The effect of insulin on the heart

Part 1: Effects on metabolism and function

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Positive inotropic effects of insulin were described early after the isolation of insulin from the pancreas but data on the effect of insulin on the heart are conflicting. Systemic insulin administration results in a reduction in circulating free fatty acids and an improvement in myocardial glucose uptake, which causes an efficiency improvement in the myocardial cell. There is strong evidence that insulin administration results in functional improvement in dysfunctional myocardium. (Neth Heart J 2010;18:197-201.)

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After the first isolation of insulin from the pancreas in the early 1920s, Visscher and Muller were probably the first to attribute a positive inotropic effect to insulin in an isolated heart preparation.¹ However, data on the effects of insulin on cardiac function and metabolism remain conflicting. Several aspects of the effect of insulin on myocardial function and metabolism have been studied. In this first of a two part article dealing with the effect of insulin on the heart, we discuss the research that focused on metabolism, function and coronary blood flow.

Insulin administration in intact organisms

Research focusing on the effect of insulin on the heart can be divided into research with isolated heart preparations and research with intact organisms (animals or patients). In an isolated heart preparation, or even isolated cardiac muscle strips, sim-

ple addition of insulin to the perfusate or medium will cause myocardial exposure to insulin, without effects on the glucose content of the perfusate or medium. *In vivo*, however, systemic administration of insulin causes a drop in glucose level, followed by a secondary response to restore the blood glucose level, with an increase in norepinephrine and glucagon levels. To prevent this drop in blood glucose levels, insulin administration is combined with infusion of glucose, and potassium is usually added to prevent hypokalaemia caused by simultaneous entry into the cell with glucose.

Infusion protocols with glucose, insulin and potassium can be distinguished in two types: first, protocols that use infusions with a fixed composition and pay less attention to the blood glucose level, as long as it does not become too low (glucose-insulin-potassium (GIK) infusions, e.g. the protocol described by Rogers and co-workers²) and second, protocols which have a target of (high-dose) insulin administration with euglycaemic control, effectuated by a fixed insulin dose and variable glucose infusion rates, resembling the euglycaemic hyperinsulinaemic clamp (EHC) procedure described by DeFronzo.³ Confusingly, terminology is frequently mixed up in the literature, so reports on the effect of insulin on the heart have to be judged carefully for the procedure used.

Effects of insulin on metabolism

In vivo animal studies

During GIK administration, the uptake of free fatty acids (FFAs) was reduced,⁴ and glucose uptake was enhanced,^{4,5} or at similar levels as in controls.⁶ Compared with controls, lactate production was higher^{5,7} or at similar levels,⁶ and one study even observed increased lactate uptake.⁴ According to one study, the adenosine triphosphate (ATP) derived from lactate production was actually used by the myocardium, as ATP content was not different from controls.⁷ Finally, several authors were not able to show a net effect on myocardial oxygen consumption.^{5,7,8}

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Human studies and metabolic effects of GIK

GIK infusion in humans results in a reduction in circulating FFAs,⁹⁻¹⁴ often below the myocardial uptake threshold that has been determined to be between 100 and 200 $\mu\text{mol/l}$.⁹ As a result, myocardial uptake of FFAs minimises^{9-11,13-15} and the uptake of glucose and lactate increases.^{9-11,13,14} Myocardial respiratory quotient (RQ) changes towards 1.0 (in fasting state, when FFAs are predominantly used as fuel, myocardial RQ is around 0.7).^{11,13} However, similar to studies in animals, most studies that determined myocardial oxygen consumption during insulin infusion in humans did not observe a change.^{11,13-15}

Only one study related myocardial oxygen consumption to a clinical determinant of oxygen consumption (polyvinyl acetate (PVA) loops) and observed a reduced or 'normalised' oxygen consumption, especially in the unloaded heart, when GIK was administered.¹⁵ Thus, a remarkable energetic advantage was achieved when metabolism was changed towards glucose metabolism by GIK, while contractility, myocardial blood flow and the slope of the PVA relationship remained unchanged.

The observed effects on plasma FFA levels probably cause a transition from myocardial FFA metabolism (the 'preferred substrate') towards carbohydrate metabolism, and it can be calculated that carbohydrate metabolism is more oxygen efficient than fatty acid metabolism.¹⁶ Also, cytosolic glycolysis is enhanced with increased production of cytosolic ATP, which is then directly available to ion pumps localised in the cell membrane and the endoplasmic reticulum, as well as to the cross-bridges on the myofilaments. This is thought to be one of the ways that GIK infusions may protect (post)-ischaemic myocardium and improve function.

Positive inotropic action of insulin in normal and abnormal myocardium

Several groups made similar observations of the positive inotropic effect of insulin, such as Visscher and Müller,¹ for example in dogs¹⁷⁻¹⁹ but also in isolated preparations of piglets and kittens,²⁰ in hearts from diabetic lambs,²¹ in hearts from guinea pigs or rats,²² and in sheep with streptozotocin-induced diabetes.²³ However, others have not been able to reproduce these results.^{13,24-27} These conflicting results may be due to the already normal function of myocardium, in which it is more difficult to enhance myocardial function than in already dysfunctional myocardium, e.g. dysfunction caused by ischaemia.

Effects of insulin administration in patients with left ventricular dysfunction

Reports studying the effects of insulin administration on myocardial function in patients with left ventricular dysfunction are summarised in table 1.²⁸⁻³⁵

The results of these studies strongly suggest that GIK infusion enhances left ventricular func-

tion, both in patients with recent myocardial infarction as well as in patients with chronic myocardial infarction. Importantly, the studies reporting improvement in left ventricular or segmental myocardial function used high-dose insulin infusion. Furthermore, insulin administration seems to produce a similar enhancement of segmental function as low-dose dobutamine infusion.

Effects of high-dose insulin administration in patients who underwent cardiac surgery

Hiesmayr and co-workers compared low-dose dobutamine infusion with GIK infusion and observed that GIK administration led to an increase in cardiac index in this patient group; the effect was significant compared with baseline but smaller than the increase obtained by administering low-dose dobutamine.³⁶ Whole-body oxygen consumption was reduced during GIK infusion.³⁶ Studies by others suggested less need for inotropic support and higher cardiac index during GIK infusion and faster weaning from intra-aortic balloon pumping after surgery.^{37,38} A reduction in mortality was reached in refractory heart failure patients.³⁹ Also in patients with diabetes mellitus, the need for inotropic support was reduced and higher cardiac index was observed.⁴⁰ No difference in the occurrence and size of myocardial damage resulting from cardiac surgery was observed in two studies and cardiac index was the same as in saline infusion in one.^{41,42} Thus, it was suggested that there is a positive (inotropic) effect from high-dose insulin administration in patients who underwent cardiac surgery, but this has to be confirmed in larger, possibly randomised trials.

Coronary blood flow

Data on the effect of insulin administration on coronary blood flow are limited. Increased coronary sinus flow during GIK administration was determined in a number of studies.^{11,43,44} The observed increases in blood flow are relatively small (10 to 20%); however, and this small increase was confirmed in a study by Iozzo⁴⁵ in healthy humans using PET determined blood flow. It was also observed that insulin augmented the adenosine-induced blood flow increase by 25% in low-dose and 40% in high-dose insulin administration.⁴⁶ However, Ferrannini and co-workers¹³ did not observe an effect of insulin administration on coronary blood flow, determined with direct measurements in the coronary sinus during euglycaemic hyperinsulaemic clamp.

Summary

Insulin administration reduces free circulating FFAs and enhances myocardial glucose uptake, especially at high doses. Probably, high-dose insulin infusion enhances myocardial function significantly, especially in patients with myocardial dysfunction due to coronary artery disease. ■

Table 1. Insulin and cardiac function improvement.

Author	Number and type of subjects	Protocol/modality	Insulin equivalent $\mu\text{U/kg/h}$	Result
Khoury ²⁸	N=30 Chronic LV dysfunction due to CAD	Insulin 160 U/l + glucose 100 g/l + KCl 40 mmol/l at 30 ml/h for 4 hours vs. LDD wall motion improvement (max 40 $\mu\text{g/kg/min}$) Echocardiography	64†	Wall motion improvement in 62/244 dysfunctional segments with dobutamine and in 54/219 dysfunctional segments with GIK 79% agreement between wall motion improvement with GIK and with dobutamine Small but significant decrease in end-systolic volume with GIK No change in heart rate or blood pressure
Klein ²⁹	N=39 LV dysfunction due to (non-) STEMI, 5-8 days after MI	Insulin 100 mU/kg/h, glucose 200 g/l + KCl 40 mmol/l at variable rate vs. LDD 10 $\mu\text{g/kg/min}$ and placebo (6 controls receiving NaCl instead of GIK) Echocardiography	100	Wall motion improvement in 88/203 dysfunctional segments with dobutamine and in 98/198 dysfunctional segments with GIK 93% agreement between wall motion improvement with GIK and with dobutamine No change in heart rate or blood pressure
Yetkin ³⁰	N=32 Recent anterior wall MI (7±2 days old)	Insulin 100 $\mu\text{U/kg/h}$, glucose 250 g/l + KCl 80 mmol/l at 1 ml/kg/h† vs. LDD 10 $\mu\text{g/kg/min}$ Echocardiography	0.1 (100?)‡	LDD: improvement in wall motion in 57/285 segments GIK: improvement in wall motion in 62 of 288 segments Agreement 96% on patient level Similar improvement in wall-motion index During GIK: increase in blood pressure, heart rate and RPP similar to LDD
Yetkin ³¹	N=21 proven CAD and reduced LV function	Insulin 100 $\mu\text{U/kg/h}$, glucose 250 g/l + KCl 80 mmol/l at 1 ml/kg/h† vs. LDD 10 $\mu\text{g/kg/min}$ Echocardiography	0.1 (100?) ‡	LDD: improvement in wall-motion in 44/265 dysfunctional segments GIK: improvement in wall-motion in 52/265 dysfunctional segments Agreement on patient level 95% During GIK: increase in blood pressure, heart rate and RPP similar to LDD
Cottin ³²	N=12 LV dysfunction and stable CAD (MI > 6 months old)	Insulin 300 U/l + glucose 300 g/l + potassium 6 g/l at 1 ml/kg/h for 20 minutes Echocardiography	300	Improvement in wall motion score index at 20 minutes with further improvement at 40 and 60 minutes Reduction in end-systolic dimension and improvement in EF and fractional shortening at 40 and 60 minutes (but not at 20 minutes). End-diastolic volume unchanged.
Marano ³³	N=21 patients with recent MI	Insulin 40 U/l + glucose 100 g/l + KCl 80 mmol/l at 1 ml/kg/h for 24 hours (12 patients) vs. saline 0.9% at 1 ml/kg/h (9 patients) Tetrofosmin SPECT	40	Wall motion improvement in 22/155 segments with GIK, 1/144 with saline
Sasso ³⁴	N=44 22 diabetics, reduced LV function 22 normal subjects	Insulin 100 mU/kg/h + glucose 0.72 ml/kg/h for 2 hours vs. saline 2 ml/kg/h for 2 hours Gated blood pool scans (rest and stress)	100	Saline: no effect on EF at rest or at stress GIK: increase in rest EF in diabetics and increased EF with exercise in diabetics and in healthy volunteers
Alan ³⁵	N=30 Stable CAD and EF <40%	Insulin 300 U/l + glucose 300 g/l + potassium 6 g/l at 1 ml/kg/h for 24 hours Echocardiography, SPECT scintigraphy	300	Increase in EF (32±8% to 43±12%, $p<0.01$) Prolongation in diastolic filling period Decrease in pulmonary capillary wedge pressure

†Calculated for a subject of 75 kg. ‡ Probably erroneously reported as 100 $\mu\text{U/kg/h}$ instead of 100 mU/kg/h. CAD=coronary artery disease, EF=ejection fraction, GIK=glucose-insulin-potassium, LDD=low-dose dobutamine, LV=left ventricle, MI=myocardial infarction.

References

- 1 Visscher MB, Müller EA. The influence of insulin upon the mammalian heart. *J Physiol.* 1926;62:341-8.
- 2 Rogers WJ, Stanley AW Jr, Breinig JB, Prather JW, McDaniel HG, Moraski RE, et al. Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin-potassium infusion. *Am Heart J.* 1976;92:441-54.
- 3 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol.* 1979;237:E214-23.
- 4 Haneda T, Ganz W, Burnam MH, Katz J. Metabolic effects of glucose-insulin-potassium in the ischemic myocardium. *Jpn Heart J.* 1978;19:376-82.
- 5 Zhu P, Lu L, Xu Y, Greyson C, Schwartz GG. Glucose-insulin-potassium preserves systolic and diastolic function in ischemia and reperfusion in pigs. *Am J Physiol.* 2000;278:H595-603.
- 6 Heng MK, Norris RM, Peter T, Nisbet HD, Singh BN. The effect of glucose-insulin-potassium on experimental myocardial infarction in the dog. *Cardiovasc Res.* 1978;12:429-35.
- 7 Cave AC, Ingwall JS, Friedrich J, Liao R, Saupe KW, Apstein CS, et al. ATP synthesis during low-flow ischemia: influence of increased glycolytic substrate. *Circulation.* 2000;2:101:2090-6.
- 8 Hjermann I. A controlled study of peroral glucose, insulin and potassium treatment in myocardial infarction. *Acta Med Scand.* 1971;190:213-8.
- 9 Stanley AW, Jr., Moraski RE, Russell RO, Rogers WJ, Mantle JA, Kreisberg RA, et al. Effects of glucose-insulin-potassium on myocardial substrate availability and utilization in stable coronary artery disease. Studies on myocardial carbohydrate, lipid and oxygen arterial-coronary sinus differences in patients with coronary artery disease. *Am J Cardiol.* 1975;36:929-37.
- 10 Russell RO Jr, Rogers WJ, Mantle JA, McDaniel HG, Rackley CE. Glucose-insulin-potassium, free fatty acids and acute myocardial infarction in man. *Circulation.* 1976;53:1207-9.
- 11 Rogers WJ, Russell RO, Jr., McDaniel HG, Rackley CE. Acute effects of glucose-insulin-potassium infusion on myocardial substrates, coronary blood flow and oxygen consumption in man. *Am J Cardiol.* 1977;40:421-8.
- 12 McDaniel HG, Papapietro SE, Rogers WJ, Mantle JA, Smith LR, Russell RO Jr, et al. Glucose-insulin-potassium induced alterations in individual plasma free fatty acids in patients with acute myocardial infarction. *Am Heart J.* 1981;102:10-5.
- 13 Ferrannini E, Santoro D, Bonadonna R, Natali A, Parodi O, Camici PG. Metabolic and hemodynamic effects of insulin on human hearts. *Am J Physiol.* 1993;264:E308-15.
- 14 Szabo Z, Arnqvist H, Hakanson E, Jorfeldt L, Svedjeholm R. Effects of high-dose glucose-insulin-potassium on myocardial metabolism after coronary surgery in patients with Type II diabetes. *Clin Sci (Lond).* 2001;101:37-43.
- 15 Korvald C, Elvenes OP, Myrnes T. Myocardial substrate metabolism influences left ventricular energetics in vivo. *Am J Physiol Heart Circ Physiol.* 2000;278:H1345-51.
- 16 Klein LJ, Visser FC, Knaapen P, Peters JH, Teule GJJ, Visser CA, et al. ¹⁴C-acetate as a tracer of myocardial oxygen consumption. *Eur J Nucl Med.* 2001;28:651-68.
- 17 Lucchesi BR, Medina M, Kniffen FJ. The positive inotropic action of insulin in the canine heart. *Eur J Pharmacol.* 1972;18:107-15.
- 18 Ahmed SS, Lee CH, Oldewurtel HA, Regan TJ. Sustained effect of glucose-insulin-potassium on myocardial performance during regional ischemia. Role of free fatty acid and osmolality. *J Clin Invest.* 1978;61:1123-35.
- 19 Liang C, Doherty JU, Faillace R, Mackawa K, Arnold S, Gavras H et al. Insulin infusion in conscious dogs. Effects on systemic and coronary hemodynamics, regional blood flows, and plasma catecholamines. *J Clin Invest.* 1982;69:1321-36.
- 20 Lee JC, Downing SE. Effects of insulin on cardiac muscle contraction and responsiveness to norepinephrine. *Am J Physiol.* 1976;230:1360-5.
- 21 Downing SE, Lee JC. Myocardial and coronary vascular responses to insulin in the diabetic lamb. *Am J Physiol.* 1979;237:H514-9.
- 22 Schmidt HD, Koch M. Influence of perfusate calcium concentration on the inotropic insulin effect in isolated guinea pig and rat hearts. *Basic Res Cardiol.* 2002;97:305-11.
- 23 Ramanathan T, Shiota K, Morita S, Nishimura T, Huang Y, Hunyor SN. Glucose-insulin-potassium solution improves left ventricular mechanics in diabetes. *Ann Thorac Surg.* 2002;73:582-7.
- 24 Meijler FL, Offerijns FG, Willebrands AG, Groen J. Contractiemechanisme en elektrolythuishouding van het geïsoleerde, overlevende rattehart, mede in verband met de werking van insuline [Contraction mechanism and electrolyte balance of isolated surviving rat's heart, with reference to an insulin effect]. *Ned Tijdschr Geneesk.* 1959;103:1479-86.
- 25 Markovitz LJ, Hasin Y, Freund HR. The effect of insulin and glucagon on systolic properties of the normal and septic isolated rat heart. *Basic Res Cardiol.* 1985;80:377-83.
- 26 Airaksinen J, Lahtela JT, Ikaheimo MJ, Sotaniemi EA, Takkunen JT. Intravenous insulin has no effect on myocardial contractility or heart rate in healthy subjects. *Diabetologia.* 1985;28:649-52.
- 27 Regan TJ, Frank MJ, Lehan PH, Hellems HK. Relationship of insulin and strophanthidin to myocardial metabolism and function. *Am J Physiol.* 1963;205:790-4.
- 28 Khoury VK, Haluska B, Prins J, Marwick TH. Effects of glucose-insulin-potassium infusion on chronic ischaemic left ventricular dysfunction. *Heart.* 2003;89:61-5.
- 29 Klein LJ, van Campen LC, Sieswerda GT, Kamp O, Visser CA, Visser FC. Glucose-insulin-potassium echocardiography detects improved segmental myocardial function and viable tissue shortly after acute myocardial infarction. *J Am Soc Echocardiogr.* 2006;19:763-71.
- 30 Yetkin E, Senen K, Ileri M, Atak R, Tandogan I, Yetkin O, et al. Comparison of low-dose dobutamine stress echocardiography and echocardiography during glucose-insulin-potassium infusion for detection of myocardial viability after anterior myocardial infarction. *Coron Artery Dis.* 2002;13:145-9.
- 31 Yetkin E, Senen K, Ileri M, Atak R, Battaoglu B, Yetkin O, et al. Identification of viable myocardium in patients with chronic coronary artery disease and myocardial dysfunction: comparison of low-dose dobutamine stress echocardiography and echocardiography during glucose-insulin-potassium infusion. *Angiology.* 2002;53:671-6.
- 32 Cottin Y, Lhuillier I, Gilson L, Zeller M, Bonnet C, Toulouse C, et al. Glucose insulin potassium infusion improves systolic function in patients with chronic ischemic cardiomyopathy. *Eur J Heart Fail.* 2002;4:181-4.
- 33 Marano L, Bestetti A, Lomuscio A, Tagliabue L, Castini D, Taricone D, et al. Effects of infusion of glucose-insulin-potassium on myocardial function after a recent myocardial infarction. *Acta Cardiol.* 2000;55:9-15.
- 34 Sasso FC, Carbonara O, Cozzolino D, Rambaldi P, Mansi L, Torella D, et al. Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. *J Am Coll Cardiol.* 2000;36:219-26.
- 35 Alan S, Ulgen M, Dedeoglu I, Kaya H, Toprak N. Long-term glucose insulin potassium infusion improves systolic and diastolic function in patients with chronic ischemic cardiomyopathy. *Swiss Med Wkly.* 2003 26;133:419-22.
- 36 Hiesmayr M, Haider WJ, Grubhofer G, Heilingner D, Keznickl FP, Mares P, et al. Effects of dobutamine versus insulin on cardiac performance, myocardial oxygen demand, and total body metabolism after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth.* 1995;9:653-8.
- 37 Coleman GM, Gradinac S, Taegtmeyer H, Sweeney M, Frazier OH. Efficacy of metabolic support with glucose-insulin-potassium for left ventricular pump failure after aortocoronary bypass surgery. *Circulation.* 1989;80:191-6.
- 38 Lazar HL, Philippides G, Fitzgerald C, Lancaster D, Shemin RJ, Apstein C. Glucose-insulin-potassium solutions enhance recovery after urgent coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1997;113:354-60.
- 39 Taegtmeyer H, Goodwin GW, Doenst T, Frazier OH. Substrate metabolism as a determinant for postischemic functional recovery of the heart. *Am J Cardiol.* 1997;80:3A-10A.
- 40 Lazar HL, Chipkin S, Philippides G, Bao Y, Apstein C. Glucose-insulin-potassium solutions improve outcomes in diabetics who have coronary artery operations. *Ann Thorac Surg.* 2000;70:145-50.

- 41 Bruemmer-Smith S, Avidan MS, Harris B, Sudan S, Sherwood R, Desai JB, et al. Glucose, insulin and potassium for heart protection during cardiac surgery. *Br J Anaesth.* 2002;88:489-95.
- 42 Lell WA, Nielsen VG, McGiffin DC, Schmidt FE Jr, Kirklin JK, Stanley AW Jr. Glucose-insulin-potassium infusion for myocardial protection during off- pump coronary artery surgery. *Ann Thorac Surg.* 2002;73:1246-51.
- 43 McNulty PH, Pfau S, Deckelbaum LI. Effect of plasma insulin level on myocardial blood flow and its mechanism of action. *Am J Cardiol.* 2000;85:161-5.
- 44 McDaniel HG, Rogers WJ, Russell RO Jr, Rackley CE. Improved myocardial contractility with glucose-insulin-potassium infusion during pacing in coronary artery disease. *Am J Cardiol.* 1985;55:932-6.
- 45 Iozzo P, Charconthaitawee P, Di TM, Betteridge DJ, Ferrannini E, Camici PG. Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans. *Am J Physiol Endocrinol Metab.* 2002;282:E1163-71.
- 46 Sundell J, Nuutila P, Laine H, Luotolahti M, Kalliokoski K, Raitakari O, et al. Dose-dependent vasodilating effects of insulin on adenosine-stimulated myocardial blood flow. *Diabetes.* 2002;51:1125-30.