DPP-4 Inhibition by Sitagliptin Improves the Myocardial Response to Dobutamine Stress and Mitigates Stunning in a Pilot Study of Patients With Coronary Artery Disease

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Background—Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted postprandially that promotes myocardial glucose uptake. The active amide GLP-1 (7-36) is degraded by the enzyme DPP-4, and drugs that inhibit this enzyme (such as sitagliptin) have been introduced to treat type 2 diabetes. We assessed the hypothesis that increasing the plasma concentration of GLP-1 by DPP-4 inhibition would protect the heart from ischemic left ventricular (LV) dysfunction during dobutamine stress echocardiography in patients with coronary artery disease.

Methods and Results—Fourteen patients with coronary artery disease and preserved LV function awaiting revascularization were studied. After either a single dose of 100 mg sitagliptin or placebo, 75 g of glucose was given orally to promote GLP-1 secretion and dobutamine stress echocardiography was conducted with tissue Doppler imaging at rest, peak stress, and 30 minutes. After sitagliptin, plasma GLP-1 (7-36) was increased at peak stress (16.5±10.7 versus 9.7±8.7 pg/mL; $P=0.003$) and in recovery (12.4±5.5 versus 9.0±5.5 pg/mL; $P=0.01$), and the LV response to stress was enhanced (ejection fraction, 72.6±7.2 versus 63.9±7.9%, $P=0.0001$; mitral annular systolic velocity, 12.54±3.18 versus 11.49±2.52 cm/s; $P=0.0006$). DPP-4 inhibition also improved LV regional function in the 12 paired nonapical segments assessed by peak systolic tissue Doppler (velocity, 10.56±4.49 versus 9.81±4.26 cm/s, $P=0.002$; strain, −15.9±6.3 versus −14.6±6.6%, $P=0.01$; strain rate, −2.04±1.04 versus −1.75±0.98 s^{-1}, $P=0.0003$). This was predominantly due to a cardioprotective effect on ischemic segments (velocity in ischemic segments, 9.77±4.18 versus 8.74±3.87, $P=0.007$; velocity in nonischemic segments, 11.51±4.70 versus 11.14±4.38, $P=0.14$). In recovery, sitagliptin attenuated the postischemic stunning seen after the control study.

Conclusions—The augmentation of GLP-1 (7-36) by inhibition of DPP-4 improves global and regional LV performance in response to stress and mitigates postischemic stunning in humans with coronary artery disease.

Clinical Trial Registration—URL: http://www.isrctn.org. Unique identifier: ISRCTN78649100.

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Key Words: coronary disease ■ ischemia ■ glucagon-like peptide ■ stress echocardiography ■ ventricular function

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted mainly by the enteroendocrine cells of the intestine in response to nutrients. It facilitates glucose-induced insulin release and suppresses glucagon.[1] The effects are dependent on the prevailing glucose concentration minimizing the risk of hypoglycemia. The active amide GLP-1 (7-36) has a half-life of only 1 to 2 minutes and is rapidly degraded by the enzyme DPP-4 to a truncated metabolite GLP-1 (9-36). This has fostered the development of specific inhibitors that prevent the rapid postprandial fall in the plasma concentration of GLP-1. DPP-4 inhibition is well tolerated and is now approved as a therapy for type 2 diabetes in the United Kingdom and United States.

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Fatty acid oxidation provides the predominant source of energy in the healthy heart.[2] However, during ischemia there is increased utilization of glucose as a substrate for energy production that requires less oxygen to generate an equivalent amount of ATP compared with fatty acids.[3] The GLP-1 receptor is widely expressed in islet cells, kidney, lung, brain, the gastrointestinal tract, and also in the heart.[4] In animal models, infusion of GLP-1 has been shown to promote myocardial glucose uptake and improve left ventricular (LV) performance in dogs with advanced heart failure[5] and also to enhance recovery from ischemic myocardial stunning.[6] Recent human pilot studies have shown similar effects. Intravenous infusion of GLP-1 for 72 hours to patients with severe

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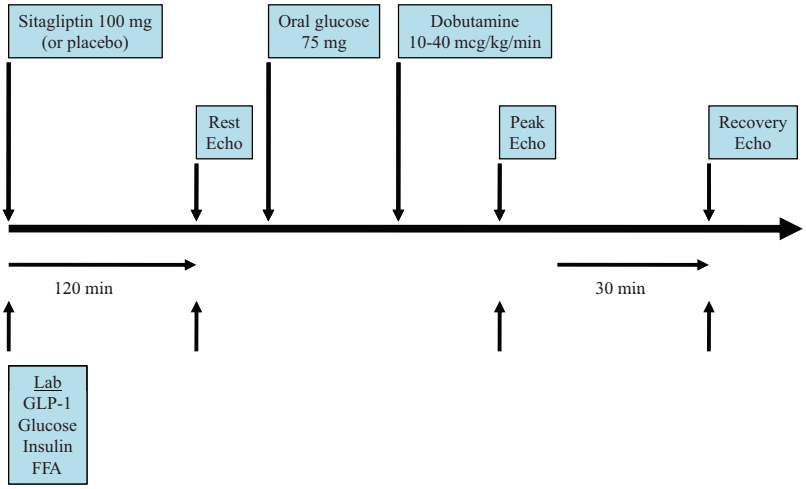

Figure 1. Flow chart illustrating the study design and timeline.

LV dysfunction after primary angioplasty for acute myocardial infarction significantly improved global and regional LV function.[7]

We proposed that the increase in the plasma concentration of GLP-1 after sitagliptin would protect the heart against postischemic LV dysfunction and improve the myocardial response to dobutamine stress in patients with significant coronary artery disease.

Methods

Study Population

Patients with coronary artery disease and normal resting LV function who were awaiting elective revascularization were invited to participate. All patients had undergone recent coronary angiography before enrollment in the study. Exclusion criteria included abnormal LV regional wall motion at rest, a history of myocardial infarction within the previous 3 months, conduction abnormalities, valvular heart disease, and diabetes receiving insulin. The study was approved by the local ethics committee, and the study protocol complied with the guidelines set out in the Declaration of Helsinki. All participants gave written informed consent.

Dobutamine Stress Echocardiography

All subjects underwent dobutamine stress echocardiography (DSE) on 2 occasions approximately 1 week apart (Figure 1). They were asked to omit β-blockers for 48 hours before each scan, and oral hypoglycemic agents were omitted on the morning of the study. After an overnight fast, patients received 75 g oral glucose before each DSE to stimulate GLP-1 secretion. As the peak effect of sitagliptin (Januvia, MSD) occurs at 2 hours after dose,[8] patients were given a single dose of 100 mg sitagliptin orally 2 hours before the oral glucose for one of the scans and the other study acted as a control. The order of the 2 scans was randomized.

A standard clinical protocol for DSE was used. Dobutamine was administered using an infusion pump in incremental doses (10 μg/kg/min initially, then increased at 3-minute intervals to 20, 30, and 40 μg/kg/min if tolerated) and up to 2 mg of atropine if necessary to achieve the target heart rate. Criteria for stopping the test were achievement of target heart rate of (220−age)×0.85 bpm, ischemic ECG changes (>2 mm ST depression), angina, systolic blood pressure increase to >240 mm Hg or decrease to <100 mm Hg, and severe arrhythmias. Two-dimensional echocardiography (Vivid 7, GE Medical Systems) was performed with the patient in the left recumbent position, and images were recorded at rest, during each stage of dobutamine stress, and in recovery. Three cardiac cycles of the apical 4-, 3-, and 2-chamber views were captured with tissue Doppler imaging. The image sector width was kept as narrow as possible to maximize the frame rate. All recordings were made in gently held midexpiration to minimize beat-to-beat variability, and the data were stored for subsequent off-line analysis (EchoPac, GE Medical Systems).

Blood samples were taken to measure glucose, insulin, free fatty acids (FFA), and GLP-1 (7-36) at several time points before and after the DSE. The syringes for the collection of GLP-1 samples were pre-prepared with DPP-4 inhibitor (Millipore) to prevent GLP-1 degradation. Plasma GLP-1 levels were measured using a commercially available assay (Meso Scale Discovery).

Echocardiographic Analysis

The scans were analyzed off-line by a reviewer who was blinded to the treatment strategy (control versus sitagliptin). Regional wall LV motion was assessed using a 12-segment model. This comprises the base and mid level of 6 regional walls (septal, lateral, anterior, inferior, anteroseptal, and posterior) obtained from the 3 apical views. LV volumes and ejection fraction was calculated using the Simpson biplane method according to the guidelines of the American Society of Echocardiography. Global LV function was also assessed by mitral annular systolic velocity averaged from 6 sites.[9] Peak systolic tissue velocity (V_s) and strain and strain rates were calculated from tissue Doppler velocity data averaged over 3 consecutive beats. The timings of aortic valve opening and closure were made from the tissue Doppler waveform.[10] The MYDISE study demonstrated that coronary artery disease could be diagnosed accurately and objectively from off-line measurements of myocardial velocities recorded by tissue Doppler echocardiography during dobutamine stress.[11] In particular, strain rate imaging has been shown to provide objective evidence of inducible ischemia[12] and may be a superior parameter to peak tissue velocity.[13]

A diameter stenosis of >50% on coronary angiography was considered hemodynamically significant. Myocardial segments were assigned to the perfusion territories of stenosed vessels, considering the left anterior descending coronary artery to supply the mid septal, anterior, and anteroseptal segments, the circumflex artery to supply the lateral wall, and the right coronary artery to supply the basal septum (if dominant) and inferior segments. The posterior wall was assigned to the circumflex or right coronary artery, depending on the relative size of the vessels.

Statistics

The number of subjects had been calculated on the basis of previous work in patients with coronary artery disease in whom ejection fraction increased from 57±5.6% to 66.0±6.7% when dobutamine stress was performed during a hyperinsulinemic, euglycemic clamp. To detect a change in global LV ejection fraction of 5% after dobutamine stress (standardized effect size of 1), 17 patients were required (paired t test, α=0.05, β=0.20). Interim analysis was conducted after the first 10 participants to make adjustments to the

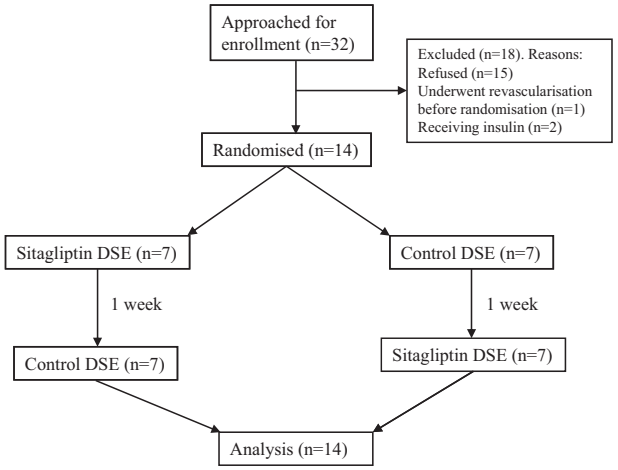

Figure 2. Consort diagram illustrating study recruitment and randomization.

sample size if required and therefore avoid patients undergoing dobutamine stress unnecessarily. Comparisons were made between the sitagliptin and control DSE scans. All data are expressed as mean±SD. Each patient acted as their own control. For continuous data, the paired Student *t* test was used to compare means between 2 groups. A probability value of <0.05 was considered as statistically significant. Intraobserver and interobserver variabilities were expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD divided by the average value of the variable).

Results

Study Population

Interim analysis of the first 10 patients had shown significant results and therefore the number of subjects required was reduced. Fourteen patients were randomly assigned (Figure 2) and completed the study (Table 1). They were awaiting revascularization (percutaneous coronary intervention or coronary artery bypass grafting) for single-vessel (n=10, 71%), double-vessel (n=2, 14%), and triple-vessel disease (n=2, 14%). The left anterior descending artery was involved in 71%, the left circumflex artery in 21%, and the right coronary artery in 50% of patients.

DSE

The 2 DSEs were conducted 7.6±4.4 days apart. There was no difference in the rate-pressure products at peak stress (Table 2) between the sitagliptin and control scans.

Biochemistry

Before oral glucose, sitagliptin had no effect on any measured parameter (Figure 3). The DSE images at rest were obtained taken in the fasted state before the oral glucose load. At baseline, there were no differences in the plasma concentration of GLP-1 (7-36) ($P=0.19$), plasma glucose ($P=0.20$), insulin ($P=0.44$), or FFA ($P=0.59$).

At peak dobutamine stress after sitagliptin, the plasma glucose concentration was lower (mean difference to control, 1.1±1.1 mmol/L, $P=0.003$) and the plasma GLP-1 (7-36) concentration greater than control (mean difference, 6.8±7.3 pg/mL, $P=0.004$). The plasma level of insulin increases during DSE due to the effect of dobutamine on the pancreas.[14]

Table 1. Demographics and Clinical Data of Participants

Demographics	
Age, y	63.6±7.4
Male sex	13 (93)
BMI, kg/m^2	28.9±4.4
Type 2 diabetes	1 (7)
Active/ex-smoker	9 (64)
Hypertension	5 (36)
Previous MI	3 (21)
Biochemistry	
Total cholesterol, mmol/L	4.0±0.9
HOMA IR	1.0±0.7
HbA1c, %	6.0±0.5
Anti-anginal medications	
β-blockers	11 (79)
Calcium channel antagonist	6 (43)
Long-acting nitrate	3 (21)
Nicorandil	4 (29)
Ivabradine	1 (7)

Data are presented as mean±SD or n (%). BMI indicates body mass index; HOMA IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated hemoglobin.

However, at peak stress, there was a trend for the rise in insulin concentration to be less after sitagliptin ($P=0.14$), although there was no change in the plasma level of FFA ($P=0.80$) (Figure 3).

After dobutamine, the GLP-1 (7-36) concentration remained higher after sitagliptin ($P=0.01$) and the plasma glucose concentration was lower ($P=0.01$), although there were no differences in the plasma concentration of insulin ($P=0.23$) or FFA ($P=0.78$).

Global LV Function

At rest, LV function was similar before both studies (ejection fraction, 60.1±6.3% [sitagliptin] versus 60.1±5.9% [control], $P=0.83$). At peak stress, there was a greater increase in myocardial performance after sitagliptin (Figure 4; 72.6±7.2% [sitagliptin] versus 63.9±7.9% [control], $P=0.0001$), and this improved performance was maintained at 30 minutes (64.6±6.2% [sitagliptin] versus 55.5±7.7% [control], $P<0.0001$). During the control scan there was evidence of postischemic LV dysfunction (stunning) compared with baseline (55.5±7.7 versus 60.1±5.9%; $P=0.005$), whereas after sitagliptin, LV function was maintained (Figure 4).

Table 2. Hemodynamic Data During DSE Scans

	Control	Sitagliptin	*P* Value
Heart rate, bpm	128±9.3	127±9.7	0.59
Systolic blood pressure, mm Hg	155±27	153±24	0.69
Diastolic blood pressure, mm Hg	67±13	69±9.0	0.33
Rate-pressure product, mm Hg · bpm	19 855±3761	19 448±3229	0.54

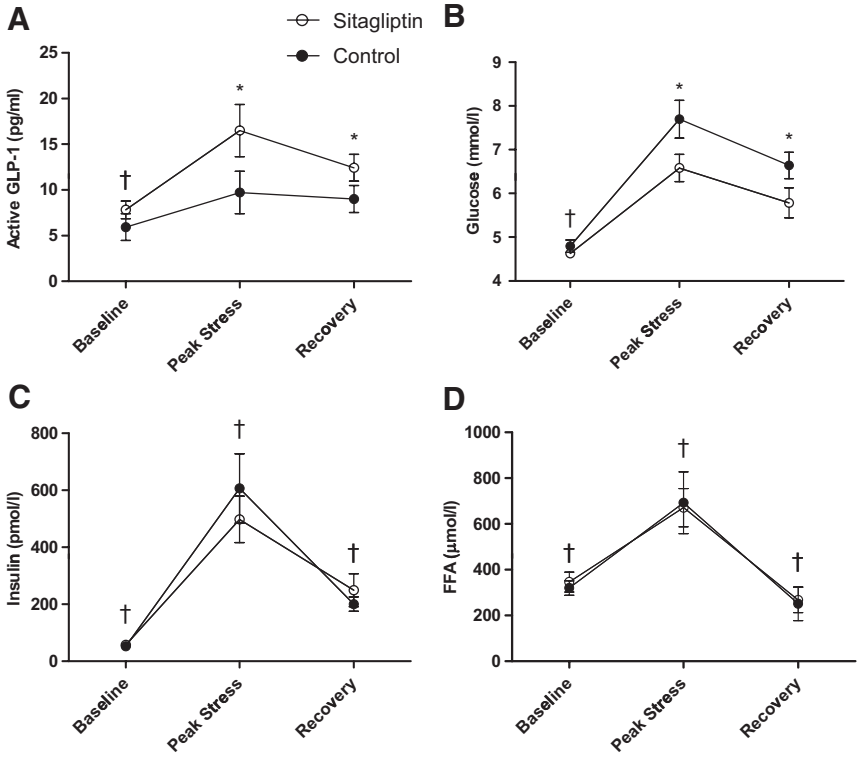

Figure 3. Biochemical data (mean±SEM) during the DSE scans at baseline, peak stress, and 30-minute recovery. A, Plasma active GLP-1 (7-36) levels; B, glucose; C, insulin; D, free fatty acid. *$P<0.05$. †No significant difference for comparisons between sitagliptin and control.

Global LV function assessed by mitral annular systolic velocity confirmed these findings. There was no difference in LV function at rest (6.10±1.00 [sitagliptin] versus 5.86±1.04 [control] cm/s; $P=0.2$), but LV performance was enhanced after DPP-4 inhibition at peak stress (12.54±3.18 [sitagliptin] versus 11.49±2.52 [control] cm/s; $P=0.0006$) and at 30 minutes after cessation of dobutamine (5.99±1.54 [sitagliptin] versus 5.62±1.04 [control] cm/s; $P=0.0004$). There was again evidence of postischemic LV dysfunction (stunning) in the control scan compared with baseline (5.62±1.04 versus 5.86±1.04 cm/s; $P=0.04$), but this was not seen after sitagliptin.

Regional Wall LV Function

For the 12 paired nonapical segments, there was no difference at rest between the sitagliptin and control DSEs. However, at peak stress, sitagliptin increased regional wall function assessed by velocity and strain and strain rates (Table 3). This improvement in function after sitagliptin remained present at 30 minutes into the recovery period.

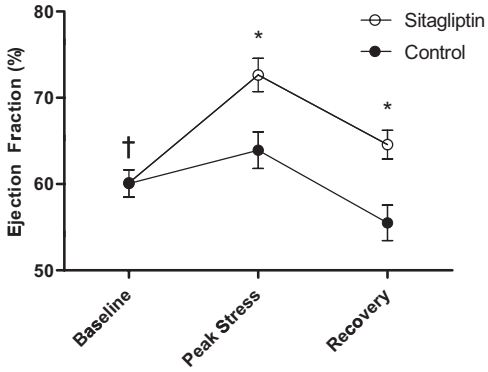

Figure 4. Global LV function assessed by LV ejection fraction (mean±SEM) at baseline, peak stress, and 30-minute recovery. *$P<0.001$. †No significant difference for comparisons between sitagliptin and control.

Ischemic Versus Nonischemic Segments

Ischemic segments were defined as those subtended by a coronary artery with a stenosis of >50% on coronary angiography. Sitagliptin had a greater beneficial effect on ischemic than on nonischemic segments (Table 4).

Reproducibility

Reproducibility was assessed in 8 randomly selected patients for the images recorded at rest, peak stress, and in recovery. The intraobserver and interobserver variabilities for the tissue Doppler imaging parameters were, respectively, 0.37 cm/s (7%) and 0.41 cm/s (8%) for tissue velocity, 1.8% (11%) and 2.1% (13%) for strain, and 0.12 s^{-1} (13%) and 0.14 s^{-1} (15%) for strain rate. For LV ejection fraction, the intraobserver variability was 3.6% (6%) and the interobserver variability was 4% (7%).

Discussion

This study demonstrates that in patients with coronary artery disease, metabolic manipulation using DPP4 inhibition to prevent the degradation of GLP-1 can protect the heart from ischemic LV dysfunction during dobutamine stress and mitigate postischemic stunning. Global and regional wall LV performance was greater after sitagliptin at peak stress and at 30 minutes into recovery compared with control.

We used an oral glucose load to produce a rise in the plasma level of GLP-1. The peak surge of GLP-1 was greater and persisted for longer after sitagliptin than control. As

Table 3. Regional Wall LV Function

	Baseline			Peak Stress			Recovery		
	Control	Sitagliptin	*P* Value	Control	Sitagliptin	*P* Value	Control	Sitagliptin	*P* Value
V_s, cm/s	4.58±1.62	4.55±1.71	0.63	9.81±4.26	10.56±4.49	0.002	4.39±1.65	4.66±1.95	0.002
Strain, %	−15.8±6.6	−16.0±6.8	0.62	−14.6±6.6	−15.9±6.3	0.01	−13.2±7.4	−14.6±6.8	0.003
Strain rate, s^{-1}	−1.07±0.46	−1.09±0.45	0.71	−1.75±0.98	−2.04±1.04	0.0003	−0.94±0.46	−1.08±0.51	<0.0001

expected, the rise in plasma glucose was suppressed by sitagliptin. The rise in plasma insulin was also reduced by sitagliptin, which suggests that the beneficial effect on the heart was due to GLP-1 and not to insulin. At baseline, before oral glucose was given, there was no difference in GLP-1 levels between the 2 scans and no difference in global or regional wall function. However, at peak stress, sitagliptin improved both global function assessed by ejection fraction and mitral annular velocity, and regional wall function assessed by velocity-derived strain and strain rate. This was primarily driven by increasing the performance of the ischemic segments. In the recovery period, there was evidence of postischemic stunning in the control scans with reduced global and regional wall function compared with baseline. However, sitagliptin protected the heart from ischemia and mitigated this effect.

Postischemic Myocardial Dysfunction (Stunning)

The hallmark of myocardial stunning is reversible contractile dysfunction in the absence of continuing ischemia.[15] Exercise and dobutamine stress result in a similar degree of postischemic global LV dysfunction.[16] The severity of stunning is related to both the intensity and duration of the preceding bout of ischemia.[17] During ischemia, there is increased glucose utilization by the heart, but fatty acid oxidation continues to dominate. This requires higher oxygen expenditure and may also have other detrimental effects on the myocardium including lactate and proton accumulation.[18] The ability of the heart to rapidly change from fatty acid oxidation to glucose metabolism may protect myocytes from ischemic injury. Patients with type 2 diabetes are at a greater risk of heart failure, and cardiovascular disease accounts for almost half of the premature deaths among people with diabetes in the developed world.[19] In a recent large trial of patients with type 2 diabetes and coronary artery disease, revascularization did not improve outcome at 5 years compared with medical therapy.[20] The concept of metabolic modulation to induce a shift toward glucose utilization may be a particularly useful strategy for these patients.

Cardioprotection by GLP-1

In rat models, GLP-1 (7-36) has been shown to have a direct effect on the heart to increase myocardial glucose uptake, enhance recovery of cardiac function after ischemia,[21] and limit myocardial infarction.[22] Reduction in infarct size has also been demonstrated in a porcine model using exenatide, which is a GLP-1 receptor agonist.[23] There have been relatively few studies looking at the effect of GLP-1 on the heart in humans. Intravenous infusion of GLP-1 has been shown to reduce infarct size in patients undergoing primary angioplasty for acute myocardial infarction[7] and to reduce inotrope requirements during coronary artery bypass grafting.[24] Chronic subcutaneous infusion of GLP-1 over 5 weeks improved LV function, functional status, and quality of life in patients with severe heart failure.[25]

GLP-1 (7-36) is rapidly degraded by DPP-4 to its metabolite, GLP-1 (9-36). The activity of this metabolite is controversial. In humans, it has no effect on insulin secretion from the pancreas, and its glucose lowering potential is small compared with GLP-1 (7-36).[26] The GLP-1 receptor in the human heart has the same amino acid sequence as the receptor in the pancreas.[4] However, in a canine model, infusion of GLP-1 (9-36) was shown to mimic the effects of GLP-1 (7-36) in promoting myocardial glucose uptake and improving LV hemodynamics.[27] These effects are independent of insulin. In rats, the GLP-1 receptor agonist exendin-4 limits infarct size, whereas GLP-1 (9-36) does not, although they both improve LV performance during reperfusion.[28] Exendin-9, a GLP-1 receptor antagonist, completely blocked the effect of exendin-4 to limit infarct size but only partially antagonized the effects on LV function during reperfusion. The divergent effects suggest that there may

Table 4. Ischemic Versus Nonischemic Segments

	Peak Stress			Recovery		
	Control	Sitagliptin	*P* Value	Control	Sitagliptin	*P* Value
Ischemic segments						
V_s, cm/s	8.74±3.87	9.77±4.18	0.007	4.10±1.72	4.47±1.94	0.002
Strain, %	−14.9±6.5	−16.1±6.4	0.16	−13.1±7.7	−14.2±6.3	0.04
Strain rate, s^{-1}	−1.65±0.87	−2.02±1.11	0.0004	−0.90±0.43	−1.06±0.45	0.003
Nonischemic segments						
V_s, cm/s	11.14±4.38	11.51±4.70	0.14	4.72±1.52	4.92±1.95	0.26
Strain, %	−15.4±5.8	−16.1±6.4	0.18	−14.0±6.2	−15.0±7.4	0.29
Strain rate, s^{-1}	−1.86±1.07	−2.07±0.98	0.12	−0.97±0.44	−1.11±0.57	0.02

be more than 1 type of GLP-1 receptor in the heart. In our study, DPP-4 inhibition produces a beneficial effect to protect against ischemic LV dysfunction. This suggests that GLP-1 (7-36) has a direct effect on the heart rather than acting via its metabolite GLP-1 (9-36).

Limitations

In this study, we have assessed the cardioprotective effect of GLP-1 on echocardiographic end points during dobutamine stress. The study was not powered to examine the effect on any clinical end points. All attempts were made to conduct the 2 DSE scans for each patient in identical fashion and obtain the peak stress images at the same degree of dobutamine stress. However, there may be some variation in patients' response to dobutamine on the 2 separate study days. The patients in this study had normal LV ejection fraction and stable angina, but further studies would be required to assess whether the effect also occurs in those with suppressed LV ejection fraction or in other clinical scenarios such as acute coronary syndromes.

Clinical Implications

The pharmacological properties of GLP-1 make it an attractive cardioprotective agent. It is well tolerated with minimal risk of hypoglycemia. The beneficial effects have been observed in both diabetics and also in nondiabetics such as in our study. We have demonstrated an acute cardioprotective effect after DPP-4 inhibition by a single dose of sitagliptin. Further studies are required to assess whether there is a long-term benefit from chronic DPP-4 inhibition, which would be particularly useful in patients who have type 2 diabetes and coronary artery disease.

Conclusion

The inhibition of DPP-4 augmented plasma levels of GLP-1 (7-36), which improved global and regional wall LV function during dobutamine stress and mitigated postischemic stunning in the recovery period. This was predominantly driven by a cardioprotective effect on ischemic segments and was independent of insulin.

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Disclosures

None.

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CLINICAL PERSPECTIVE

This study has demonstrated the potential of glucagon-like peptide-1 (GLP-1) to provide cardiac protection against ischemia using the DPP-4 inhibitor sitagliptin. These agents are licensed for the treatment of type 2 diabetes as second-line therapy following trials that have shown reduction in HbA1C. Patients who have type 2 diabetes and coronary artery disease are difficult to treat and have a worse outcome from revascularization compared with nondiabetics. Improvement in medical treatment strategies for these patients could have a large clinical impact. We have shown that DPP-4 inhibitors can produce an acute beneficial effect to protect against ischemic left ventricular dysfunction. Further studies are required to examine whether GLP-1 agents such as DPP-4 inhibitors or GLP-1 receptor agonists could have chronic beneficial effects on the heart for the diabetic with coronary disease. The potential cardiac use of GLP-1 may also be broader than the treatment of stable coronary artery disease. Its pharmacological properties as a cardioprotective agent are attractive. It is well tolerated with minimal side effects and there is very low risk of hypoglycemia which obviates the need for concomitant glucose infusion. Further work is needed to assess its potential benefits in other clinical settings such as in patients with heart failure or in acute coronary syndromes.