Detecting Hibernated Myocardium with SPECT and Thallium-Glucose-Insulin Infusion

Flavio Tartagni, Francesco Fallani, Claudio Corbelli, Antonio Balletta, Roberto Franchi, Alessandro Lombardi, Bartolomeo Bellanova, Augusto Sardella, Nicoletta Franco and Nino Monetti

Institute for Cardiovascular Diseases and Nuclear Medicine Department, University of Bologna, Bologna, Italy

Because thallium kinetics, like potassium kinetics, may be affected by serum insulin levels, we performed two pilot studies to identify severely ischemic myocardium using different protocols based on the infusion of a thallium, insulin, potassium and glucose solution. Results were compared with those obtained with two currently used protocols based on rest injection or reinjection of ^{201}Tl. **Methods:** In the first study (Protocol 1) of 15 men with a previous large myocardial infarction, perfusion was evaluated by SPECT in 20 segments after a 30-min infusion of ^{201}Tl (111 MBq), insulin (5 U) and potassium (10 mEq) in 10% glucose solution (250 ml). Imaging was repeated 30 min later and the results were compared with those obtained from stress and 3-hr reinjection images. In the second study (Protocol 2), 15 patients were evaluated randomly at rest and 3 hr later (rest-redistribution). On a separate day, the patients were then re-evaluated after infusion of ^{201}Tl (111 MBq), potassium (10 mEq) and insulin (5 U) in 5% glucose (250 ml); images were obtained 90 and 180 min postinjection. **Results:** In Protocol 1, radiotracer activity in segments with no uptake during stress was detected in 35% with the reinjection technique and 58% with the insulin solution protocol. In Protocol 2, 31% of segments revealed thallium activity after insulin infusion but not at rest or rest-redistribution. Serum measurements showed high insulin levels (444 ± 138 in Protocol 1, 125 ± 33 mU/ml in Protocol 2), although glucose levels were not significantly altered (149 ± 32 versus 71 ± 20 mg/dl, respectively). Potassemia was not affected and the patients tolerated the tests satisfactorily. **Conclusion:** These results confirm that continuous infusion of ^{201}Tl with a low dose of insulin in a glucose/potassium chloride solution is safe and may enhance cellular uptake of the radiotracer in severe ischemic regions, thereby improving viable myocardium detection.

Key Words: viable myocardium; thallium-201; glucose-insulin infusion; myocardial scintigraphy

J Nucl Med 1995; 36:1377–1383

Although PET is considered the gold standard for assessing myocardial viability, alternative procedures based on radionuclide imaging have been proposed. The ability of ^{201}Tl to react as a potassium analog and concentrate and redistribute only in viable tissue has led to its widespread use in the detection of hibernating myocardium (*1–5*). The results reported by these clinicians appear satisfactory. Nevertheless, the fact that viable myocardium is still underestimated justifies efforts to find new protocols that might provide an alternative to PET in terms of feasibility and cost. Thallium is both a metabolic and a perfusion marker. Therefore, we decided to investigate its myocardial uptake before or during insulin infusion. Aside from its main effect on glucose and cations metabolism, insulin might enhance the uptake of the radiocompound in those regions with low coronary blood flow and impaired cellular function by the following mechanisms: increased coronary blood flow (*6–7*), membrane stabilizing and free radical scavenging effects (*8–10*) and preservation of cardiac glycogen stores (*11–12*). To enhance the washin phase, insulin infusion should precede or coincide with thallium administration. Later administration of insulin without ^{201}Tl would in fact speed up the washout phase by potassium/thallium displacement. Since many variables affect maximum uptake of severely ischemic areas, such as compound dosage (thallium, insulin) and times (infusion, imaging), we evaluated two different protocols that might encourage larger studies in the future.

METHODS

Protocol 1

Patients. Fifteen men (mean age 61 ± 5 yr; range 56–68), with previous myocardial infarction (10 anterior, 5 inferior) were studied. Patients with diabetes or glucose intolerance were not evaluated. All patients underwent coronary angiography and ventriculography by standard techniques. Eight patients had triple-vessel, four double-vessel and three single-vessel disease (defined as equaling 70% lumen reduction). Mean ejection fraction was 37% ± 9%. Scintigraphic studies were performed after a 12-hr overnight fast and in the absence of antianginal medication. All patients gave informed consent.

Study Design. A SPECT study was performed after thallium injection (111 MBq) at maximum symptom-limited effort (Fig. 1A). A second study was repeated 3 to 4 hr later after reinjection of a second dose (37 MBq) of thallium. On a different day, another SPECT study was performed after a 30-min infusion of 111 MBq ^{201}Tl in 250 ml of 10% glucose plus insulin (5 U) and 10 mEq potassium chloride. Imaging was repeated 1 hr later. Two catheters were inserted in the antecubital veins, one for infusion of the radiolabeled solution and one for blood sampling. The infusion

Received Dec. 22, 1993; revision accepted Oct. 24, 1994.
For correspondence or reprints contact: Flavio Tartagni, MD, Ist. di Malattie Cardiovascolari, Ospedale S. Orsola-Malpighi, Via Massarenti, 40138 Bologna, Italy.

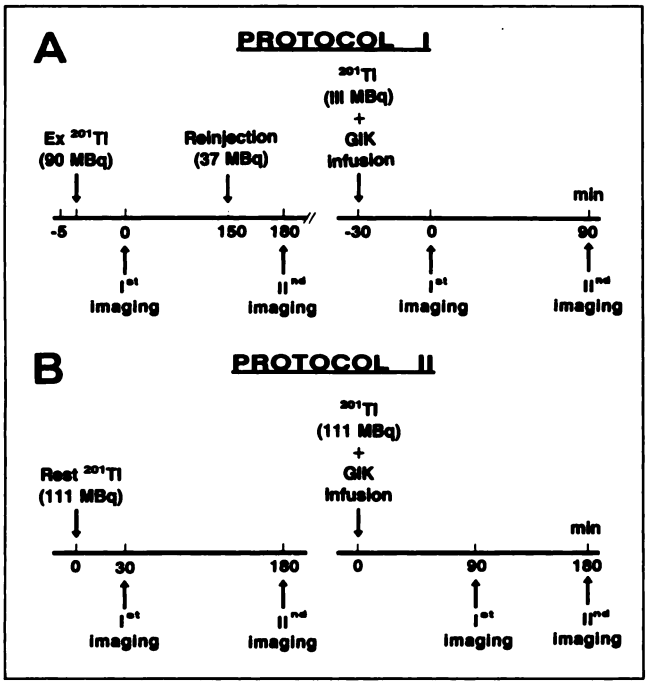

FIGURE 1. Comparison of the two protocols. Thallium and insulin doses are similar in contrast to solutes and infusion/imaging times. GIK = glucose, insulin and potassium solution.

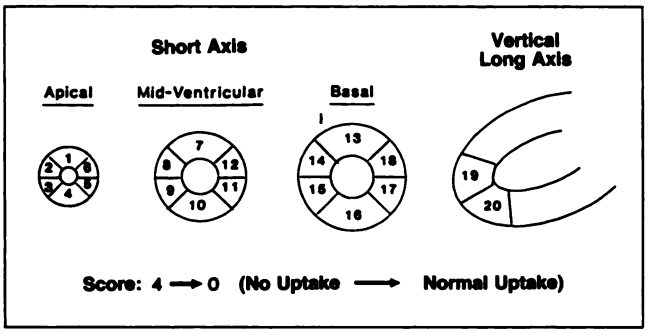

FIGURE 2. Subdivision of left ventricle into 18 anatomic short-axis regions (left) and 2 long-axis apical regions (right). Thallium uptake was visually scored.

rate was adjusted using an automatic pump and blood samples were taken at 8–10-min intervals to measure plasma glucose and at 30-min intervals for plasma-insulin and potassium assessment.

Protocol 2

Patients. Fifteen men (age 57 ± 4; range 51–65 yr) with previously documented large myocardial infarction (nine anterior, six inferior) were included in the study. Two patients had single-vessel, six had double-vessel and seven had triple-vessel disease. Mean ejection fraction was 40% ± 8%. Medication was discontinued from the day before the examination. Fasting was not required since the protocol study lasted many hours. As in Protocol 1, patients with low glucose tolerance were not evaluated.

Study Design. Patients were randomly submitted to rest and rest-redistribution studies on one day and pharmacological investigation on another. The interval between the studies was not less than 1 wk (Fig. 1B). Thallium (111 MBq) was added to a 5% glucose solution with insulin (5 U) plus potassium chloride (10 mEq) and infused through a vein catheter over 180 min with an automatic pump. Blood samples were obtained and analyzed as described in Protocol 1. SPECT imaging was performed after 90 min and at the end of infusion (180–200 min from the beginning). All patients gave informed consent.

Analytical Procedures

Plasma-glucose was measured by a readily available blood glucose meter, and potassium activity was determined in duplicate by flame photometry. Plasma-free insulin was measured by radioimmunoassay.

Image Acquisition and Processing

For all SPECT studies, the patients were positioned supine and data were collected over a 180° rotational arc in a step-and-shoot mode using a single-head tomograph. All data were corrected for deadtime and reconstructed in a 128 × 128 matrix. No correction was made for attenuation. Myocardial images were divided into 18 segments in the short axis (apical, midventricular and basal slices) plus two segments in the vertical long axis for apical perfusion (Fig. 2). Three expert observers assessed thallium uptake blindly by visual inspection based on a 0–4 score, in which 0 = normal perfusion, 4 = uptake, 1 = mild perfusion defects, 2 = moderate perfusion defects and 3 = severe perfusion defects. Disagreements were resolved by consensus. Image quality was subjectively assessed using a four-point scoring system (1 = poor, 2 = fair, 3 = good, 4 = excellent) based on visual myocardial-to-background activity ratios, left ventricular endocardial and epicardial border definition and contrast of perfusion defects.

Statistical Analysis

Differences in metabolic parameters were determined by paired t-test or by one-way analysis of variance for multiple measures. The extent of perfusion in different subgroups was analyzed by McNemars test.

RESULTS

Protocol 1

Side effects. No patient experienced major side effects. Two patients reported dizziness and one patient had sinus tachycardia (heart rate >120 bpm). Glucose administration succeeded in rapidly suppressing these disturbances in all three patients.

Biochemistry. Plasma serum glucose, insulin and potassium levels at the beginning and end of the glucose-insulin-potassium (GIK) infusion are summarized in Table 1. Insulin levels were affected significantly by exogenous administration (19 ± 7 mU/ml at baseline versus 444 ± 138 after GIK infusion; $p < 0.001$). Insulin blood concentrations were larger than those used in other studies, which demonstrated a pharmacological effect of insulin on the sodium/potassium membrane cell pump (*13,14*). Glycemia increased during GIK infusion from 89 ± 16 mg/dl to 149 ± 32 mg/dl and then rapidly decreased in the following 30 min to 67 ± 12 mg/dl. All values reached statistical significance by Bonferroni testing. Blood glucose was below 50 mg/dl at 30 min at the end of the GIK infusion in two patients (13%). Potassium levels were not affected by this protocol.

Image Quality. Visual quality was judged fair in all image sets. Good or excellent image quality was observed in 14, 11, 12 and 11 patients during the stress, reinjection,

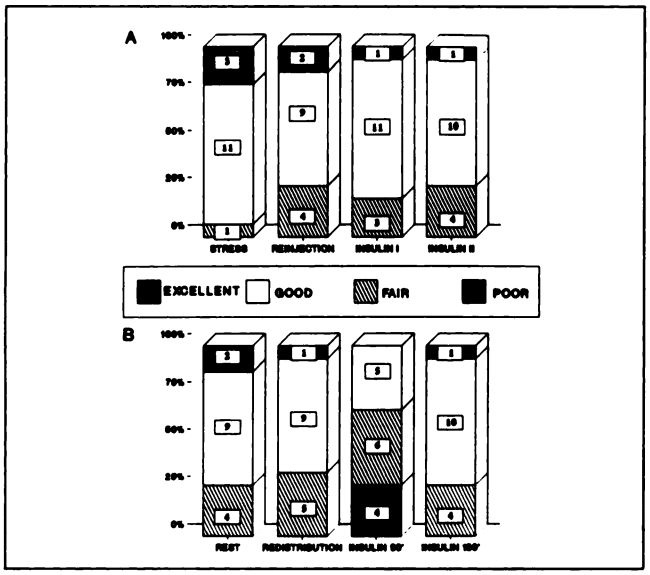

FIGURE 3. Relationship between image quality and different studies in the two protocols (A, B). The numbers on the bar graphs indicate the patients associated with the image quality. The studies in Protocols 1 (A) and 2 (B) are reported below each bar.

early and late GIK infusion studies, respectively (Fig. 3A). In four patients, early images after GIK were better than the reinjection images, while the opposite was found in four other patients.

Perfusion Analysis. The segmental myocardial uptake score is reported in Figure 4. Since imaging and viable myocardium detection were better in early versus late GIK studies (74 versus 95 segments scored 3 or 4; $p < 0.001$), we compared the early image with the reinjection study. Improved perfusion in the 146 (49%) severely underperfused segments at stress (score 3 or 4) was observed in 25% of patients who had the reinjection study and in 53% who had GIK infusion ($p < 0.001$). The improvement in the perfusion score was 41 and 139, respectively. Seventy-three segments (24%) had a score of 4 with the reinjection study, as did 51 segments (17%) with GIK infusion ($p < 0.001$).

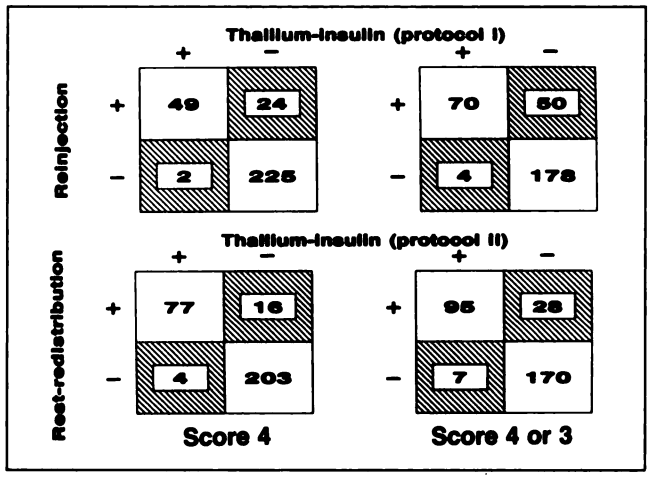

FIGURE 4. Agreement for detection of myocardial perfusion in segments with low (score 3) or no uptake (score 4) in Protocols 1 and 2. Only the reinjection and early insulin studies are considered for Protocol 1, while only the rest-redistribution and 180-min insulin studies are considered for Protocol 2.

	Stress	Reinjection	Insulin I	Insulin II	Rest	Rest-red.	Insulin 90'	Insulin 180'
Score 0	85	107	119	110	102	102	104	111
Score 1	31	41	57	45	31	41	37	46
Score 2	38	32	50	40	26	34	27	41
Score 3	59	47	23	36	37	30	33	21
Score 4	87	73	51	69	104	93	99	81
	Protocol I				Protocol II			

FIGURE 5. Differences in score uptake of thallium in the 300 segments evaluated by the different studies (top) in the two protocols (bottom).

There were 120 (38%) and 74 (25%) severely underperfused segments (score 3 or 4) with the reinjection and GIK infusion studies, respectively ($p < 0.001$) (Fig. 5). Score differences between the two studies are summarized in Figure 6. A significant score improvement (>2) of the severely underperfused segments in at least three segments was observed in four patients (27%) with the ^{201}Tl GIK infusion.

Protocol 2

Side Effects. No major side effects occurred. One patient experienced dizziness with spontaneous recovery.

Biochemistry. Increased insulin levels induced by this GIK protocol were lower than that in Protocol 1 (12 ± 6 mU/ml at baseline versus 125 ± 33 mU/ml after GIK infusion; $p < 0.001$) (Table 1). Glycemia decreased after GIK infusion from 98 ± 19 mg/dl to 71 ± 20 mg/dl ($p < 0.05$). Glycemia did not fall below 50 mg/dl in any case. Potassium values were unchanged.

TABLE 1
Seric Parameters for Protocols 1 and 2

	Protocol 1		
	Baseline	GIK	p
Plasma insulin (μU/ml)	19± 7	444±138	<0.001
Plasma glucose (mg/dl)	89± 16	149± 32	<0.01
Plasma potassium (mEq/liter)	4.4±0.4	4.3± 0.3	ns
	Protocol 2		
	Baseline	GIK	p
Plasma insulin (μU/ml)	12± 6	125± 33	< 0.001
Plasma glucose (mg/dl)	98± 19	71± 20	< 0.05
Plasma potassium (mEq/liter)	4.1±0.2	3.9± 0.4	ns

GIK = Glucose, insulin and potassium solution.

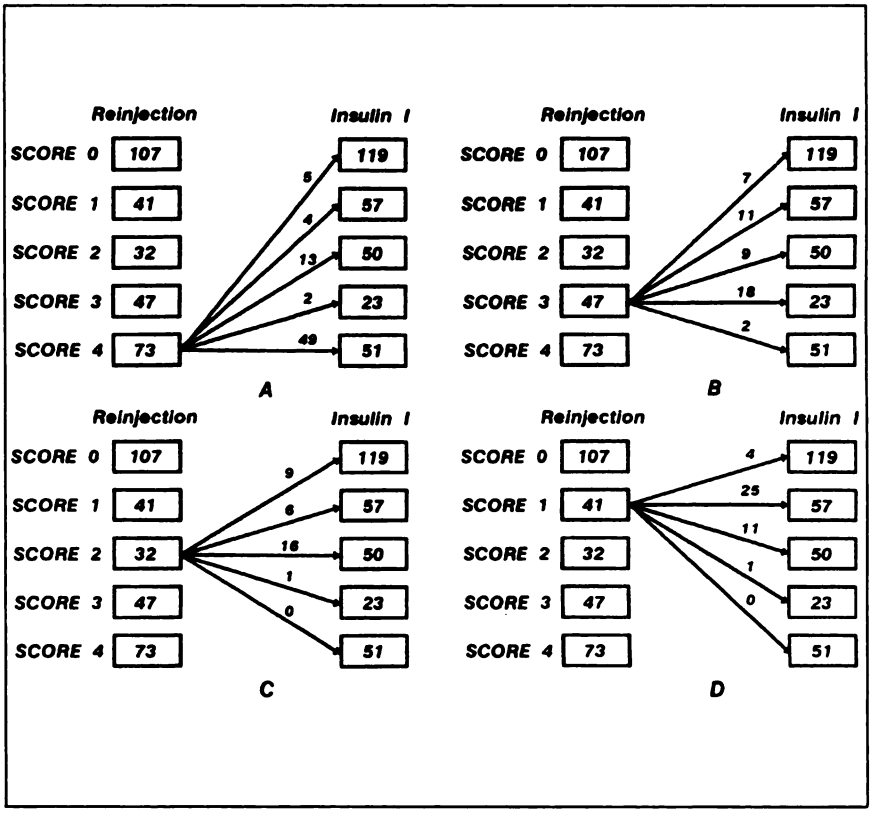

FIGURE 6. Variations of thallium uptake in segments with scores from 4 to 1 (from A to D, respectively) in Protocol 1. Only the reinjection and early insulin studies are considered.

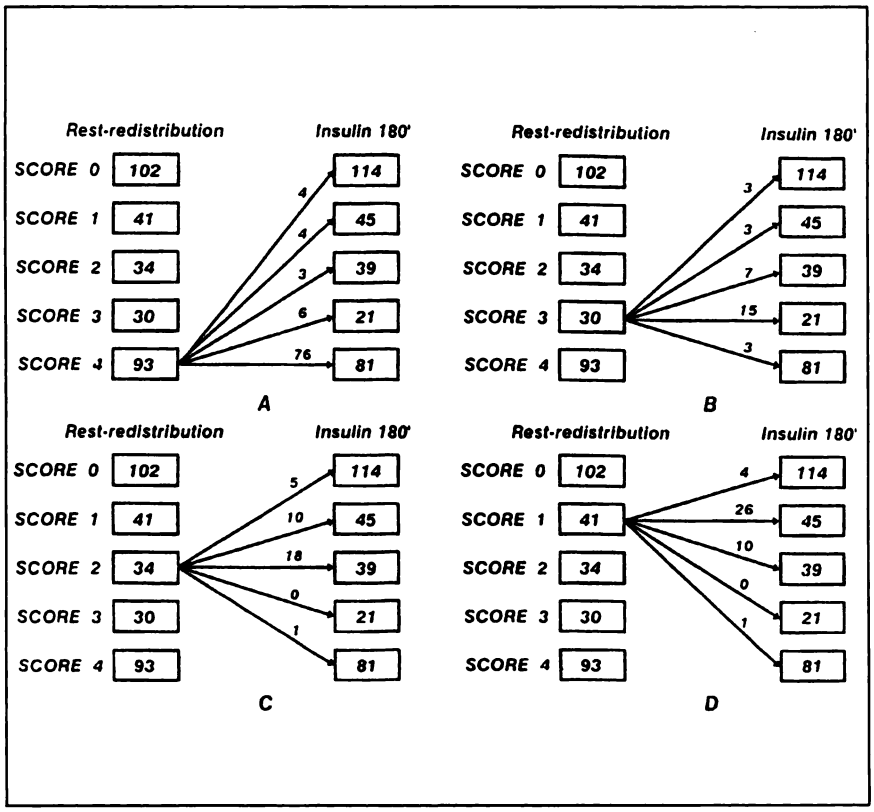

FIGURE 7. Variations of thallium uptake in segments with scores from 4 to 1 (from A to B respectively) in Protocol 2. Only the rest-redistribution and late (180 min) insulin studies are considered.

Image Quality. Visual quality was considered fair in all image sets, except the images of four patients (27%) that were obtained 90 min after GIK infusion (Fig. 3B). No significant differences were observed in image quality between rest-redistribution and later (180 min) GIK infusion.

Perfusion Analysis. Segmental myocardial uptake results are reported in Figure 4. A comparison between rest-redistribution and Tl-GIK infusion at 30 min was made with regard to detection of myocardial viability. There was good correlation between the two studies for severe underperfused myocardial segments (Fig. 5). Ninety-three segments (31%) from the rest-redistribution study had a score of 4, whereas 81 segments from the GIK study (27%) had a score of 4 ($p < 0.05$). For the rest-redistribution and GIK studies, 123 (41%) and 102 (34%) segments were judged severely underperfused (score 3 or 4, $p < 0.01$). Score differences between the two studies are summarized in Figure 7.

A significant score improvement (>2) of the severely underperfused segments in at least three segments at rest-redistribution was observed in three patients (20%) with the GIK study.

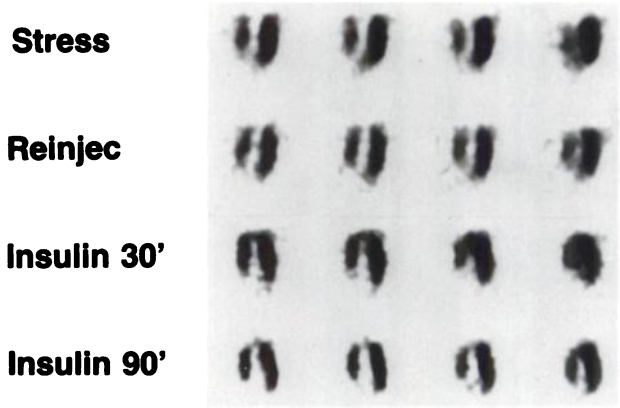

FIGURE 8. Horizontal long-axis tomograms: apical and septal defects in stress and after reinjection studies. Tracer uptake is clearly increased in both the apical and septal walls after thallium and insulin infusion (Protocol 1), especially in the early images.

DISCUSSION

Because of the similarities in thallium and potassium kinetics (*15–17*), thallium may be affected by insulin administration. Few data exist, however, on the effects of insulin on the cellular dynamics of thallium and myocardial thallium uptake in humans. The most important and well known insulin-induced effect is on glucose metabolism (*18*). Insulin effects on potassium cellular turnover, although independent of metabolic changes (*19–20*), are likewise very important and have been documented in skeletal (*20–22*) and cardiac muscle (*23–24*) as well as adipose tissue (*21–25*). Insulin also elicits many effects that may be potentially helpful in detecting hypoperfused, though still viable, myocardium.

In an earlier experimental study, Hellmuth et al. found no improved thallium uptake in five dogs (*26*). Hellmuth et al., however, only studied thallium effects in normal myocardium after bolus injection with high extraction under basal conditions (89%). The GIK solution following a bolus load resulted in a net increase in ^{201}Tl clearance in normal and ischemic myocardium (*27*). The differences found between normal and ischemic zones may explain recorded clinical results when poststress redistribution was evaluated after ingestion of a high carbohydrate meal (*28–29*). Indeed, a faster release of thallium in ischemic areas might explain the reduced redistribution.

Low insulin levels of endogenous or exogenous origin should be maintained when a diagnostic test for acute ischemia is performed, since displacement of ^{201}Tl already inside the myocardial cell by enhanced potassium entry would limit detection of late redistribution. Insulin administration before or during thallium infusion, however, should favor thallium cellular uptake, especially in severely ischemic regions where the extraction fraction after bolus injection is markedly reduced.

Knuuti et al. used PET and metabolic intervention with the euglycemic hyperinsulinemic clamp to stimulate myocardial glucose activity (*30*). Although technically more demanding, this method has definite advantages over studies performed with oral glucose load, such as improved image quality and detection of viable myocardium. The use of ribose in animal models and humans appears to facilitate ^{201}Tl redistribution, although the actual mechanisms have not been elucidated (*31–33*).

Insulin acts on cations by increasing membrane conductance through activation of the Na/K ATP-sensitive pump (*34*); passive influx is then favored by sodium efflux as a consequence of electrical gradient. Clinically, it is known that hypokalemia may follow insulin infusion. This effect has been used in reducing high potassium levels in patients with renal failure, in whom a solution containing insulin showed rapid, effective action (*13*). Small increases in plasma levels (25–40 mU/ml) stimulate potassium uptake by muscle, adipose and other tissue, although splanchnic effects may precede those involving other organs (*14,35,36*).

It is extremely important to identify optimal times for detecting hibernating myocardium. The most favorable conditions would be when the heart-to-background ratio is high and the ratio between normal and ischemic myocardial regions is low. A more rapid potassium/thallium turnover in normal regions may favor detection of myocardial zones that are metabolically impaired.

Results from Protocol 1 showed marked improvement in myocardial imaging (Fig. 8). The fact that we did not perform redistribution imaging before reinjection is open to criticism, since thallium uptake is undetected because of reverse redistribution phenomena in 5%–10% of patients. Redistribution imaging, however, would not have altered the final outcome of the study significantly.

While the results of Protocol 2 are more modest than Protocol 1, there was improved myocardial detection in

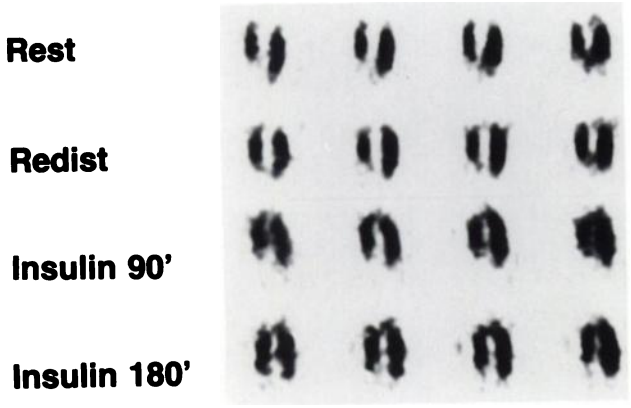

FIGURE 9. Horizontal long-axis tomograms: apical defect in rest images. After thallium and insulin infusion (Protocol 2), thallium uptake is increased in the apex. Redist = redistribution.

almost half of the patients. Image quality was satisfactory in most cases, especially when late studies were considered (Fig. 9).

The poor image quality obtained from some of the early exams can be ascribed to the lower dose of infused thallium at the time of the first imaging session. Lower heterogeneity during insulin studies must be considered a consequence of real and not relative increased uptake, since ultrasonography has shown that there is no change in transmural wall thickness during GIK infusion (*27*).

Special attention should be paid to the patient's physical reaction to the tests. Although the insulin dose is low and not specifically titrated on body weight, it can induce remarkable effects on biochemical parameters. The multifold increase of plasma-insulin levels can induce severe hypoglycemic effects if not counterbalanced by high glucose parenteral and oral administration. A 10% glucose solution in 250 ml can supply adequate intake to prevent hypoglycemia and promote endogenous production of insulin. Possible hypoglycemic states may occur in some patients at late control (controls are not part of the protocol, they are intended as clinical surveillance controls) (1–2 hr after late imaging). Even in the absence of clinical problems, we advise patients to eat a light carbohydrate meal after completion of the exam. No significant modifications were observed in serum potassium with parenteral potassium chloride supplementation. Continuous thallium infusion can elicit improved uptake in underperfused areas. A bolus injection may favor higher extraction in normal myocardium versus ischemic zones and is highly preferable for detecting acute ischemia.

Conversely, slow infusion may enhance thallium uptake in cells where perfusion is low and membrane pumps underoperative. We were unable to ascertain to what extent the slow administration of thallium might affect uptake. A recent study by Burns et al. (*37*) seemed to demonstrate that continuous thallium infusion can improve the detection of viable myocardium. In a preliminary study (unpublished data), we found that insulin may enhance the washin phase of thallium even further. Additional studies are necessary to distinguish the roles of these two variables.

Alternative protocols could lead to even better results. Insulin, for instance, could be administered as a bolus injection before thallium or between two split doses of the radiotracer, or at higher dosages, although phlebitis secondary to hypertonic solutions with glucose and potassium chloride might ensue. The high incidence of open vessels and hypo-akinetic segments (not dyskinetic) in areas with improved uptake (77% and 68%, respectively) in our study, however, is consistent with myocardial viability. Since many of our patients will undergo cardiac revascularization, we can verify the outcome on myocardial contractility.

CONCLUSION

We believe that high insulin levels should be avoided when cardiac diagnostic tests are performed. They may, however, be useful in some patients in whom the detection of even small amounts of viable myocardium may be important. Insulin infusion may be particularly helpful in determining revascularization therapies and in identifying patients with poor prognosis due to electrical instability and ventricular arrhythmias (*38*). From this viewpoint, a more elaborate investigation would be clinically justified and rewarding.

ACKNOWLEDGMENTS

The authors thank Drs. Stefano Boschi and Maurizio Levorato for blood analysis and Dr. Steve Jewkes for translation expertise.

REFERENCES

1. Iskandrian AS, Jaekyeong H, Thach N. Assessment of myocardial viability. *Am Heart J* 1990;120:1012–1014.
2. Yang LD, Berman DS, Kiat H, et al. The frequency of late reversibility in SPECT thallium-201 stress-redistribution studies. *J Am Coll Cardiol* 1990; 15:334–340.
3. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990;323:141–146.
4. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction. *Circulation* 1991;83:26–37.
5. Dondi M, Tartagni F, Fallani F, et al. A comparison of rest sestamibi and rest-redistribution thallium single-photon emission tomography: possible implications for myocardial viability detection in infarcted patients. *Eur J Nucl Med* 1992;127:26–31.
6. Groeneveld ABJ, Lambalgen A, van den Bos GC, Nauta JJP, Thijs LG. Metabolic vasodilatation with glucose-insulin potassium does not change the heterogeneous distribution of coronary blood flow in the dog. *Cardiovasc Res* 1992;26:757–764.
7. Liang CS, Doherty JU, Faillace R, et al. Insulin infusion in coscious dogs. Effects on systemic and coronary hemodynamics, regional blood flow and plasma catecholamines. *J Clin Invest* 1982;69:1321–1336.
8. Opie LH. Metabolism of free fatty acids, glucose and catecholamines in acute myocardial infarction. *Am J Cardiol* 1975;36:938–952.
9. Muller JE, Mochizuki S, Koster JK, Collins J, Cohn LH, Neely JR. Insulin terapy for depressed myocardial contractility after prolonged ischemia. *Am J Cardiol* 1978;41:1215–1221.
10. Hess ML, Okabe E, Poland J, Warner M, Stewart JR, Greenfield LJ. Glucose, insulin and potassium protection during the course of hypothermic global ischemia and reperfusion: a new proposed mechanism by scavenging of free radicals. *J Cardiovasc Pharmacol* 1983;5:35–43.
11. Gelli MG, Enhorning G, Hultman E, Bergstrom J. Glucose infusion in the

pregnant rabbit and its effect on glycogen content and activity of the foetal heart under anoxia. *Acta Paediatr Scand* 1968;57:209–215.
12. Lagerstrom CF, Walker WE, Taegtmeyer H. Failure of glycogen depletion to improve left ventricular function of the rabbit heart after hypothermic ischemic arrest. *Circ Res* 1988;63:81–88.
13. Blumberg A, Weidmann P, Shaw S, Markus G. Effects of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988;85:507–508.
14. Margaret J, DeFronzo RA. Extrarenal potassium homeostasis. *Am J Physiol* 1981;240:F257–F268.
15. Krivokapich J, Shine KI. Effects of hyperkalemia and glycoside on ^{201}Tl exchange in rabbit ventricle. *Am J Physiol* 1981;240:H612–H616.
16. L'Abbate A, Biagini A, Michelassi C, Maseri A. Myocardial kinetics of ^{201}Tl and potassium in man. *Circulation* 1979;60:776–782.
17. Ku D, Akera T, Tobin T. Effects of monovalent on cardiac Na+, K+-ATPase activity on contractile force. *Arch Pharmacol* 1975;290:113–118.
18. Lienhard GE, Slot JW, James DE, Mueckler MM. How cells absorb glucose. *Sci Am* 1992;86–91.
19. Zierler KL. Hyperpolarization of muscle by insulin in a glucose free environment. *Am J Physiol* 1951;197:524–526.
20. Zierler KL. Effect of insulin on potassium efflux from rat muscle in the presence and absence of glucose. *Am J Physiol* 1968;198:1066–1070.
21. Clausen T, Hansen O. Active Na-K transport and the rate of ouabain binding. The effect of insulin and other stimuli on skeletal muscle and adipocytes. *J Physiol London* 1977;270:415–430.
22. Gourley DRH. Effect of insulin on potassium exchange in normal and ouabain-treated skeletal muscle. *J Pharmacol Exp* 1965;148:339–347.
23. Rogers WJ, Russell RO, McDaniel HG, Rockley CR. Acute effects of glucose-insulin-potassium infusion on myocardial substrates, coronary blood flow and oxygen consumption in man. *Am J Cardiol* 1977;40:421–428.
24. Regan TJ, Frank MJ, Lehan PH, Hellems HK. Relationship of insulin and strophanthidin to myocardial metabolism and function. *Am J Physiol* 1963; 205:790–794.
25. Perry MC, Hales CN. Rates of efflux and intracellular concentrations of potassium, sodium, and chloride ions in isolated fat cells from the rat. *Biochem J* 1969;115:865–871.
26. Hellmuth FW, Strauss HW, Pitt BP. The extraction of ^{201}Tl by the myocardium. *Circulation* 1977;56:188–191.
27. Wilson RA, Okada RD, Strauss HW, Pohost MG. Effect of glucose-insulin-potassium infusion on thallium myocardial clearance. *Circulation* 1983;68: 203–209.
28. Angello DA, Wilson RA, Palac RT. Effect of eating on ^{201}Tl myocardial redistribution after myocardial ischemia. *Am J Cardiol* 1987;60:528–533.
29. Wilson RA, Sullivan PJ, Okada RD, Boucher CA, Morris C, Pohost GM, Strauss HW. The effect of eating on thallium myocardial imaging. *Chest* 1986;89:195–201.
30. Knuuti MJ, Nuutila P, Ruotsalainen U, et al. Euglicemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992;33:1255–1262.
31. Angello DA, Wilson RA, Gee D. Effect of ribose on ^{201}Tl myocardial redistribution. *J Nucl Med* 1988;12:1943–1950.
32. Michael G, Hegewald MD, Robert T, Palac MD, Angello DA, Neal SP, Richard AW. Ribose infusion accelerates thallium redistribution with early imaging compared with late 24-hr imaging without ribose. *J Am Coll Cardiol* 1991;18:1671–1681.
33. Perlmutter NS, Wilson RA, Angello DA, Palac RT, Lin J, Brown BG. Ribose facilitates ^{201}Tl redistribution in patients with coronary heart disease. *J Nucl Med* 1991;32:193–200.
34. Runnman EM, Lamp ST, Weiss JN. Enhanced utilization of exogeneous glucose improves cardiac function in hypoxic rabbit ventricle without increasing total glycolytic flux. *J Clin Invest* 1990;86:1222–1233.
35. DeFronzo RA, Felig P, Ferranninie E, Wharen J. Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. *Am J Physiol* 1980;238:421–427.
36. DeFronzo RA, Lee R, Jones A, Bia M. Effect of insulinopenia and adrenal hormone deficiency on acute potassium tolerance. *Kidney Int* 1980;17:586–594.
37. Burns RJ, Wright LM, Lumsden CH, Zielinski A, Ogilvie RI. Hibernating Myocardium: detection by rest ^{201}Tl infusion SPECT [Abstract]. *Circulation* 1993;88:2877.
38. Di Carli MF, Davidson M, Little R, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. *Am J Cardiol* 1994;73:527–533.