td>
<td>dog-alloxan serial low doses</td>
<td>36 wk</td>
<td>in vivo substrates</td>
<td>regional in vivo, 1 h</td>
<td>SV, EDP</td>
</tr>
</tbody>
</table>

HR = heart rate; PSP = peak systolic pressure; CO = cardiac output; LVP = left ventricular pressure; EDV = end-diastolic pressure.

Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Model, dose (mg/kg)</th>
<th>Duration of diabetes</th>
<th>Substrates</th>
<th>Ischemic flow</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogel and Apstein [111]</td>
<td>rabbits–alloxan, 125</td>
<td>8–16 wk</td>
<td>0.4 glucose, 1 lactate, 0.25 octanoic</td>
<td>low flow: 90% reduction, 90 min</td>
<td>LVP and infarct size</td>
</tr>
<tr>
<td>Beatch and McNiell [112]</td>
<td>rat-STZ, 55</td>
<td>9 wk</td>
<td>in vivo substrates</td>
<td>regional in vivo</td>
<td>arrhythmias</td>
</tr>
<tr>
<td>Paulson et al. [52]</td>
<td>rat-STZ, 60</td>
<td>8 wk</td>
<td>22 glucose, 1.2 palmitate</td>
<td>low flow: 0.85 ml/min, 90 min</td>
<td>CO, LVP</td>
</tr>
<tr>
<td>Pijl et al. [113]</td>
<td>rat-STZ, 60</td>
<td>8 wk</td>
<td>11 glucose</td>
<td>low flow: 90% reduction, 30 min</td>
<td>CO, LVP</td>
</tr>
<tr>
<td>Peper and Gross [114–116]</td>
<td>rat-STZ, 55</td>
<td>9 wk</td>
<td>5.5 glucose</td>
<td>zero flow I</td>
<td>LVP, HR</td>
</tr>
<tr>
<td>Lopaschuk [50]</td>
<td>rat-STZ, 60</td>
<td>6 wk</td>
<td>11 glucose, 1.2 palmitate</td>
<td>zero flow I, 25 min</td>
<td>HR × PSP</td>
</tr>
<tr>
<td>Tosaki et al. [58]</td>
<td>rat-STZ, 65</td>
<td>4 and 6 wk</td>
<td>10 glucose</td>
<td>zero flow, 30 min</td>
<td>arrhythmias</td>
</tr>
</tbody>
</table>

HR = heart rate; PSP = peak systolic pressure; CO = cardiac output; LVP = left ventricular pressure.
all, the duration of diabetes was usually longer, a more severe model of diabetes was used, or a model of low-flow ischemia was used. Even the in vivo studies, which employed zero-flow regional ischemia, were all performed in diabetic dogs where the degree of collateral blood flow was greater than most species (e.g., rat) [68–70]. Thus, regional zero-flow ischemia in the dog was more likely to exhibit low-flow characteristics. In addition, elevated fatty acids were present in the in vivo studies as well as some of the in vitro perfused heart studies. The addition of insulin to the perfusion medium also may be a complicating factor. These experimental conditions provided a situation where the diabetic heart was now more sensitive to ischemic injury.

One of the main factors that may affect the ability of a diabetic heart to recover from a period of ischemia with reperfusion appears to be the duration and severity of the diabetic state. In nearly all of the studies which have shown the diabetic heart to be more sensitive to ischemic injury, the duration of diabetes was 6 weeks or more [50,68–72,110]. In those studies which used a shorter duration of diabetes, but found that the diabetic heart was more sensitive to ischemic injury, the dose of STZ or alloxan was relatively high and the severity of the diabetic state was greater [47,73,74]. This relationship between the duration of the diabetic state and recovery of the diabetic heart from ischemia was most clearly demonstrated by Tosaki et al. [58]. In this study, following 2, 4, 6, and 8 weeks of diabetes, hearts were isolated and subjected to 30 min global zero-flow ischemia followed by reperfusion. In the 2-week diabetics, a reduction in the incidence of ventricular fibrillation and tachycardia as well as improved contractile function was found relative to age-matched controls. This beneficial effect of diabetes on the ischemic heart was not observed in 4- and 6-week diabetic rats. After 8 weeks, the diabetic hearts exhibited depressed recovery after global zero-flow ischemia relative to control hearts. The severity of diabetes, as indicated by plasma glucose, appeared to worsen as the duration of diabetes increased. The relationship between the severity of the diabetic condition and the recovery from ischemia can also be seen in another study where a very high dose of STZ was used. After only 48 h of diabetes, these animals were severely diabetic and ketoacidotic [74]. These diabetic hearts when subjected to 20 min of zero-flow ischemia exhibited depressed recovery of contractile performance with reperfusion as compared to non-diabetic hearts. It appears that the protective mechanisms described above allow the diabetic heart to be more resistant to zero-flow ischemia/reperfusion injury during the early phases of mild diabetes. However, as the duration or severity of diabetes increases, these adaptive mechanisms are not as effective and the protection is eventually lost. The diabetic heart then becomes more sensitive to ischemic injury.

The degree of flow reduction during ischemia may also play a role in determining the ability of control and diabetic hearts to recovery from a period of ischemia and reperfusion. During zero-flow ischemia, glycolysis and subsequent acidosis may be detrimental as described above. The diabetic heart, because of reduced glycolysis and sarcolemmal Na⁺/H⁺ and Na⁺/Ca²⁺ exchange activities, may be more resistant to mechanisms responsible for cell damage and death during zero-flow ischemia. However, during low-flow ischemia, the degree of intracellular acidosis is less because of the washout of lactate. Under these conditions, glycolysis may be beneficial, particularly to a diabetic heart that already has reduced rates of glycolysis. Thus, the diabetic heart may be more vulnerable to a reduction in glycolysis during low-flow ischemia than a non-diabetic heart. There are also other differences between low-flow and zero-flow that may account for the different results between control and diabetic hearts. Low-flow ischemia causes build-up of both myocardial long-chain acyl carnitine and long-chain acyl CoA while zero-flow ischemia does not alter levels of long-chain acyl carnitine and produces only a small transient increase in long-chain acyl CoA [75]. Although controversial, the accumulation of these lipid intermediates has been implicated in ischemic damage [76] and the induction of arrhythmias [77]. High-energy phosphate depletion is also greater in zero-flow ischemia. In those studies that found the diabetic heart to be more sensitive to ischemic injury, a model of low-flow ischemia was used [47,51,71,78–82]. It is suggested that the cellular responses to low-flow ischemia are more deleterious to the diabetic heart than non-diabetic hearts, resulting in less recovery of contractile function.

The role of elevated exogenous fatty acids in ischemic reperfusion injury may be of particular importance in the diabetic heart since hyperlipidemia is a common complication of this condition. In addition, the detrimental effects of excess fatty acids may be different in control and diabetic hearts and may also be different in zero-flow and low-flow ischemic models. For example, it has been suggested that an excess of free fatty acids could increase the severity of ischemic damage and possibly be arrhythmogenic [83]. However, excess fatty acids may only be arrhythmogenic in models of low-flow ischemia, since it has been shown that elevated exogenous fatty acids actually decreased the incidence of arrhythmias in non-diabetic hearts subjected to zero-flow ischemia [84]. We have shown previously that the presence of elevated exogenous free fatty acids will decrease the recovery of contractile function in control hearts exposed to low-flow ischemia, but not zero-flow ischemia [75]. Diabetic hearts perfused under diabetic substrate conditions (elevated glucose and fatty acids) and subjected to 75 min of low-flow ischemia followed by 30 min of reperfusion recovered less contractile function than control hearts [51]. Lopaschuk et al. [50] showed that a high level of fatty acids during the actual period of zero-flow ischemia in control hearts was not detrimental to the subsequent recovery of function during
reperfusion. However, in diabetic hearts, the presence of high levels of fatty acids during zero-flow ischemia and reperfusion resulted in depressed recovery with reperfusion. The explanation why high levels of exogenous fatty acids have a depressant effect on diabetic rat hearts, but not in the control hearts, is unclear and needs further investigation. By inhibiting glucose utilization, increased exogenous fatty acids may adversely affect overall energy metabolism of the ischemic and reperfused heart. Since the diabetic heart already has decreased glycolytic and glucose oxidative rates, fatty acids may be even more detrimental to an ischemic-reperfused diabetic heart than a control heart. Excess fatty acids may also cause increased accumulation of long-chain acyl CoA and carnitine esters in the diabetic heart, which may enhance ischemic-reperfusion damage and the induction of arrhythmias [76,77].

2.3. No differences in the response to ischemic injury

Because of the multiple factors that differentially affect the ability of control and diabetic hearts to recover from a period of ischemia and reperfusion, it is not surprising that some studies have found no difference in the ability of control and diabetic hearts to recover from a period of ischemia and reperfusion (Table 3). However, if one examines these studies and the apparent inconsistencies, particularly those from the same laboratory, the results support many of the above assertions. For example in my laboratory, we have obtained data indicating no differences between control and diabetic hearts, which appeared to conflict with our previous findings that 90 min of low-flow ischemia followed by 30 min of reperfusion resulted in less recovery of contractile function in diabetic hearts than control hearts [51]. These rats were diabetic for 10 weeks and the hearts were perfused with buffer containing diabetic concentrations of glucose (22 mM) and palmitate (1.2 mM). However, in a separate study, using the same dose of streptozotocin and duration of diabetes, we found that the recovery of cardiac contractile performance between diabetic and control rats was similar [52]. The only difference between these two studies was the coronary flow rate during ischemia. In the first study, the ischemic coronary flow rate was 1.0 ml/min for both control and diabetic rats. However, because of differences in heart weights between control and diabetic rats, the normalized ischemic flow rates were 4.0 and 4.9 ml/min/g dry wt, respectively. Consequently, the diabetic heart actually had higher ischemic flow rates than control, but recovered less. In the second study, coronary flow rates were adjusted for heart weight differences between control and diabetic rats: 1.18 ml/min for control and 0.85 ml/min for diabetic or 4.4 ml/min/g dry wt for both groups. Under these conditions, there were no differences in the recovery of contractile function between control and diabetic hearts. These findings suggest that the diabetic heart, when subjected to low-flow ischemia, is more vulnerable to damage. However, when the ischemic flow rate is decreased further, they have the ability to withstand the acidosis and the other mechanisms responsible for cell injury.

Another factor that may affect the ability of the diabetic heart to recover from a period of ischemia and reperfusion is the severity of the diabetic state. This point is supported by the conflicting studies from Lopaschuk’s laboratory [49,50]. In one study, diabetes was induced in rats using 55 mg/kg STZ [49]. After 6 weeks of diabetes, hearts were perfused with 11 mM glucose, 1.2 mM palmitate and 20 μU/ml insulin and subjected to 30 min of zero-flow ischemia followed by 60 min of reperfusion. The diabetic hearts exhibited an enhanced recovery of heart rate and peak systolic pressure relative to control. However, in a different study, this same group found no difference in the ability of 6-week diabetic hearts to recover from an identical period of ischemia and reperfusion with the same buffer substrate conditions [50]. The only difference between these two studies was the dose of STZ used to induce diabetes. The latter study used a dose of 60 mg/kg which presumably would have produced a more severe form of diabetes than the previous study which used a dose of 55 mg/kg. Unpublished observations from my laboratory have indicated that this small difference in the dose of STZ will affect the severity of the cardiac depression seen at 6 weeks.

3. Other factors contributing to ischemic injury in the diabetic heart

There are a number of factors that may account for the differences amongst the various clinical and experimental studies on the sensitivity of the diabetic heart to ischemia. There are many differences between humans and experimental animals in terms of characteristics of the diabetic state, nutritional status and cardiac function. Other factors contributing to the high post-myocardial-infarct mortality among diabetic patients may be the combined presence of ischemia and diabetic cardiomyopathy [1,24,85–87]. Substantial evidence has been accumulated that substantiates the presence of myocardial dysfunction in diabetic patients in the absence of ischemic, valvular and hypertensive heart disease [88–93]. A number of autopsy studies have demonstrated the existence of a specific cardiomyopathy in diabetic patients without coronary artery disease. Numerous other clinical studies, evaluating cardiac function of diabetics, have demonstrated the existence of altered contractile function in diabetic patients, particularly in response to a stress [94–97]. In these patients, diastolic dysfunction appears to precede systolic dysfunction [98]. Thus, when a compromised diabetic heart is subjected to ischemia and reperfusion, it may be more likely to fail. It is interesting to note that 6 weeks of diabetes appears to be the cut-off point where the IDDM diabetic rat heart no longer exhibits enhanced recovery from ischemia. This time point coin-
cides with the induction of the intrinsic cardiac depression associated with this model of diabetes [99]. It has also been shown that a correlation exists between the severity of the diabetic state and the degree of cardiomyopathy [100].

Another explanation for the apparent discrepancy between the clinical observations and some of the in vitro perfused heart studies on diabetic hearts is the lack of blood components. In vivo, the diabetic heart is perfused with platelets, neutrophils and other blood components which may contribute to the enhanced vulnerability of the diabetic heart to ischemia. Both platelets and neutrophils have been suggested to play a key role as mediators of cellular damage during ischemia and reperfusion.

Diabetic patients have altered platelet and fibrinolytic function; these disturbances may also contribute to the mortality and the high rate of recurrences [101,102]. Platelet aggregation, secretion and turnover are increased while platelet survival is decreased by diabetes [103–106]. Experimental studies have shown that addition of platelets to the perfusion medium of isolated perfused rabbit hearts enhanced ischemic damage [107]. The mechanism for the deleterious effects of platelets on the ischemic reperfused experimental studies have shown that addition of platelets to the perfusion medium of isolated perfused rabbit hearts enhanced ischemic damage [107]. The mechanism for the deleterious effects of platelets on the ischemic reperfused heart may be related to the release of platelet activating factor which has been shown to impair myocardial contractile function and be arrhythmogenic. Contributing to the altered platelet function in the diabetic may be elevated levels of plasminogen activator inhibitor (PAS-1) [108]. PAS-1 is a fast-acting inhibitor of fibrinolysis which alters the balance between thrombosis and fibrinolysis in favor of vascular occlusion. This compound is synthesized both by vascular endothelium and by the liver. Levels of PAS-1 have been shown to be elevated in young survivors of myocardial infarction and to predict the recurrence of infarction. Those diabetic patients with elevated PAS-1 levels were more likely to have persistent occlusion and have re-infarction during the hospital stay.

Neutrophils isolated from diabetic animals and humans are less deformable and generate larger quantities of oxygen radicals than neutrophils from non-diabetics [109]. A greater percentage of circulating neutrophils are carried in the blood in the activated state. In addition, ischemia and reperfusion have been shown to elicit significantly enhanced leukocyte adhesion, emigration and albumin leakage in diabetic rats.

4. Summary

Based upon the available evidence, it appears that the sensitivity of the diabetic heart to ischemic injury depends upon the experimental conditions. With only a few exceptions, most studies showing that the diabetic heart is less sensitive to ischemic injury used a model of short-duration diabetes, glucose was the only metabolic substrate available and/or zero-flow ischemia was used. Other studies showed that if a longer duration of diabetes was used, if fatty acids were present and/or a model of low-flow ischemia was used, the diabetic heart was more sensitive to ischemic injury than non-diabetic hearts. These findings suggest that there are multiple causes of ischemic injury in both control and diabetic hearts. Depending on the ischemic model, the primary cause of injury may be different. Clinically, diabetes is a long-term condition. The diabetic heart is always perfused with fatty acids and, in most cases, elevated exogenous lipids are present. In addition, most cases of clinical ischemia involve a form of partial coronary artery occlusion resulting in low-flow ischemia, at least initially. Thus, the finding that the diabetic heart is less sensitive to ischemia does not reflect the in vivo clinical condition.

References


