Review

Insulin and myocardial blood flow

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Abstract

The renaissance of glucose–insulin–potassium infusion (GIK) as a treatment of acute myocardial infarction both in diabetic and nondiabetic subjects has raised new interests to clarify the effects and mechanisms of insulin on myocardium. Although the action of insulin on substrate metabolism is quite well studied in heart, the cardiovascular effects were until recent years poorly known. Insulin induces skeletal muscle vasodilation mainly via the endothelium-dependent mechanism and appears to have an important role in normal vascular function. There is increasing amount of evidence that insulin acts as a vasodilatory hormone also in coronary arteries. Insulin enhances myocardial blood flow and decreases coronary vascular resistance in a dose-dependent manner in healthy subjects. Moreover, insulin is able to increase myocardial blood flow also in subjects who are characterized by coronary dysfunction such as subjects with obesity, type 1 diabetes and coronary artery disease. However, vasodilatory effect of insulin may be blunted in these patients. Since already very small increase in myocardial blood flow can reduce significantly myocardial ischemia, these vasodilatory actions of insulin in coronary arteries might partly contribute to beneficial effects of GIK therapy. On the other hand, in contrast to these acute beneficial effect of insulin, epidemiological studies have indentified chronic hyperinsulinemia, a common feature in subjects with insulin resistance to glucose uptake, as an independent risk factor for coronary artery disease. The present article review the physiological and pathophysiological role of insulin in cardiac vasculature and its clinical importance during myocardial ischemia and development of coronary artery disease.

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1. Introduction

In addition to effect on substrate metabolism, insulin has effects on nerve function, hemostasis, lipoprotein metabolism and vascular function [1]. Insulin resistance has been classically considered as a blunted response to insulin-mediated glucose uptake. However, insulin resistance may involve any of insulin’s biological effects.

Based on recent findings it appears that insulin has an important role in the normal vascular function [2]. In healthy subjects insulin increases not only blood flow but also blood volume in skeletal muscle classifying insulin as a true vasodilatory hormone [3]. In peripheral vasculature mainly via the endothelium-dependent mechanism, insulin induces a time- and dose-dependent vasodilation in healthy subjects [4,5]. However, insulin-induced skeletal muscle vasodilation is impaired in obese, hypertensive and diabetic subjects [6–11]. This vascular insulin resistance appears to be an important mediator of vascular pathophysiology [2]. In addition, vascular insulin resistance and resistance to insulin actions on glucose metabolism appears to be differently regulated [12,13].

The renaissance of glucose–insulin–potassium infusion (GIK) as a treatment of acute coronary events both in diabetic and nondiabetic subjects has raised new interests to clarify the effects and mechanisms of insulin on myocardium. Since differences in the regulation of vasodilation between coronary and peripheral arteries have been
observed [14], previous studies targeting insulin’s effects on the skeletal muscle vasculature can not be directly applied to the coronary vasculature. Although the action of insulin on substrate metabolism is quite well studied in heart, the cardiovascular effects were poorly known. There is increasing amount of evidence which demonstrate that insulin has vasodilatory properties also in cardiac vasculature [15–20]. These findings may be clinically important. The vasodilatory effects of insulin might partly contribute to the beneficial effects of GIK therapy [21–23]. On the other hand, epidemiological studies have indentified chronic hyperinsulinemia, a common feature in subjects with insulin resistance to glucose uptake, as an independent risk factor for coronary artery disease [24–26]. In this article we review the physiological and pathophysiological role of insulin in cardiac vasculature and its clinical importance.

2. Physiology

2.1. The effects of insulin on myocardial blood flow in healthy subjects

In animal studies myocardial blood flow has been found to be either increased [27–32] or unchanged [33–36] by insulin. In humans, insulin has been most frequently demonstrated to increase myocardial blood flow [15–20]. In two studies, insulin did not enhance myocardial perfusion in healthy subjects [37,38]. Physiological hyperinsulinemia (plasma insulin ~70 mU/l, which mimics postprandial conditions) for 100 min had no effect on basal great cardiac vein flow measured by thermodilution catheter technique [38]. Moreover, insulin bolus of 2 U i.v. did not change coronary sinus flow or coronary resistance [37]. However, since insulin is a slow vasodilator and induces vasodilation in a time-dependent manner [5,13], it is unlikely to observe any increase in myocardial blood flow when only insulin bolus is used [37].

True direct vasodilatory effects of insulin in heart are difficult to investigate. In resting conditions flow and myocardial work (oxygen consumption) are tightly coupled and autoregulation is strong. Via inotropic and chronotropic effects insulin increases oxygen demand [39,40] and thus, indirectly enhances blood flow in myocardium. To avoid the insulin-induced changes in left ventricular contractility and heart rate, β-blockade has been used although these agents may have also direct effects on coronary arteries via β-receptors. In contrast to the resting conditions, during hyperemia (e.g. during adenosine stimulation) the metabolic control of flow is uncoupled, which allows to test the effect of insulin on the other regulators such as endothelial function and neural control [14].

We have recently demonstrated that physiological hyperinsulinemia for 1 h enhances adenosine-stimulated myocardial blood flow in healthy humans [15,16]. This is concordant with the findings in periphery, where insulin has been found to enhance the hyperemic flow before any changes in basal blood flow can be detected [6,12]. In addition, we found that supraphysiological hyperinsulinemia (serum insulin ~460 mU/l) was able to further enhance the hyperemic myocardial blood flow indicating that insulin increases coronary flow in a dose-dependent manner [16]. These flow responses to insulin were not explained by changes in systemic hemodynamic since coronary vascular resistance, which takes into account changes in blood pressures, was also significantly and dose-dependently decreased by insulin (Fig. 1). The underlying mechanism of insulin’s ability to enhance adenosine-stimulated myocardial perfusion can not be directly answered by the present studies but one mechanism might be that insulin further enhances endothelium-dependent vasodilation. However, measurements during hyperemia might reduce insulin-induced increase in coronary flow.

3. Mechanisms

The mechanisms of insulin-induced vasodilation are well characterized but mainly studied in peripheral vasculature. Although the effect of insulin on glucose uptake is rapid and precedes the effect on blood flow [4,5], insulin-induced vasodilation is not explained by its metabolic actions. Insulin induces vasodilation via the endothelium-dependent mechanisms including l-arginine nitric oxide pathway and Na⁺,K⁺-ATPase [41,42]. In addition, the sympathetic nervous system participates to the regulation of insulin-induced vasodilation [41].

3.1. Endothelium-dependent mechanisms

The most important mediator of insulin-induced vasodilation is l-arginine nitric oxide pathway in endothelium [41,42] (Fig. 2). In peripheral vasculature insulin has been found to rapidly and dose-dependently stimulate nitric
NO synthase, GTP already low physiological insulin concentrations rapidly be hypothesized that vascular insulin resistance provides nervous system [53–55]. In contrast to vasodilation, important role in the normal vascular function [2], it might sympathetic nervous system does not play a major role in regulating insulin action on cardiac perfusion in healthy subjects [15]. On the other hand, intra-arterial insulin infusion increases also myocardial blood flow indicating local vasodilatory mechanism of insulin [19,29]. Concordantly, based on findings in peripheral vasculature both β-blockade and atropine has no effect on insulin-induced vasodilation in healthy subjects [28,57]. Moreover, hypotension [58,59] and exaggerated vasodilation has been demonstrated after administration of insulin in type 1 diabetic patients with autonomic neuropathy [60]. Therefore, insulin-induced sympathetic activity may oppose insulin’s vasodilatory endothelial effects and thus, at least partly, explain why insulin is such a slow vasodilator [52].

4. Pathophysiology

As discussed above in healthy subjects the net effect of insulin is vasodilation which appears to be mainly dependent on endothelial NO production. Many diseases such as hypertension, obesity, diabetes and coronary artery disease are characterized by endothelial dysfunction [12,61–64]. Thus, vascular effect of insulin may have role also in the pathophysiology of coronary arteries.

The endothelial cells line all vessels of the body in a continuous monolayer with the surface area of approximately 1000 m² and weight of about 1 kg. Since this huge surface is the first barrier between blood and vessel, the endothelium appears to be also very vulnerable. It has been hypothesized that risk factors for coronary artery disease damage endothelial cells and impair its function leading to the increased release of endothelium-derived vasoconstrictory factors [65] (Fig. 3). Concordantly, the first step in the atherosclerotic process has been suggested to be endothelial dysfunction since impaired coronary endothelium-dependent vasodilation seems to be one of the earliest abnormalities associated with coronary artery disease [64].

Insulin is predominantly endothelium-dependent vasodilator [41,42] and thus, subjects with endothelial dysfunction are often characterized by blunted vascular response to insulin (Fig. 3). This vascular insulin resistance, consistent with endothelial dysfunction, appears to originate from imbalance between endothelium-derived vasoconstrictory and vasodilatory factors [66]. Since insulin seems to have important role in the normal vascular function [2], it might be hypothesized that vascular insulin resistance provides

![Diagram of insulin-induced endothelium-derived nitric oxide (NO) synthesis and action](https://academic.oup.com/cardiovascres/article-abstract/57/2/312/306547)
3. Risk factors for coronary artery disease damage endothelial cells leading to endothelial dysfunction, an imbalance between endothelium-derived vasodilative (NO = nitric oxide, EDHF = endothelium-derived relaxing factor, PGI$_2$ = prostacyclin I$_2$) and vasoconstrictive (ET-1 = endothelin-1, PGH$_2$ = prostaglandin H$_2$, TXA$_2$ = thromboxane A$_2$, O$_2$ = superoxide anions) factors. Endothelial dysfunction characterizes all phases during atherosclerotic process and endothelial dysfunction can be detected at the early phase of atherosclerotic process by reduced endothelium-dependent vasodilation, e.g. blunted response to acetylcholine and insulin with quantitative coronary angiography (invasively) or positron emission tomography (PET) (noninvasively).

CA = coronary angiography, CAD = coronary artery disease, UAP = unstable angina pectoris, AMI = acute myocardial infarction, † = ischemic sudden death.

4.1. The effects of insulin on myocardial blood flow in subjects with insulin resistance to glucose uptake

Most studies have shown decreased coronary vasoactivity and coronary endothelial dysfunction in diabetic patients [63,67]. We have previously demonstrated with positron emission tomography (PET) that during euglycemic physiological hyperinsulinemia hyperemic myocardial blood flow is 29% lower in type 1 diabetic than nondiabetic subjects ($P<0.05$) [67]. In our recent PET study we found that although hyperemic myocardial blood flow is reduced in diabetic patients, insulin-induced coronary vasodilation was similar in diabetic and nondiabetic subjects with or without short-term hyperglycemia [17] (Fig. 4). However, whether insulin induces coronary vasodilation in a dose-dependent manner also in type 1 diabetic patients is at present unknown. In type 2 diabetic patients, endothelium-dependent vasodilation of brachial artery has been found to increase after 3 months of additional insulin therapy indicating that insulin might improve endothelial function in diabetic patients [68]. However, no studies addressing the direct effect of insulin on myocardial perfusion has been performed in type 2 diabetic patients.

Blunted insulin-induced skeletal muscle vasodilation has been usually demonstrated in diabetic and obese subjects during long infusion time or high doses of insulin. Recently, endothelial dysfunction has been demonstrated also in obese subjects’ coronary arteries [62]. Concordantly, in normal dogs an intracoronary insulin infusion increased dose-dependently coronary blood flow and coronary vasodilation but with weight gain the vasodilator response to insulin was lost [29]. We have recently demonstrated that coronary flow response to insulin is impaired in insulin resistant obese subjects (Fig. 5) [18]. Physiological hyperinsulinemia induced a significant vaso-
dilation but in contrast to healthy nonobese subjects supraphysiological hyperinsulinenia was not able to further enhanced the flow in obese humans. Thus, although insulin resistance to glucose uptake appears not localized to myocardium [69,70], coronary vascular resistance to insulin characterized obese subjects.

4.2. The effects of insulin on myocardial blood flow in patients with coronary artery disease

Patients with established atherosclerosis such as coronary artery disease are characterized by endothelial dysfunction [71] (Fig. 3). In patients with coronary artery disease a 60-min intracoronary insulin infusion increased coronary blood flow in the absence of increase in myocardial oxygen demand indicating that insulin was able to induce direct coronary vasodilation in these patients [19]. Moreover, in patients with stable coronary artery disease already 10 min of GIK infusion increases coronary sinus blood flow and decreases coronary vascular resistance [20]. Recently, in a single photon emission computed tomography (SPECT) study, GIK therapy was found to improve regional myocardial perfusion and function mainly in segments adjacent to the recently infarcted area [72]. However, whether the magnitude of insulin’s effect is preserved or blunted in patients with coronary artery disease is at present unknown.

In many other diseases such as hypertension, coronary endothelial dysfunction has been demonstrated [12,61] but the effect of insulin on myocardial blood flow has not been studied.

4.3. Insulin therapy and acute myocardial infarction

GIK therapy has been found to be beneficial in the treatment of acute myocardial ischemia even among nondiabetic patients [21,22]. The ECLA study reported 66% reduction in the relative in-hospital mortality risk when GIK therapy was added to reperfusion during acute myocardial infarction [22]. Moreover, high dose GIK infusion was superior when compared to the lower dose GIK infusion in mortality reduction [22]. Concordantly, the meta-analysis of nine trials showed that GIK therapy seems to have important role in reducing the in-hospital mortality after acute myocardial infarction [21]. Diabetic patients especially benefit from intravenous insulin therapy during acute myocardial ischemia [23,73] and current evidence is already strong enough to recommend routine use of GIK therapy for these patients [74]. In addition, GIK infusion enhances recovery and is effective in preventing myocardial ischemia after coronary artery bypass grafting [75–77]. GIK therapy has been also found to enhance left ventricular function during acute myocardial infarction [78] or prolonged ischemia in humans [79] and animals [35,36,80]. However, this insulin’s effect has not been demonstrated in all studies [81,82]. Recently, intensive insulin therapy has been found to be beneficial to reduce morbidity and mortality even among nondiabetic critically ill patients in the surgical intensive care unit [83]. Several mechanisms may relate to the beneficial effect of GIK therapy. Insulin’s effect on substrate metabolism are well known [73,84–88]. Insulin-stimulated glucose and free fatty acid uptake have been found to be preserved in the chronically dysfunctional but viable myocardium [84,85]. In addition, GIK therapy has beneficial effects on oxygen utilisation [89] and it stabilizes ischemic cells [90]. In addition to these effects on substrate metabolism insulin is able to induce coronary vasodilation in patients with diabetes [17] and coronary artery disease [19,20]. This may be due to improvement of endothelial function by insulin [68]. Since already very small increase in myocardial blood flow can reduce significantly myocardial ischemia [91], the vasodilatatory effects of insulin might partly contribute to beneficial effects of intravenous insulin therapy in patients with myocardial ischemia.

4.4. Insulin resistance to glucose uptake as a risk factor for coronary artery disease

In contrast to above mentioned acute beneficial effect of insulin, chronic hyperinsulinenia, which often characterized subjects with insulin resistance to glucose uptake, seems to act as an independent risk factor for coronary artery disease [24,26]. The underlying pathophysiological mechanisms for this non-classic risk factor might relate to its harmful long-term effects on endothelial function (Fig. 3). Chronic exposure to hyperinsulinenia increase the release of endothelin-1 (ET-1) in subjects with insulin resistance to glucose metabolism [92,93] whereas short-term hyperinsulinenia mimicking postprandial conditions appears not to stimulate ET-1 production in healthy subjects [94,95]. Therefore, it might hypothesized that in contrast to acute beneficial effect of insulin in healthy subjects, chronically high serum insulin concentrations in subjects with insulin resistance to glucose uptake damage
endothelial cells. In addition, insulin may also promote smooth muscle cell proliferation and cause cholesterol ester accumulation in the arterial wall [96]. Moreover, insulin increases sympathetic activity in a dose-dependent manner [16,55] and impaired coronary endothelial function is associated with marked increase in sensitivity to the constrictor effects of catecholamines [97]. Thus, this chronic exposure to hyperinsulinemia might lead to the augmented coronary vasoconstriction mediated by α-receptors in subjects with endothelial dysfunction.

5. Conclusions

In healthy subjects insulin acts as a true vasodilatory hormone not only peripheral but also in cardiac vasculature [15,16]. Insulin enhances myocardial blood flow and decreases coronary vascular resistance [15] in a dose-dependent manner in healthy subjects [16]. Moreover, insulin is able to increase myocardial blood flow in subjects who are characterized by endothelial dysfunction such as subjects with type 1 diabetes, obesity and coronary artery disease [17–20]. This may be due to improvement of endothelial function by insulin [68]. However, consistent with peripheral vasculature this vasodilatory effect of insulin may be blunted in some disease states [18]. Thus, although insulin resistance to glucose uptake is not localized to myocardium [69,70], coronary vascular resistance to insulin may exist. Since insulin seems to have important role in the normal vascular function [2], it might be hypothesized that vascular insulin resistance provides one novel mechanism in the progression towards coronary artery disease. Moreover, more studies addressing insulin’s effects on myocardial perfusion are needed to clarify the insulin’s vasodilatory actions in patients with diabetes and coronary artery disease.

Intravenous insulin therapy has beneficial effect on patients with acute myocardial infarction [21–23]. The vasodilatory effect of insulin may partly provide mechanism to explain the beneficial effects of GIK therapy on myocardial ischemia in nondiabetic [21,22] and diabetic subjects [23]. Moreover, this mechanism may be important since already very small increase in myocardial blood flow can reduce significantly myocardial ischemia [91]. However, more studies are needed to investigate the exact effects of insulin on myocardial blood flow in patients with acute myocardial infarction or unstable angina pectoris. In contrast to these acute beneficial effect on insulin, chronic hyperinsulinemia, a hallmark of insulin resistance to glucose uptake, seems to act as an independent risk factor for coronary artery disease [24,26].

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References


