Controversies on the sensitivity of the diabetic heart to ischemic injury: the sensitivity of the diabetic heart to ischemic injury is decreased

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Abstract

Controversy exists as to whether the diabetic heart is more or less sensitive to ischemic injury. Although a considerable number of experimental studies have directly determined the effects of ischemia on the diabetic heart, there is still no general agreement as to whether metabolic changes within the myocardium contribute to the severity of ischemic injury. This paper reviews the evidence suggesting that the diabetic heart can actually be less sensitive to an episode of severe ischemia. Possible reasons for this decreased sensitivity to injury are discussed, which include a decreased accumulation of glycolytic products during ischemia (lactate and protons), as well as alterations in the regulation of intracellular pH in the diabetic heart. Based on existing studies, we suggest that although impaired glucose metabolism in the diabetic heart contributes to injury in hypoxic hearts or in hearts subjected to low-flow ischemia, diabetes-induced decreases in glycolysis can actually be beneficial to the diabetic heart during and following a severe ischemic episode. A decreased clearance of protons via the Na⁺/H⁺ exchanger may also contribute to the decreased sensitivity to ischemic injury in the diabetic heart.

Keywords: Diabetes; Myocardial ischemia; Na⁺/H⁺ exchange; pH, intracellular

1. Introduction

Diabetics have a significantly greater incidence and severity of angina, acute myocardial infarctions (AMI), congestive heart failure, and other manifestations of atherosclerosis than the non-diabetic population [1–5]. Even in the absence of ischemic heart disease, impairment of ventricular performance (diabetic cardiomyopathies) can occur [1,6–9]. Although an increased incidence of atherosclerosis in diabetics contributes to these complications, population-based studies have shown that non-coronary factors are also important contributing factors [10]. As an example, the incidence and severity of complications associated with AMI are greater in the diabetic population even though the size of the infarct is not significantly different, and may even be smaller, compared to the non-diabetic population [11–13]. Diabetes-induced changes within the heart appear to be important contributing factors to injury during and following an AMI [7,10–12,14–18]. Both heart failure following an AMI and diabetic cardiomyopathies have been correlated with the acute metabolic status of the patient [12,19].

Although epidemiological data and clinical studies have convincingly demonstrated that the diabetic has increased susceptibility to ischemic injury, experimental studies are inconsistent in this regard, demonstrating both an increased or decreased sensitivity of the diabetic heart to ischemic injury. This review will make a case for the observation that the diabetic heart is less sensitive to ischemic injury and we will discuss potential subcellular mechanisms that may be responsible for this decreased sensitivity to ischemic injury.
2. Experimental studies involving diabetes and myocardial ischemia

Although clinical evidence suggests that the diabetic heart is more sensitive to ischemic injury, experimental studies are divided on this issue. In vivo studies have not resolved this issue. In alloxan-induced diabetic dogs, Haider et al. [20] showed that occlusion of the left anterior descending coronary artery results in a greater decrease in stroke volume and work, as well as a greater rise in end-diastolic pressure and volume, than in control dogs. This occurs despite comparable size of the ischemic area. However, in open-chested streptozotocin-induced diabetic rats, infarct size has been shown to be substantially reduced compared to control rats following a 35–45 min period of left coronary artery occlusion [21].

Although in vivo studies investigating the effects of diabetes on severe ischemia are controversial, in vitro studies are more consistent in demonstrating that diabetic hearts are less susceptible to injury following a severe episode of ischemia. Prior to defending this statement, we feel it is important to point out that diabetic hearts can be more susceptible to ischemic injury if they are subjected to mild ischemia, moderate ischemia, hypoxia or anoxia [22–29], see review by Dennis Paulson in this issue). It is also important to point out many of the studies which suggest that the diabetic heart is more sensitive to ischemic injury are measuring experimental parameters of injury during the actual ischemic period, as opposed to during reperfusion following ischemia. As will be discussed below, most of the studies showing that the diabetic heart is not more sensitive to ischemic injury have monitored the recovery of mechanical function following a severe ischemic episode. Confusing this issue further is the fact that most of the experimental studies which have addressed this topic have used widely differing experimental conditions. These studies not only have differences in the severity of ischemia, but also differences in the duration of the diabetes and the isolated heart perfusion conditions. This latter factor is important since the sensitivity of the diabetic heart to ischemia is related to the reliance of the heart on fatty acids as an energy substrate [27,28]. In this regard, many of the studies that have addressed the issue of the sensitivity of the diabetic heart to ischemic injury have not included fatty acids in the perfusion medium. It also needs to be recognized that all of the isolated heart studies that use crystalloid perfusion media do not reproduce the same environment as the blood-perfused heart seen in vivo. However, the importance of blood perfusion versus crystalloid perfusion in altering the sensitivity of the diabetic heart to ischemic injury has yet to be directly addressed.

A number of studies from various laboratories have shown that hearts from diabetic rats will recover to the same degree as non-diabetic hearts following an episode of no-flow or very-low-flow ischemia [30–34]. In fact, depending on the experimental conditions, the diabetic rat heart can actually be more resistant than non-diabetic hearts to an episode of severe ischemia [21,35–37]. Tani and Neely [35] showed that if isolated hearts from streptozotocin-diabetic rat hearts were subjected to a period of no-flow ischemia, recovery of function was significantly better than in non-diabetic hearts subjected to the same protocol. Similar results were also obtained from our laboratories [36,37]. A recent study by Liu et al. [21] has also demonstrated that diabetic rat hearts are more readily preconditioned than control hearts, suggesting that metabolic changes at the level of the myocardium can contribute to ischemic injury.

As pointed out, the issue of whether the diabetic heart is more resistant to a severe episode of ischemia is still controversial, and it should be noted that other investigators have demonstrated that the mechanical function of ischemic hearts from diabetic rats can be depressed during recovery from a severe ischemia [38,39]. A number of possible explanations have been proposed as to why the myocardium of the diabetic is more sensitive to ischemic injury (see accompanying paper by D. Paulson). An increased susceptibility to free radicals and eicosanoid-mediated injury are two mechanisms which have been proposed [38,39]. Alterations in control of intracellular pH and Ca2+ handling may also be important. However, as will be discussed, alterations in the latter two parameters may in fact decrease the sensitivity of the diabetic heart to ischemic injury [35].

3. Effects of diabetes on energy substrate use in the ischemic and reperfused ischemic heart

Myocardial energy substrate utilization by the heart is a highly regulated process which is primarily controlled by the energy demand of the muscle and the energy substrate supply to the heart. Normally, fatty acids and glucose are the primary energy substrates of the heart, with fatty acids accounting for 50–70% of the total oxygen consumption. In diabetes, however, glucose utilization is markedly reduced and fatty acids account for 90–99% of the total myocardial oxygen consumption (see review by Stanley et al. in this issue). One reason for this decrease in glucose utilization is a decrease in insulin-dependent glucose uptake. Another key reason for the decreased use of glucose is the inhibition of glycolytic flux and glucose oxidation due to increased circulating and endogenous levels of fatty acids [40,41]. Use of fatty acids for mitochondrial oxidative metabolism results in a marked decrease in both pyruvate dehydrogenase activity, the first irreversible reaction in the mitochondrial oxidation of glucose, and phosphofructokinase activity, the rate-limiting step in glycolysis [41]. Inhibition of pyruvate dehydrogenase by fatty acids is primarily due to an increase in the intramitochondrial acetyl CoA/CoA ratio [40,41]. Inhibition of phosphofructokinase activity by fatty acids is primarily medi-
ated by an increase in citrate levels [42] and a decrease in fructose 2,6-bisphosphate levels [43].

During ischemia, oxidative metabolism of fatty acids and glucose decreases with a concomitant increase in glycolysis. It has long been recognized that anaerobic glycolysis can provide an important source of ATP production in ischemic myocardium (see Ref. [44] for review). However, a number of studies have challenged the theory that increasing glycolysis during the actual ischemic event is beneficial. Neely and Grototyohann [45] demonstrated that accumulation of glycolytic products in situations of very-low-flow or no-flow ischemia may actually be detrimental to the heart. Accumulation of lactate, and the accompanying decrease in myocardial pH may contribute to myocardial cell injury [45]. Furthermore, decreasing glycolysis by depleting the myocardial glycogen pool prior to ischemia results in a decrease in lactate accumulation during ischemia, and an enhanced recovery of mechanical function during reperfusion. Studies both supporting and refuting the involvement of glycolytic products have appeared in the literature since this initial report (see Ref. [30] for review). This issue is relevant to diabetes, since marked changes in glycolysis occur in the diabetic heart [29,46,47]. In this setting of severe ischemia it is possible that decreased glycolytic rates may actually be beneficial to the heart.

Glycolytic rates during ischemia are also dependent on the levels of glycogen in the heart prior to ischemia. However, the issue of whether pre-ischemic glycogen levels are beneficial or detrimental to the outcome of ischemic injury is controversial [45,48]. Whether high glycogen pre-ischemia contributes to ischemic injury appears to depend on the severity of ischemic injury, with low glycogen levels being beneficial if hearts are subjected to a severe no-flow ischemia. These low levels of glycogen will decrease the potential for glycolytic product accumulation during an episode of severe ischemia. The relationship between pre-ischemic glycogen levels in the diabetic rat heart and ischemic injury has yet to be clearly established. Pre-ischemic glycogen levels can be elevated in the diabetic rat heart. A recent study by Higuchi et al. [49] has shown that in chronically streptozotocin-diabetic rats (6 weeks duration) glycogen levels are approximately twice the levels seen in control hearts or diabetic rats of 1-week duration. If hearts were subjected to low-flow ischemia, during the first 20 min of ischemia diastolic tension was less in the 6-week than in the 1-week diabetic rats. However, at the end of 60 min of underperfusion diastolic tension increased twice as much. These authors concluded that high glycogen helps delay the onset of injury, but that the degree of injury depends on the duration of diabetes.

When looking at the sensitivity of hearts to ischemic injury, it is important to consider the experimental conditions chosen to study glycolytic product accumulation during ischemia. Of importance is the fact that high levels of fatty acids markedly decrease myocardial glucose utilization. If hearts are perfused with physiological concentrations of fatty acids a 12-fold decrease in glucose utilization under aerobic conditions occurs compared to rates seen in hearts perfused in the absence of fatty acids [50]. In hearts perfused in the presence of relevant concentrations of fatty acids, glycolytic product enhancement of ischemic injury may only become important if glucose use is markedly stimulated, such as is seen if hearts are perfused in the absence of fatty acids (see Ref. [30] for review). Our studies also suggest that glycolytic product formation may even be less important in diabetic rat hearts [31,36]. In fact, our data suggest that glycolytic rates during ischemia can actually fall below a critical level necessary to maintain cellular function [27–29,36].

While serum fatty acid concentrations in normal individuals range from 0.2–0.5 mM, during an acute myocardial infarction (AMI), or during cardiac bypass surgery, serum fatty acids can increase above 1 mM [51–54]. In both instances this increase can occur very rapidly, and in patients undergoing elective cardiac bypass surgery the increase in fatty acids can occur even before the onset of myocardial ischemia [54]. In diabetics serum fatty acids can be elevated even in the absence of an AMI. We have recently observed that levels in poorly controlled diabetics suffering an AMI can exceed 2 mM [Davies and Lopaschuk, unpublished observations]. The increase in fatty acids in both diabetics and non-diabetics during an AMI appears to result primarily from catecholamine stimulation of adipocyte tissue lipolysis. Several investigators have suggested an association between serum fatty acid levels and adverse outcomes in AMI patients (including clinical left ventricular failure, malignant ventricular arrhythmias, and death) [51–53]. A number of experimental studies have examined the involvement of fatty acids during ischemia, and possible mechanisms by which fatty acids contribute to injury. Fatty acids clearly promote and accelerate arrhythmias, decrease mechanical function, and impair membrane integrity and suborganelle performance (see Ref. [30] for review). Even in the absence of diabetes, high levels of fatty acids can potentiate myocardial ischemic injury, which appears to be related to the effects of fatty acids on glucose utilization, both during ischemia and during reperfusion following ischemia (see Ref. [30] for review). Our studies suggest that stimulation of glucose utilization during ischemia in diabetic rat hearts is more important than stimulation of glucose utilization following ischemia [27–29]. In particular, during low-flow or no-flow ischemia, glycolytic rates in the diabetic rat heart appear to fall below a minimal acceptable level, particularly in the presence of high concentrations of fatty acids. In contrast, fatty acid inhibition of glucose oxidation during reperfusion is less critical in diabetic rat hearts than in non-diabetic control rats. The reason for the differences between diabetic and control hearts has not yet been determined. Differences in metabolic control of myocardial pH and Ca2+ handling may partly explain these effects.
4. Myocardial calcium handling during ischemia in the diabetic heart

Accumulation of large amounts of intracellular Ca\(^{2+}\) in the myocardium appears to be of primary importance in the initiation of irreversible cell damage [55–57]. Studies which measured intracellular Ca\(^{2+}\) have demonstrated that cytosolic Ca\(^{2+}\) can increase substantially even during short periods of ischemia [55,58,59]. Increases in total cellular Ca\(^{2+}\), however, appear to occur primarily during reperfusion of ischemic hearts [56,60–62]. The mechanisms responsible for the increased influx of Ca\(^{2+}\) in ischemic or reperfused-ischemic hearts is not well understood. A number of potential mechanisms could be involved including leaky membranes due to loss of membrane integrity (i.e., free radical injury), increased sarcolemmal Ca\(^{2+}\) channel activity, altered sarcolemmal or sarcoplasmic Ca\(^{2+}\)-ATPase activity, or altered Na\(^{+}\)/Ca\(^{2+}\) exchange activity (either directly, or secondary to changes in Na\(^{-}\)-K\(^{+}\)-ATPase or Na\(^{+}\)/H\(^{+}\) exchange activity). In all likelihood all of these pathways may contribute to Ca\(^{2+}\) accumulation to some degree. The activity of the ion pumps, channels, or exchangers have all been demonstrated to be altered during or following ischemia (see Refs. [63] and [64] for examples). Studies from a number of laboratories have also shown that sarcolemmal (SL) Na\(^{-}\)-K\(^{+}\)-ATPase and Ca\(^{2+}\)-ATPase, SL Ca\(^{2+}\) channel activity, SL Na\(^{-}\)/Ca\(^{2+}\) exchange, and sarcoplasmic reticulum (SR) Ca\(^{2+}\)-ATPase activity are all depressed in diabetic hearts (see Refs. [14,17] and [65] for reviews). During ischemia, most of the myocyte’s ATP requirements is produced from anaerobic glycolysis. Therefore, low glycolytic rates in the diabetic heart may accelerate Ca\(^{2+}\) accumulation during ischemia. Little is known, however, concerning the involvement of glycolysis on Ca\(^{2+}\) accumulation during ischemia, particularly in the diabetic.

Studies by Tani and Neely [35] have suggested that alterations in sarcolemmal Ca\(^{2+}\) transport systems in the diabetic myocardium may actually be beneficial to the heart during reperfusion following ischemia. If acutely diabetic rat hearts were reperfused following a period of no-flow ischemia, they recovered to a greater extent than control hearts, which was highly correlated to a reduced Ca\(^{2+}\)-uptake. These authors suggested that a reduced activity of the Na\(^{+}\)/Ca\(^{2+}\) exchanger may be responsible, the theory being that increases in intracellular Na\(^{+}\) that accumulate during ischemia could not as readily exchange for Ca\(^{2+}\) due to the defective exchanger activity in diabetic rats. In subsequent studies [60–62], these authors demonstrated in non-diabetic rat hearts that high rates of glycolysis during ischemia result in an accumulation of H\(^{+}\) which exchanges for Na\(^{+}\) via the Na\(^{+}\)/H\(^{+}\) exchanger, especially at the onset of reperfusion. During reperfusion this increased Na\(^{+}\) caused excessive Ca\(^{2+}\) accumulation and depressed recovery of cellular functions. Therefore, it is possible that diabetic rat hearts may be protected during reperfusion following global ischemia due to both lower glycolytic rates during ischemia and depressed Na\(^{+}\)/H\(^{+}\) exchanger and Na\(^{+}\)/Ca\(^{2+}\) exchanger activity. The relationship between glycolytic rates during ischemia and exchanger activity in diabetic hearts, however, has not been pursued.

5. Intracellular pH (pH\(_{i}\)) control during and following ischemia

The maintenance of a steady-state pH\(_{i}\) range (7.1–7.2) is of paramount importance for myocyte contractility. The mechanisms employed by cells to maintain their pH within that range include a combination of both intracellular buffering of H\(^{+}\) [66] and of specific sarcolemmal transport mechanisms which extrude excess acid (or alkali) from the cell [67]. In this context, myocardial metabolic changes associated with diabetes [68] may very well influence the source and fate of H\(^{+}\), especially during and following ischemia.

As discussed, the study by Tani and Neely [35] was the first to show an increased resistance of diabetic (alloxan and streptozotocin) rat hearts to whole-heart ischemia in vitro. When ischemia was maintained for 30 min at 37°C, diabetic hearts recovered 100% whereas hearts from normal animals recovered 30% of their preischemic function (i.e., developed pressure × heart rate product). This was associated with 4 times less Ca\(^{2+}\) uptake during reperfusion (and less increase in diastolic pressure) in diabetic hearts than in control hearts. When the ischemic period was extended, diabetic hearts had a depressed recovery of ventricular function and a greater Ca\(^{2+}\) overload, but reperfusion function was still significantly higher and Ca\(^{2+}\) overload significantly less than in control hearts. Moreover, when the diabetic animals were treated with insulin 2 days prior to removal of the heart, the response to 30 min exposure to ischemia was similar to that of hearts from normal rats. The same authors subsequently showed that the myocardial level of intracellular Na\(^{+}\) after 2 min of reperfusion was linearly correlated with Ca\(^{2+}\) uptake and depression of ventricular function during subsequent reperfusion.

A reduction in Ca\(^{2+}\) influx in diabetic hearts may, at least partly, and indirectly, result from a smaller H\(^{+}\) load during the ischemic period, and consequently to less activation of Na\(^{+}\)-dependent pH\(_{i}\) regulatory mechanisms. Alternatively or together, it may also result from a decreased activity of some pH\(_{i}\) regulatory mechanism involving Na\(^{+}\), upon reperfusion. Excessive stimulation of glycolytic flux and lack of wash-out during ischemia lead to proton accumulation [45]. The observation of nearly identical kinetics of a pH\(_{i}\) decrease during a zero-flow ischemic period in normal and diabetic hearts under similar perfusion conditions [69] may indicate that despite important diabetes-induced myocardial metabolic change [47,70] the
intracellular intrinsic H\(^+\) buffering power (\(\beta_1\)) remains unchanged. Intrinsic cardiac buffering capacity was estimated to be increased at lower pH\(_i\) such as occurs during ischemia [71]. However, recent experiments in single ventricular myocytes in which \(\beta_1\) was estimated, clearly show no change in \(\beta_1\) in diabetic hearts compared with normal hearts [72]. Alternatively, similar kinetics of pH\(_i\) decrease with ischemia in both groups of hearts may also favour similar activity of membrane pH\(_i\) regulatory mechanisms during the ischemic period. More likely, there is good experimental evidence indicating that the activity of at least some of these regulatory mechanisms may be rapidly affected during global ischemia. Myocardial ischemia is in fact associated with a decline of both pH\(_i\) and external pH (pH\(_e\)) [73], and extracellular pH is an important modulator of acid extrusion in the heart [74]. Thus, there is direct inhibition of Na\(^+\)/H\(^+\) exchange, one of the best characterized mechanisms for acid extrusion from cardiac cells (see review by D. Feuvray in this issue), by decreasing external pH [75]. On the other hand, little is at present known of the modulation of the Na\(^+\)-linked HCO\(_3\)\(^-\) influx (and especially of its possible sensitivity to external pH), another alkalinizing transporter that plays a role, not only in pH\(_i\) regulation but also in the control of intracellular Na\(^+\) [76,77]. Finally, removal of H\(^+\) during ischemia might also occur via lactate–H\(^+\) co-transport [78]. However, the sarcolemmal 1-lactate carrier whose kinetics have been determined in single heart cells from rat and guinea-pig hearts [79] may also be rapidly inhibited during ischemia. Inhibition may occur through either or both reduced transmembrane lactate and pH\(_i\) gradient [79]. In this regard, at least the transmembrane lactate gradient should be reduced during ischemia in diabetic hearts in comparison to normal hearts. Diabetic hearts have been shown to accumulate less lactate at the end of ischemia, probably in relation to the significant decrease in glycolytic flux [28,68]. This does not appear to affect the decrease in pH\(_i\), at least during a zero-flow ischemic period [69,80].

On the other hand, intracellular pH regulation via the degree of activation of specific sarcolemmal regulatory mechanisms may play a major role in the recovery of myocardial pH\(_i\) from ischemia, and in the recovery of myocardial contractility. The initial work by Khandoudi et al. [69], which compared pH\(_i\) data from streptozotocin-induced diabetic rat hearts with reduced activity of the Na\(^+\)/H\(^+\) exchange process [81,82] versus normal hearts with pharmacological block of the exchanger, has provided support for a critical role of the Na\(^+\)/H\(^+\) exchanger in the early stage of reperfusion. In addition, inhibition of the function of this transporter, either in diabetic hearts [69] or by amiloride and its analogues in normal hearts [62,83,84], improved the recovery of cardiac contractility after reperfusion.

Further work investigated the contribution of other specific sarcolemmal transport mechanisms of pH\(_i\) recovery in diabetic rat hearts, and their relation to recovery of ventricular function [80]. One such transport mechanism may be H\(^+\)-lactate co-efflux. Since the tissue lactate accumulated at the end of ischemia was significantly less in diabetic hearts than in normal hearts [65,80], less stimulation of this system would be expected, which may contribute to the slower pH\(_i\) recovery in diabetic hearts at the very beginning of reperfusion [80]. This study [80] also indicated that an HCO\(_3\)-dependent mechanism contributed to pH\(_i\) recovery after ischemia in diabetic rat hearts. Most recent experiments showed that the activity of this Na\(^+\)-linked HCO\(_3\)\(^-\) influx is unaffected by diabetes [77]. As a consequence, the slower pH\(_i\) recovery on reperfusion in diabetic hearts compared to normal hearts, under conditions where both Na\(^+\)/H\(^+\) exchange and Na\(^+\)-linked HCO\(_3\)\(^-\) influx can operate, is largely associated with the significant decrease in Na\(^+\)/H\(^+\) exchange activity. It may also be inferred that a major determinant of the protection of the diabetic heart against reperfusion damage following ischemia is the marked decrease in Na\(^+\)/H\(^+\) exchange activity.

This discussion has emphasized the significant decrease in Na\(^+\)/H\(^+\) exchange activity as an important component of the protection observed in the diabetic heart following an episode of ischemia-reperfusion. Although the results are clear-cut, several limitations to the conclusion on the determining role of Na\(^+\)/H\(^+\) exchange have to be taken into account. One is the duration of diabetes. Most of the studies mentioned have used relatively short-term diabetic animals (i.e., 3–4 weeks after the injection of streptozotocin). So far, there are no data available on the activity of the Na\(^+\)/H\(^+\) exchanger in relation to the progress of diabetes. Such information would be of importance in relation to susceptibility to ischemia-reperfusion injury. Another important aspect is the duration and severity of ischemia. With respect to the extracellular H\(^+\) inactivation of Na\(^+\)/H\(^+\) exchange, the latter will in fact depend on the degree of ischemia and on a residual proton washout of the extracellular space.

It should also be pointed out that most of the pH\(_i\) studies reported here were not performed in the presence of the high levels of fatty acids that are seen in the uncontrolled diabetic rat. Nevertheless, it has recently been shown [29] that isolated working hearts from chronic diabetic rats that received a high level of palmitate are also less sensitive to low-flow ischemic injury than hearts from normal rats. One remaining question concerns the influence of available metabolic substrate, and the preferential stimulation of one or other metabolic pathway, on pH\(_i\) decrease during ischemia and recovery on reperfusion. To answering this question will obviously be an objective for future studies.

6. Conclusions

Changes within the myocardium alter the ability of the diabetic heart to recover from an hypoxic or ischemic
epidemic. Two important changes that occur in the diabetic heart are alterations in glucose metabolism and pH\textsubscript{1} regulation. Based on the existing evidence, we propose that a decrease in glucose uptake and metabolism increases the sensitivity of the diabetic heart to an episode of hypoxia or mild ischemia. In contrast, a decrease in glycolytic product accumulation (lactate and H\textsuperscript{+}) as well as alterations in the control of pH\textsubscript{1} (i.e., a decrease in Na\textsuperscript{+}/H\textsuperscript{+} exchange activity) make the diabetic heart less sensitive to an episode of severe ischemia.

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