Insulin Resistance and Vasodilation in Essential Hypertension

Studies with Adenosine

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Abstract

Insulin-mediated vasodilation has been proposed as a determinant of in vivo insulin sensitivity. We tested whether sustained vasodilation with adenosine could overcome the muscle insulin resistance present in mildly overweight patients with essential hypertension. Using the forearm technique, we measured the response to a 40-min local intraarterial infusion of adenosine given under fasting conditions (n = 6) or superimposed on a euglycemic insulin clamp (n = 8). In the fasting state, adenosine-induced vasodilation (forearm blood flow from 2.6±0.6 to 6.0±1.2 ml $min^{-1}dl^{-1}$, $P < 0.001$) was associated with a 45% rise in muscle oxygen consumption (5.9±1.0 vs 8.6±1.7 μmol $min^{-1}dl^{-1}$, $P < 0.05$), and a doubling of forearm glucose uptake (0.47±0.15 to 1.01±0.28 μmol $min^{-1}dl^{-1}$, $P < 0.05$). The latter effect remained significant also when expressed as a ratio to concomitant oxygen balance (0.08±0.03 vs 0.13±0.04 μmol μmol^{-1}, $P < 0.05$), whereas for all other metabolites (lactate, pyruvate, FFA, glycerol, citrate, and β-hydroxybutyrate) this ratio remained unchanged.

During euglycemic hyperinsulinemia, whole-body glucose disposal was stimulated (to 19±3 μmol $min^{-1}kg^{-1}$), but forearm blood flow did not increase significantly above baseline (2.9±0.2 vs 3.1±0.2 ml $min^{-1}dl^{-1}$, P = NS). Forearm oxygen balance increased (by 30%, $P < 0.05$) and forearm glucose uptake rose fourfold (from 0.5 to 2.3 μmol $min^{-1}dl^{-1}$, $P < 0.05$). Superimposing an adenosine infusion into one forearm resulted in a 100% increase in blood flow (from 2.9±0.2 to 6.1±0.9 ml $min^{-1}dl^{-1}$, $P < 0.001$); there was, however, no further stimulation of oxygen or glucose uptake compared with the control forearm. During the clamp, the ratio of glucose to oxygen uptake was similar in the control and in the infused forearms (0.27±0.11 and 0.23±0.09, respectively), and was not altered by adenosine (0.31±0.9 and 0.29±0.10). We conclude that in insulin-re15-76sistant patients with hypertension, adenosine-induced vasodilation recruits oxidative muscle tissues and exerts a modest, direct metabolic effect to promote muscle glucose uptake in the fasting state. Despite these effects, however, adenosine does not overcome muscle insulin resistance. (*J. Clin. Invest.* 1994. 94:1570–1576). Key words: essential hypertension • insulin resistance • adenosine • forearm

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Introduction

Essential hypertension is frequently associated with relative refractoriness of body tissues to the main action of insulin, i.e., stimulation of glucose uptake (1–2). Forearm balance studies have demonstrated that this defect is located in skeletal muscle (3–5). The role of blood flow, and, consequently, of the supply of glucose and insulin to target tissues in the physiologic modulation of in vivo glucose metabolism has been recently reevaluated. Evidence has been provided that systemic insulin infusion with maintenance of euglycemia is associated with peripheral vasodilation (6). When regional data have been extrapolated to the whole body, the insulin-induced increase in blood flow has been estimated to explain up to 50% of the total amount of glucose taken by skeletal muscle (7). Furthermore, typical states of insulin resistance, such as obesity and diabetes mellitus, have been reported to manifest both cellular (i.e., reduced arterio–venous gradient) and vascular (i.e., blunted vasodilation) resistance to insulin action (7, 8). Thus, the concept has been proposed that insulin can amplify its own action by increasing local blood flow, thereby recruiting metabolically responsive tissue (9).

Essential hypertension is characterized by vascular resistance to several vasodilatory stimuli (10, 11), but whether this abnormality extends to insulin and partakes of the metabolic insulin resistance has not been determined. To test this hypothesis, in a group of patients with essential hypertension and insulin resistance we applied a prolonged vasodilation of forearm skeletal muscle tissue during insulin administration, and determined whether the insulin resistance could be overcome. We chose adenosine as the vasodilating agent because it is an endogenous mediator which, particularly in the heart and adipose tissue, couples blood flow to metabolic demand (12).

Methods

Subjects. 14 overweight patients with essential hypertension were recruited from the Hypertension Clinic. Each patient had a complete clinical workup to exclude secondary forms of hypertension, diabetes, hepatic, renal or other endocrine diseases. All subjects were consuming a weight-maintaining diet containing at least 200 grams per day of carbohydrate, and all drugs were discontinued at least 2 wk before the study. In six of the patients the fasting study was performed, whereas the other eight patients underwent the clamp study (see Experimental protocol). The two groups were similar in age (42±6 vs 47±3 yr), body mass index (28.4±1.4 vs 28.0±0.9 kg m^{-2}), and mean known duration of hypertension (7±1 vs 6±1 yr). Before the study, the purpose, nature, and potential risks of the experiment were explained to all

1. *Abbreviations used in this paper:* BF, blood flow; EE, energy expenditure; FBF, forearm blood flow; INS, insulin; INS/ADO, insulin plus local adenosine; RQ, respiratory quotient.

patients, and their informed voluntary consent was obtained. The study protocol was approved by the Institutional Ethical Committee.

Experimental protocol. Both the fasting and clamp studies were begun at 8:00 AM after an overnight (12–14 h) fast, with the subject lying supine in a quiet room with a constant temperature of 21–24°C. In each patient, a teflon cannula (20 or 18-G; Abbot Laboratories, Sligo, Ireland) was inserted percutaneously into the brachial artery under local anesthesia (2% xylocaine). Another cannula (20-G, 2 inch, Abbot Laboratories) was inserted retrogradely into a deep vein of the ipsilateral forearm. This cannula was considered to be correctly placed if its tip could not be palpated and if it sampled blood with an oxygen saturation < 70%. In addition, in the patients undergoing the clamp study an antecubital vein (for insulin and glucose infusion), and a deep vein of the contralateral forearm (control forearm) were also cannulated. Hereinafter, the forearm instrumented with the arterial catheter will be called infused forearm and the contralateral forearm control forearm.

The fasting study consisted of three periods of 40–50 min each: basal, adenosine infusion (ADO), and wash-out. During the last 10–15 min of each period, three sets of blood samples were drawn from the artery and the deep vein. Total forearm blood flow (FBF) was measured in both forearms with a strain-gauge plethysmograph (Vasculab Strain-Gauge Plethysmograph SPG 16; Medasonics Inc., Mountain View, CA) every 10 min and after each blood sampling. Each blood flow determination consisted of at least three separate measurements, the mean of which was then used as an estimate of FBF. Blood pressure was measured every 10 min by means of a mercury sphygmomanometer. Heart rate was measured over 20-s periods by using the trace of the plethysmograph. Before each blood sampling and blood flow measurement, blood circulation to the hand was interrupted for 2 min by inflating a pediatric cuff around the wrist at suprasystolic pressure. Adenosine, at the concentration of 40 $\mu g\ ml^{-1}$, was infused into the brachial artery with an infusion–withdrawal pump (Harvard Apparatus Ltd., Kent, England). The infusion rate was titrated to achieve a doubling of FBF; it ranged from 0.35 to 0.60 ml min^{-1}, and the titration period lasted 5–10 min on average. During the subsequent infusion period (40 min), minor adjustments of the adenosine infusion rate were made in order to maintain FBF constant at 2× the basal rate.

The clamp study consisted of three periods: basal, insulin (INS), and insulin + local adenosine (INS/ADO). During the basal period, three sets of blood samples were drawn from the artery and from the deep vein of both forearms for the determination of blood gases and metabolites. FBF, blood pressure, and heart rate were measured after each blood sampling as described above. Subsequently, insulin was infused through the superficial antecubital vein at a rate of 7 pmol $min^{-1}kg^{-1}$ while maintaining plasma glucose constant at basal values by means of a variable infusion of 20% glucose. When exogenous glucose infusion rate and arterial plasma glucose concentration were both considered to be relatively stable (90–140 min after the start of the insulin infusion), another three sets of blood samples were collected at 5-min intervals and FBF was measured. Then, an adenosine infusion in a format similar to that employed in the Fasting Study was started through the artery of the infused forearm (range: 0.34–0.79 ml min^{-1}). The infusion lasted 40–60 min depending on the length of the titration period and the stability of plasma glucose levels and glucose infusion rates. During the final 10 min of the adenosine infusion, we collected three sets of blood samples and obtained three measurements of FBF. To avoid systematic differences between the two forearms, the infused forearm was in the dominant arm in four patients, and the nondominant arm in the other patients.

Blood and plasma determinations. Each blood sample was divided into three aliquots: (*a*) 4 ml were collected in chilled tubes containing EDTA for the determination of plasma glucose, triglycerides (on an Eris Analyzer 6170; Eppendorph Geratebau, Hamburg, Germany), FFA (Wako Chemical GmbH, Neuss, Germany), and insulin (Insik 5; Sorin Biomedica, Vercelli, Italy); (*b*) 2 ml were collected in chilled tubes containing 2 ml of 1 N perchloric acid, and the supernatant was used for the enzymatic determination of glucose, lactate, pyruvate, alanine, glycerol, and β-hydroxy-butyrate (Eris Analyzer 6170; Eppendorph Geratebau); (*c*) 1.5 ml were collected in eparinized syringes for immediate blood gas determination (IL System 1302 and IL 282 CO-Oximeter; Instrumentation Laboratory, Inc., Lexington, MA).

Calculations. All forearm data are presented in three different ways: (*a*) the extraction ratio (i.e., [A-V]/A); (*b*) the standard net balance calculation (total FBF times the A − V [deep venous] concentration difference); and (*c*) the net substrate balance divided by the oxygen balance measured in the same blood sample pair. Calculation *a* provides an index of the intrinsic efficiency with which a substrate is handled (given its level of supply) when total FBF and tissue flow partition are constant. During vasodilation, if the increased blood flow (BF) results from an increased flow velocity through already perfused tissue, substrate content in a deep vein will increase in exact proportion to the rise in BF, thereby reducing the extraction ratio. Alternatively, if all of the increase in BF results from capillary recruitment in previously unperfused or underperfused tissue, the substrate content in a deep vein will remain unchanged. Between these two extremes, variable combinations of faster BF and capillary recruitment will determine the actual substrate content of deep venous blood. By comparing the changes in extraction ratio with the concomitant changes in BF, the extent of capillary recruitment can be estimated. Calculation *b* is the standard way of expressing balance data, which makes comparison with previous results possible. The rationale for calculation *c* is as follows. The greater part of forearm oxygen consumption (VO_2) is contributed by muscle oxidations (and is therefore reflected in deep venous oxygen content) because of the predominantly glycolytic metabolism of superficial tissues (13). The ratio of a substrate balance to the concomitant oxygen balance is a fully flow-independent measure (FBF cancels out in the quotient). It relates the changes in substrate handling to the concomitant level of oxygen metabolism (i.e., the mass of metabolically active tissue) in muscle. In doing so, the substrate to oxygen ratio takes into account any recruitment phenomenon.

Blood O_2 and CO_2 content, and regional energy expenditure (EE) were calculated as previously described (14). Whole-body glucose disposal was estimated by averaging the glucose infusion rates during the last 40 min of each study period, and then adjusting for changes in the body glucose pool (assuming a distribution volume of 0.250 l kg^{-1}).

Statistical analysis. For each triplet of measurements within each study period, ANOVA for repeated measures was first performed to assess intraindividual variability. When ANOVA gave a statistically not significant result, the three sets of values were averaged, and ANOVA for repeated measures was done using mean values from each period. Post-hoc tests (e.g., Scheffe's) or paired *t* test analysis were then used to assess the effect of adenosine. In the clamp study, ANOVA for doubly repeated measures (over the three study periods and the two forearms) was carried out. With this design, the effect of adenosine was evaluated as an interaction term (forearm × study period).

Results

Fasting study

During adenosine infusion, forearm blood flow was more than twice (+130%) as high as the basal value, and returned rapidly to baseline as the infusion was interrupted (Fig. 1). Both systolic and diastolic blood pressure (146±7 and 96±3 mmHg, respectively) remained stable throughout the three study periods, while heart rate increased slightly (from 67±5 to 69±6 and 70±5 b/min, $P = 0.06$ by ANOVA).

Blood gases. In the basal state, deep forearm tissues used oxygen (5.9±1.0 $\mu mol\ min^{-1}dl^{-1}$) and released carbon dioxide (4.2±0.7 $\mu mol\ min^{-1}dl^{-1}$), which corresponds to a nonprotein respiratory quotient (RQ) of 0.72±0.03. Protons were also released at a net rate of 6.2±0.7 pmol $min^{-1}dl^{-1}$, and energy expenditure averaged 0.61±0.11 cal $min^{-1}dl^{-1}$. During adenosine infusion, all these net exchange rates increased significantly, by 60% on average. The RQ rose to 0.87±0.13, a change which fell just short of statistical significance ($P = 0.06$ by

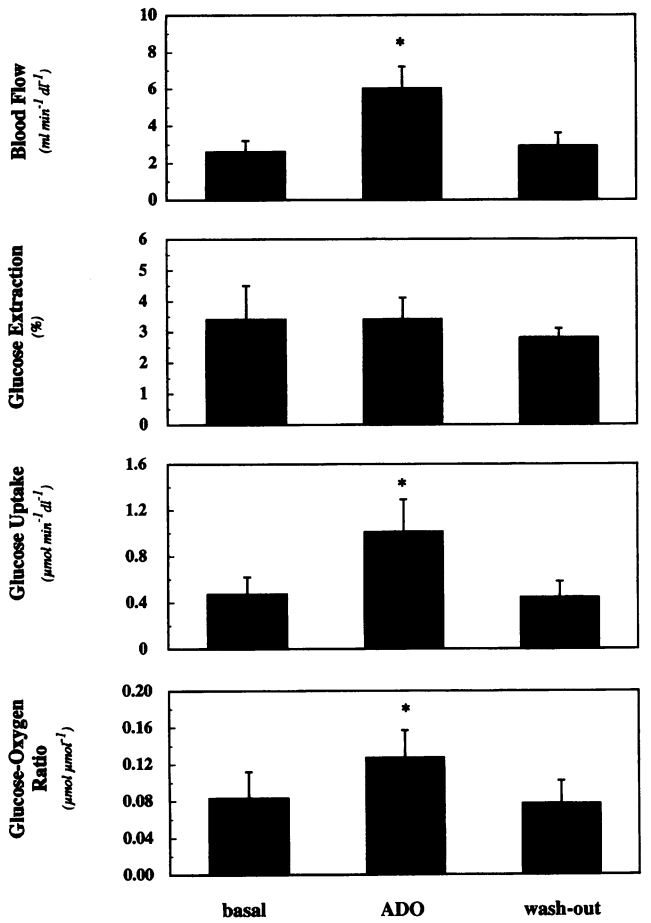

Figure 1. Forearm blood flow (*top*), glucose extraction, glucose uptake, and glucose to oxygen ratio (*bottom*) in the basal state (basal), during intraarterial adenosine infusion (ADO), and during 40 min of wash-out (wash-out) in hypertensive patients. The star indicates a statistically significant ($P < 0.05$ or less) difference in mean group values between the adenosine infusion and basal/wash-out data.

ANOVA). All exchange rates returned to baseline values during the wash-out (Table I).

Oxygen and glucose. During adenosine infusion, the basal fractional oxygen extraction fell almost 45%, whereas the oxygen balance increased by 45%. Both returned to baseline at the end of the wash-out period (Table I). Forearm fractional glucose extraction was small during the basal period (3.4±1.1%), and was unaltered by adenosine infusion (Fig. 1). As a consequence, net glucose uptake increased from 0.47±0.15 to 1.1±0.28 μmol $min^{-1}dl^{-1}$. When forearm glucose uptake was normalized by the concomitant oxygen balance, the ratio was still significantly increased (by 53%) over baseline during adenosine infusion (Fig. 1). Superimposable results were obtained when the glucose balance was calculated by using plasma instead of blood glucose values (data not shown). During the wash-out period both glucose and oxygen fluxes and their ratio returned to basal values (Table I and Fig. 1).

Metabolites. In the basal state, the forearm tissues released lactate (0.42±0.07 μmol $min^{-1}dl^{-1}$, $P < 0.005$ vs zero), alanine (0.16±0.03 μmol $min^{-1}dl^{-1}$, $P < 0.005$), and citrate (0.041±0.008 μmol $min^{-1}dl^{-1}$, $P < 0.005$), whereas the net balance for β-OH-butyrate was positive (0.21±0.04 μmol $min^{-1}dl^{-1}$, $P < 0.005$) and those for pyruvate, FFA, and glycerol were not significantly different from zero (Table II). In response to adenosine, the net release of lactate, citrate, and alanine and the uptake of butyrate all showed a similar 60–80% increase; no significant changes were observed for FFA, glycerol, or pyruvate balance. When expressed per μmol of concomitant oxygen balance, none of these metabolite balances was altered by the doubling of forearm blood flow (Table II).

Clamp study

Systemic insulin infusion resulted in steady-state plasma insulin levels of 373±21 pmol/liter. Whole-body glucose disposal averaged 19±3 μmol $min^{-1}kg^{-1}$ during the INS period, and rose to 25±3 μmol $min^{-1}kg^{-1}$ ($P < 0.002$) during the INS/ADO period. Basal FBF was superimposable in the two forearms (2.9±0.2 ml $min^{-1}dl^{-1}$), and systemic insulin infusion did not alter it in either forearm (Fig. 2). Basal blood pressure was 168±10/110±6 mmHg, and heart rate averaged 75±5 bpm. No significant hemodynamic changes were observed during the study. Adenosine infusion produced a sustained (109±32%) increment in blood flow in the infused side (Fig. 2), similar to that observed in the fasting study.

Blood gases. Carbon dioxide release from the control and infused forearm was similar in the basal period. Insulin caused a significant and similar increase in carbon dioxide release during the third (INS/ADO) experimental period in both forearms (Table III). Adenosine infusion only produced a decrease in the release ratio of carbon dioxide. The results for forearm net proton output were essentially superimposable on those of carbon dioxide. Energy expenditure increased in response to insulin in a time course similar to that of oxygen (see below), with no detectable effect of adenosine (Table III).

Oxygen and glucose. Basal oxygen balance was similar in the two forearms and to the basal values of the Fasting Study. Insulin alone caused a ~ 30% increase in oxygen balance (Table III). During adenosine-induced vasodilation, this effect was associated with a significant fall in the oxygen extraction ratio in the infused forearm. In the control forearm, basal glucose extraction (3.0±0.6%) increased threefold and fourfold during the INS and INS/ADO period, respectively ($P < 0.01$ by ANOVA) (Fig. 2). In the infused forearm, glucose extraction rates were similar to those of the control side both at baseline and during INS. In contrast, during INS/ADO glucose extraction was 50% less in the infused than in the contralateral arm. When net glucose balances were calculated, a gradual increase was evident across the study periods, but without significant differences between the two sides. When glucose uptake was expressed as a fraction of concomitant oxygen balance, this ratio rose ~ 4-fold during insulin alone, did not change further in the next study period, and was nearly identical in the infused and control forearm (Fig. 2).

Metabolites. In the basal state, there was equivalent lactate release by both the control (0.690±0.149 μmol $min^{-1}dl^{-1}$) and infused forearm (0.574±0.068 μmol $min^{-1}dl^{-1}$). Insulin caused a slight, but not statistically significant, decline (~ 30%) in forearm lactate release ratio in the face of a concomitant rise in arterial blood lactate levels (from 0.69±0.12 to 0.73±0.06 to 0.80±0.09 mM, $P < 0.01$), so that net exchange remained unaltered. Adenosine infusion was associated with a further decrease in fractional lactate release, quantitatively due to the vasodilation. Relative to oxygen balance, neither insulin nor adenosine had any effect on forearm lactate release. Basal net alanine release (0.154±0.029 μmol $min^{-1}dl^{-1}$) was maintained unchanged during the study period in spite of a significant fall

Table I. Fasting Study: Blood Gas Arterial Concentration (A), Fractional Exchange (FE), and Net Balance (NB), Respiratory Quotient (RQ), and Energy Expenditure (EE)

	Basal	ADO	Wash-out	Units
Oxygen				
A	8.7±0.3	8.6±0.2	8.6±0.3	mM
FE	32.0±5.6	18.1±2.9*	27.1±4.5	%
NB	5.9±1.0	8.6±1.7*	5.9±1.1	μmol min^{-1} dl^{-1}
Carbon dioxide				
A	21.3±0.6	21.4±0.6	21.4±0.7	mM
FE	−9.4±1.9	−6.0±1.0*	−7.9±1.3	%
NB	−4.2±0.7	−7.4±1.7*	−4.5±1.1	μmol min^{-1} dl^{-1}
Hydrogen				
A	40.5±0.7	40.7±1.0	40.5±0.8	mM
FE	−8.1±1.7	−5.2±1.2	−6.8±1.2	%
NB	−6.2±0.7	−10.2±1.8*	−7.0±1.1	pmol min^{-1} dl^{-1}
RQ	0.72±0.03	0.87±0.13	0.76±0.08	
EE	0.61±0.11	0.94±0.18*	0.63±0.12	cal min^{-1} dl^{-1}

* $P < 0.05$ or less for the comparison between the adenosine infusion period (ADO) and the basal period.

in the arterial aminoacid concentration (from 355±36 μM to 301±27 μM, $P < 0.05$). The alanine to oxygen ratio showed no significant change either in response to systemic insulinization or following local adenosine administration. Basal FFA balances were positive in both forearms (0.171±0.047 and 0.133±0.035 μmol min^{-1}dl^{-1}). Systemic insulin drastically depressed arterial plasma FFA concentrations (from 0.78±0.14 to 0.16±0.03 mM, $P < 0.001$). Extraction ratios, net balance rates, and FFA to oxygen ratios all became statistically not different from zero at all times in both forearms.

Discussion

Adenosine. Adenosine is an endogenous metabolite involved in blood flow autoregulation. It is unique among vasodilators because of its ability to effectively increase PS (the permeability–surface product) of sodium in skeletal muscle (15), augment functional capillary density, and reduce blood flow heterogeneity (16). Furthermore, in healthy individuals the infusion of adenosine into the brachial artery (at doses similar to those used in these studies) attenuates the release of norepinephrine in response to physiological stimulation of the sympathetic system (by lower body negative pressure) (17). Studies in animal models have suggested that adenosine may also exert direct effects on muscle glucose metabolism, although there is controversy as to whether such effects are stimulatory or inhibitory (18, 22). The metabolic actions of adenosine have not been explored in man. Since we chose adenosine to test the possibility that vasodilation may overcome the insulin resistance of essential hypertension, a necessary preliminary step was to study the effects of adenosine per se on skeletal muscle metabolism.

In our fasting studies, when adenosine was infused intraarterially the oxygen balance rose by 45% in the face of a doubling of forearm blood flow. Since adenosine is not a tissue-selective vasodilator (12), the increase in oxygen balance indicates recruitment of oxidizing muscle fibers in deep forearm tissues. If such recruitment can take place in the absence of any increment in external workload, then sections of muscle tissue must be in a condition of relative hypoxia in the resting state, whether from underperfusion, blood flow heterogeneity, or suboptimal metabolism. With regard to this, capillary rarefaction has been described in the skeletal muscle of hypertensive patients (23), and Greene et al. (24) have shown, through a computer-based simulation, that capillary rarefaction in muscle can generate focal areas in which oxygen saturation is below a critical level. Whether adenosine would cause recruitment of oxidative metabolism in normotensive, insulin sensitive subjects comparable to that observed in the present hypertensive subjects remains to be established.

Due to the vasodilation, all net forearm balances increased (though the change was short of statistical significance in the case of pyruvate, FFA, and glycerol due to high interindividual variability). However, since the oxygen data indicated tissue recruitment equivalent to only < 50% of total forearm dilation, there must have been also an acceleration of blood flow into already perfused tissues. Therefore these balances should be interpreted relative to the concomitant changes in oxygen balance. When this was done, adenosine had a modest stimulatory effect only on glucose uptake (Fig. 1) and not on other metabolites (Table II). In in vitro studies, inhibition of lipolysis is the most consistent metabolic effect of adenosine, and this could help explain the observed increase in glucose utilization. Indeed, under conditions of preferential reliance on lipid oxidation such as the fasting state, inhibition of lipolysis could shift oxidative processes towards carbohydrate (25). The small (though not statistically significant) rise in RQ associated with adenosine infusion (Table II) is compatible with this possibility. However, the net FFA and glycerol balances did not show detectable changes, and thus it is impossible to decide from our data whether a Randle cycle mechanism, rather than a direct effect (26), underlies the observed stimulation of glucose uptake by adenosine.

In summary, our fasting studies indicate that adenosine-mediated vasodilation is associated with some recruitment of oxidative muscle fibers. In this expanded mass of metabolically active tissue, adenosine does not impede, and in fact slightly stimulates, glucose uptake.

Insulin resistance in hypertension. The hypertensive patients in these series were mildly overweight and insulin resistant as a group. The M value (insulin-mediated whole-body

*Table II. Fasting Study. Blood Metabolite Fractional Exchange (FE), Net Balance (NB), and Metabolite to Oxygen Ratio (O_2R)**

	Basal	ADO	Wash-out
Lactate			
FE	−33.1±6.2	−27.2±5.9	−35.4±9.3
NB	−0.423±0.068	−0.771±0.131‡	0.463±0.064
O_2R	−0.079±0.017	−0.100±0.021	−0.102±0.033
Pyruvate			
FE	−9.3±6.3	−15.5±9.9	−76±68
NB	−0.072±0.074	−0.176±0.276	−0.116±0.072
O_2R	−0.002±0.002	−0.004±0.004	−0.003±0.002
Alanine			
FE	−23.6±4.3	−17.5±3.0	−22.2±4.5
NB	−0.159±0.027	−0.246±0.040‡	0.151±0.024
O_2R	−0.029±0.003	−0.032±0.003	−0.030±0.005
FFA			
FE	−13.2±15.0	−10.4±11.0	−19.4±18.1
NB	−0.093±0.169	−0.154±0.268	−0.125±0.208
O_2R	−0.091±0.078	−0.092±0.081	−0.120±0.099
Glycerol			
Fe	−44.1±19.0	−38.6±20.6	−59.3±27.2
NB	−0.061±0.033	−0.110±0.076	−0.074±0.034
O_2R	−0.017±0.008	−0.022±0.012	−0.022±0.011
Butyrate			
FE	33.2±3.9	24.4±4.2	28.3±5.0
NB	0.205±0.038	0.495±0.103‡	0.339±0.115
O_2R	0.035±0.006	0.066±0.012	0.064±0.016
Citrate			
FE	−25.2±5.3	−16.8±3.5‡	−30.8±7.4
NB	−0.041±0.008	−0.064±0.010‡	−0.049±0.007
O_2R	−0.008±0.001	−0.008±0.001	−0.010±0.001

* Units are % for FE, μmol $min^{-1}dl^{-1}$ for NB, and μmol μmol^{-1} for O_2R. ‡ $P < 0.05$ or less for the comparison between the adenosine infusion period (ADO) and the basal period.

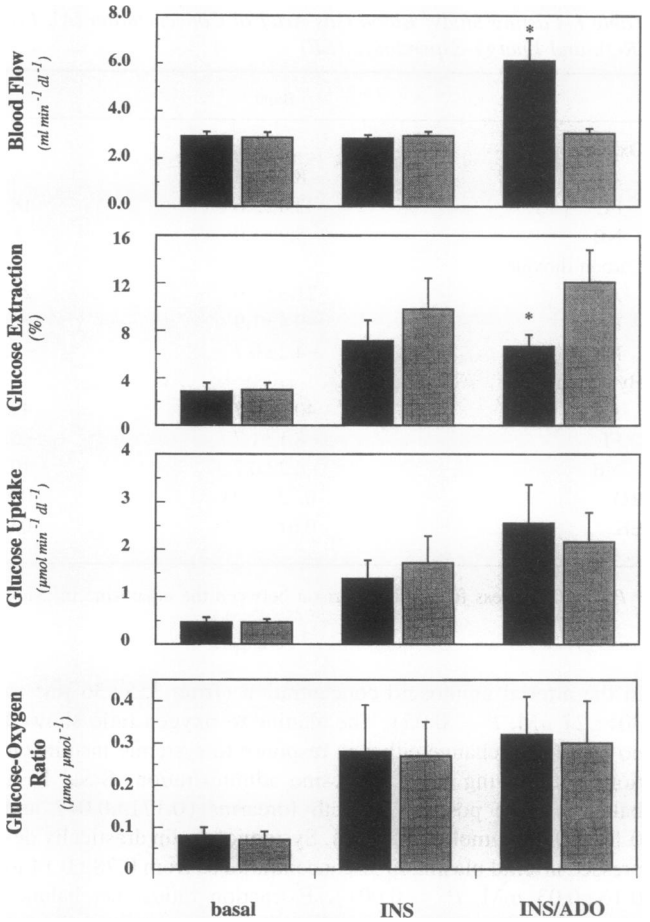

Figure 2. Forearm blood flow, glucose extraction, net glucose uptake, and glucose to oxygen ratio in the basal state (*basal*), during systemic euglycemic hyperinsulinemia (*INS*), and during intraarterial adenosine infusion superimposed on euglycemic hyperinsulinemia (*INS/ADO*) in hypertensive patients. The black bars indicate the forearm infused with adenosine during the INS/ADO period, the stippled bars indicate the contralateral (*control*) forearm, in which adenosine was not infused. The star indicates a statistically significant ($P < 0.05$ or less) difference in mean group values between the adenosine-infused and the control forearm.

glucose disposal rate) was 35% lower (19±3 μmol $min^{-1}kg^{-1}$) than our normal values (28±3 μmol $min^{-1}kg^{-1}$) for subjects of similar age (44±3 yr) and body mass (28.4±1.1 kg/m^2) (data not shown). Insulin-mediated forearm glucose uptake (2.3 μmol $min^{-1}dl^{-1}$) was similar to that measured by Lembo et al. (5) in a group of lean hypertensive individuals after 120 min of similar euglycemic hyperinsulinemia, which in turn was 40% lower than that measured in normotensive controls. In the control forearm of our subjects, we did not detect any change in blood flow during systemic insulin infusion. With regard to this, Baron et al. (6) have reported that, in normotensive and borderline hypertensive individuals mean arterial blood pressure is inversely related both to whole-body glucose uptake and to the increase in leg blood flow during maximal insulin stimulation. Thus, our finding that systemic insulin administration was not associated with forearm vasodilation could be explained by the insulin resistance of our patients. A similar finding has been reported by Lembo et al. (5) and Doria et al. (4).

During the clamp, oxygen balance increased by ~ 30% in both forearms despite unchanged total forearm blood flow. A similar finding has been reported by Kelley et al. (27) in the leg of healthy, insulin sensitive volunteers. Thus, in both insulin-resistant and insulin-sensitive subjects systemic insulin administration leads to a modest stimulation of oxygen uptake in muscle fibers, either by a direct cellular effect or by redistributing blood flow. In contrast, when insulin is administered locally, no increase in forearm oxygen metabolism occurs (14), indicating that some systemic effect of insulin (substrate shift, sympathoexcitation) may be required.

During insulin administration, adenosine infusion rates similar to those employed in the fasting studies induced similar increments in total forearm blood flow, suggesting that insulin does not interfere with the vasodilatory response to adenosine. Oxygen balance, however, did not rise above the level obtained with insulin alone (Table III). The best explanation for the lack of additional stimulation of oxygen uptake by adenosine is that, in the absence of increased metabolic demand, oxidative fiber recruitment is an intrinsically limited phenomenon. In conclusion, in the hypertensive individual adenosine (at the doses employed here) does not recruit oxidative muscle above and beyond the effect of insulin itself. Whether the effect of adenosine may be different in normotensive subjects remains to be tested.

*Table III. Clamp Study. Blood Gas Arterial Concentration (A), Fractional Exchange (FE), and Net Balance (NB), Respiratory Quotient (RQ), and Energy Expenditure (EE) in Infused and Control Forearm**

				ANOVA‡		
	Basal	INS	INS/ADO	Time	Forearm	Interaction
Oxygen						
A	8.4±0.2	8.3±0.2	8.3±0.2			
Control						
FE	29.4±3.4	31.2±3.6	33.5±3.4			
NB	6.9±0.8	7.5±0.8	8.6±1.3			
Test						
FE	25.3±2.6	27.1±4.4	18.4±3.5	NS	$P < 0.01$	$P < 0.01$
NB	6.0±0.6	6.1±0.8	8.0±0.7	$P < 0.05$	NS	NS
Carbon dioxide						
A	21.8±0.4	22.6±0.4	21.9±0.25			
Control						
FE	−9.2±0.9	−9.1±0.7	−12.8±1.6			
NB	−5.6±0.3	−6.1±0.7	−8.3±0.7			
Test						
FE	−8.2±0.9	−7.5±0.8	−8.9±2.2	NS	$P < 0.01$	$P < 0.05$
NB	−4.9±0.4	−4.7±0.5	−10.3±1.6	$P < 0.01$	NS	NS
Hydrogen						
A	39.9±0.5	39.3±0.6	39.0±0.5			
Control						
FE	−7.4±0.6	−9.3±0.9	−10.9±0.8			
NB	−8.6±0.9	−11.0±1.5	−13.4±1.8			
Test						
FE	−6.3±0.7	−7.8±0.6	−5.6±1.0	NS	$P < 0.05$	$P < 0.01$
NB	−7.1±0.8	−8.6±0.8	−13.0±3.0	$P < 0.01$	NS	NS
RQ						
Control	0.84±0.05	0.81±0.05	1.32±0.22			
Test	0.85±0.06	0.83±0.07	1.07±0.13	$P < 0.05$	NS	NS
EE						
Control	0.64±0.06	0.65±0.09	0.96±0.09			
Test	0.75±0.09	0.81±0.08	0.96±0.12	$P < 0.01$	NS	NS

* Units as in Table II.

‡ Two-way analysis of variance for doubly repeated measures. Shown are the significances of the two factors (time and forearm) and their interaction.

During intraarterial adenosine infusion, the net glucose balance did not exceed that observed in the control forearm. Thus, vasodilation only diluted out the extraction of glucose (Fig. 2). More importantly, the glucose to oxygen gradient ratio was stimulated by insulin (from a baseline of 0.08±0.02 to 0.30±0.09) in similar degree in the control and infused forearm, and was not altered by adenosine vasodilation (Fig. 2). Thus, in deep forearm tissues the peak effect of insulin was to promote the uptake of 3 μmol min^{-1} of glucose per each 10 μmol min^{-1} of oxygen regardless of blood flow. For comparison, in eight age-matched insulin sensitive subjects receiving an insulin infusion of the same duration and dose (28), the glucose to oxygen ratio in the forearm was 0.65±0.23, i.e., more than twofold higher ($P < 0.01$) than in the present hypertensive subjects. The implication of these results is that the insulin resistance of essential hypertension is predominantly a cellular phenomenon rather than a restriction in insulin and glucose delivery to muscle tissue. Whether other vasodilators may do better than adenosine in recruiting muscle in resistant individuals, thereby improving glucose disposal in the insulinized state, is an open question. Clinical experience with vasodilators in the treatment of hypertension does not support the concept that insulin sensitivity and glucose tolerance are improved by this pharmacologic means. On the other hand, physical exercise, which induces massive increments in muscle blood flow and oxygen uptake, may overcome the cellular insulin resistance of the hypertensive, particularly if contraction stimulates glucose transport through different carriers than those activated by insulin (29).

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