

The Importance of Endothelin-1 for Vascular Complications in Patients with Diabetes



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Background

Insulin resistance (IR) is a key component of the metabolic syndrome and is associated with increased cardiovascular risk. The production of the vasoconstrictor and pro-inflammatory peptide endothelin-1 (ET-1) is enhanced in IR. The objective was to investigate if ET (selective ET_A and dual ET_A + ET_B) receptor blockade improves insulin sensitivity in patients with IR and coronary artery disease.

Methods

Seven patients (Table 1) with IR and coronary artery disease completed three different hyperinsulinemic-euglycemic clamp protocols (Figure 1):

- 1) a control clamp (saline infusion),
- 2) a clamp with infusion of the ET_A receptor antagonist BQ123 (5 nmol/kg/min)
- 3) a clamp with combined infusion of BQ123 with the ET_B receptor antagonist BQ788 (4 nmol/kg/min).

The infusions started 60 min into the clamp and lasted 15 min. Splanchnic (SBF) and renal (RBF) blood flows were determined by infusions of cardiogreen and *p*-aminohippurate. The total body glucose uptake (M; mg/kg/min) was calculated during three 20-min periods from 60 to 120 min during the clamp (i.e. 60-80 min, 80-100 min and 100-120 min) and then corrected for the mean of the two plasma insulin values obtained during each period (M/I).

Results

Arterial insulin (I) did not differ between the clamps. Total body glucose uptake (M) was significantly different between the clamp protocols with the highest value in the BQ123+BQ788 clamp ($p < 0.05$). The M value corrected by insulin (M/I) was higher in the BQ123+BQ788 than in the control clamp as well as compared to the BQ123 clamp (Figure 2). There was no difference between the control clamp and the BQ123 clamp. Mean arterial pressure did not change during the control clamp, whereas it decreased during both BQ123 ($p = 0.001$) and BQ123+BQ788 ($p < 0.05$) clamps. RBF increased and renal vascular resistance decreased in the BQ123+BQ788 clamp whereas they did not change in the control or BQ123 clamps (Figures 3 and 4). There was no change in SBF or splanchnic vascular resistance in either clamp.

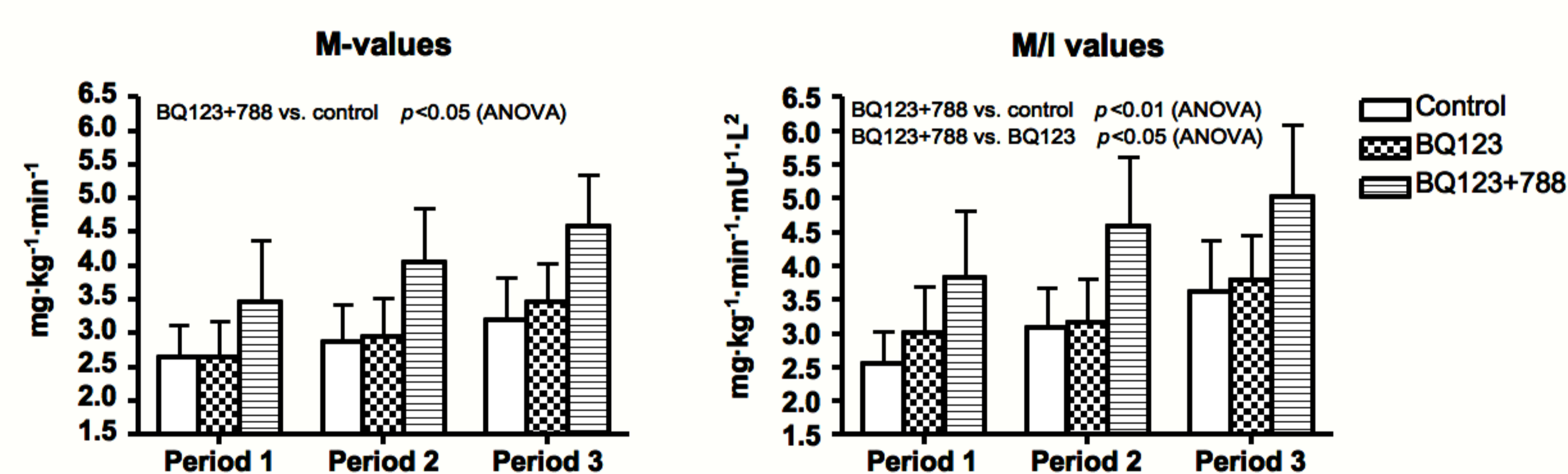


Figure 2. Change in total body glucose uptake (M) and insulin sensitivity (M/I) values during the control clamp (Control), during selective ET_A receptor blockade (BQ123) and during dual ET_A + ET_B receptor blockade (BQ123+788)

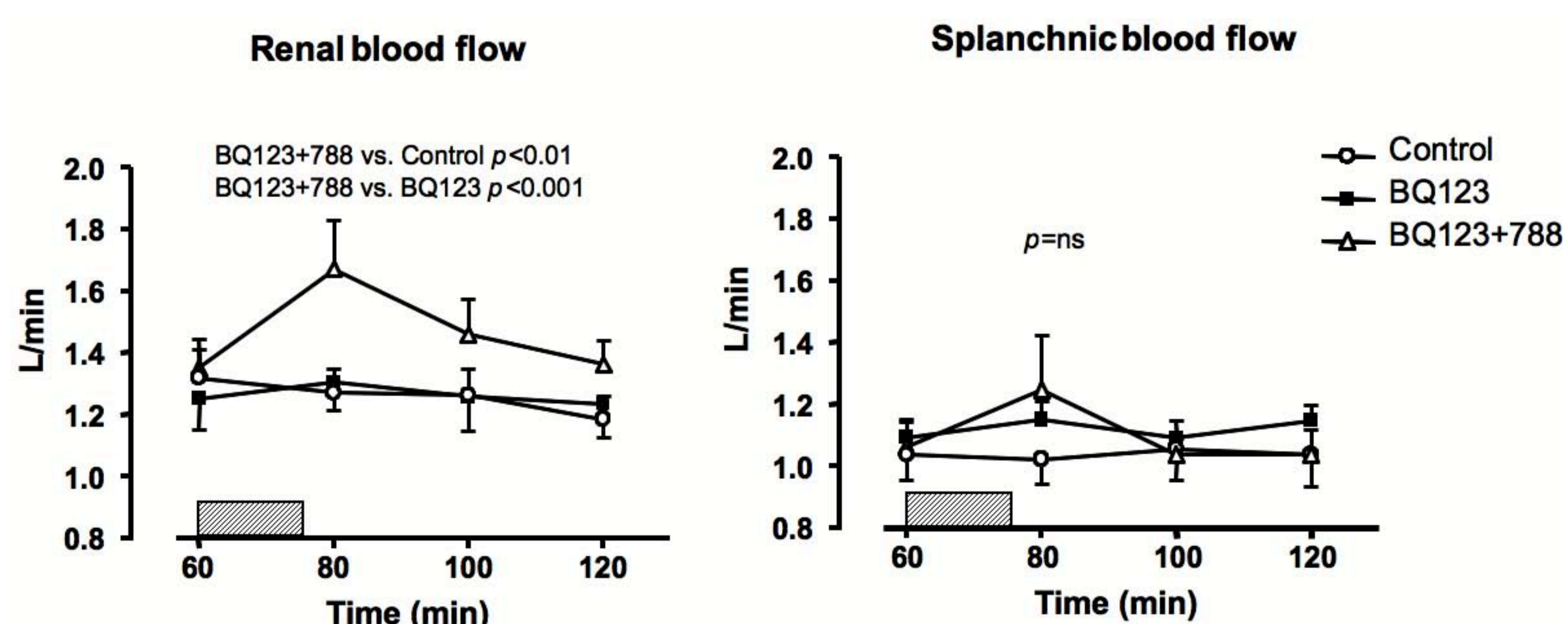


Figure 3. Change in renal (RBF) and splanchnic (SBF) blood flows during the control clamp (Control), during selective ET_A receptor blockade (BQ123) and during dual ET_A + ET_B receptor blockade (BQ123+788). Hatched bar indicates period of antagonist infusion.

		Medication	n =
Age (years)	58.1 ± 1.7		
Weight (kg)	96.6 ± 5.7	Aspirin	7
Height (m)	1.75 ± 0.03	Statins	6
Body mass index (kg/m ²)	31.7 ± 2.6	Fibrates	1
Total cholesterol (mmol/L)	4.0 ± 0.3	ACE inhibitor	5
LDL (mmol/L)	2.3 ± 0.3	Beta blockers	7
HDL (mmol/L)	0.9 ± 0.1	Oral anti-diabetics	4
TG (mmol/L)	2.5 ± 0.8		
Creatinine (μmol/L)	87 ± 5	Patients with diabetes mellitus	n = 5
		Patients with impaired glucose tolerance	2

Table 1. Basal characteristics

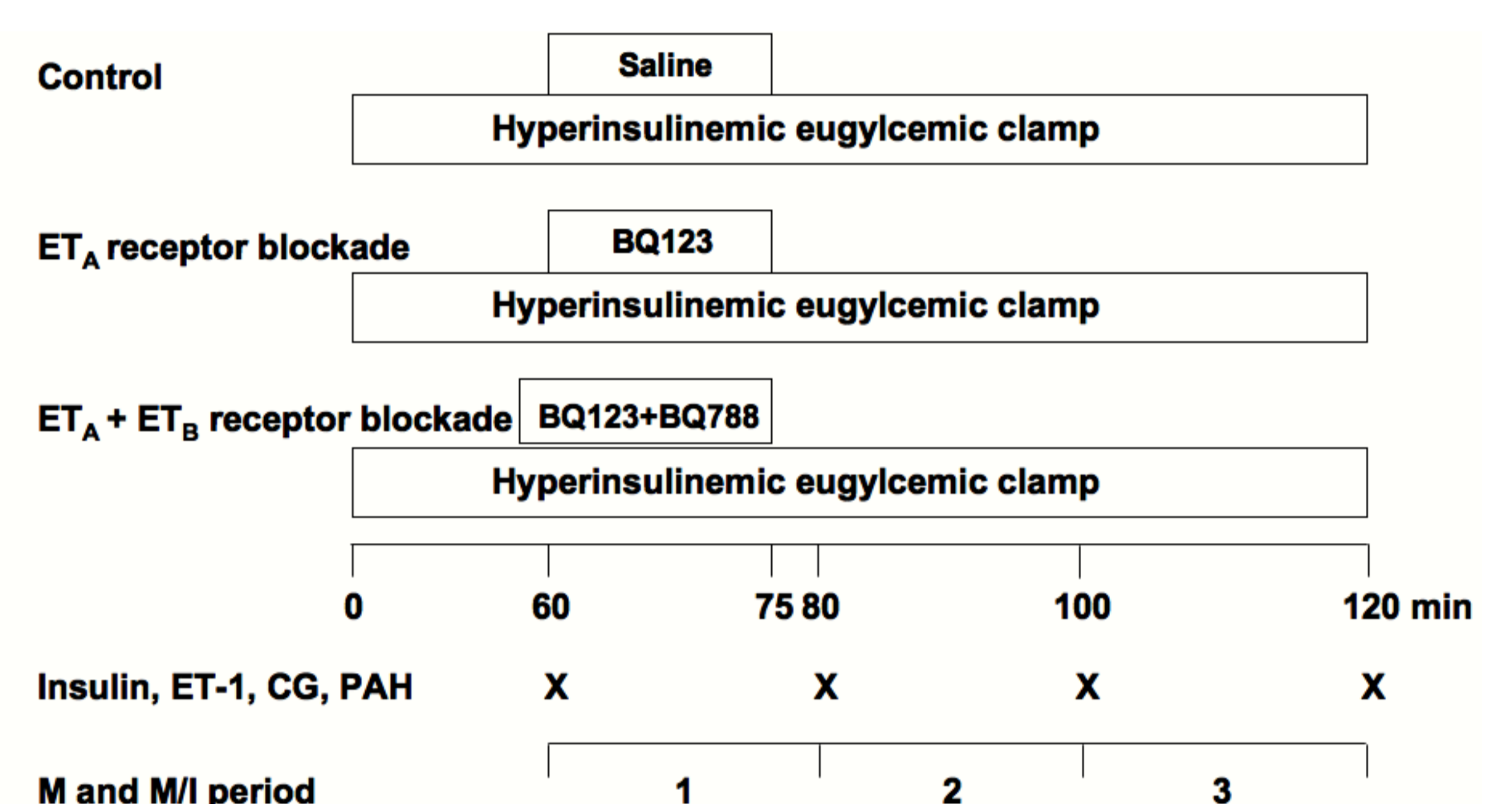


Figure 1. Study protocols

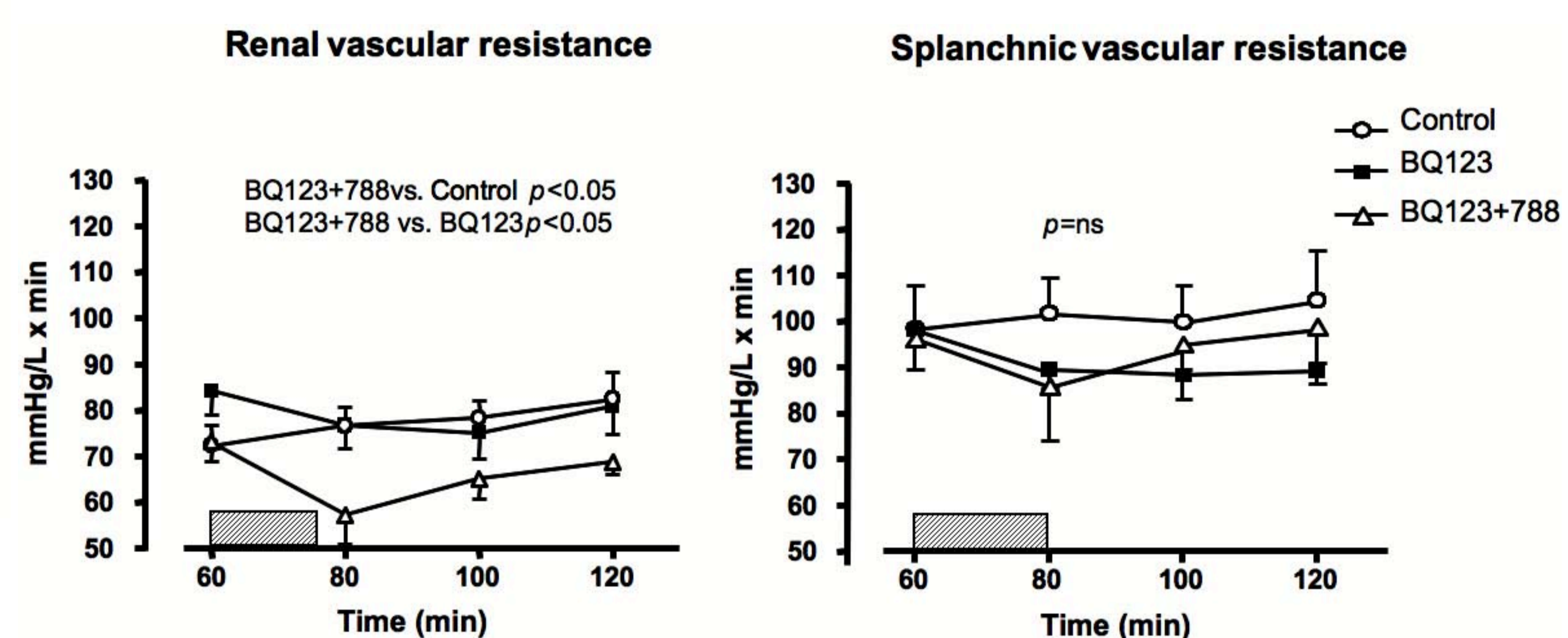


Figure 4. Change in renal (RVR) and splanchnic (SpVR) vascular resistances during the control clamp (Control), during selective ET_A receptor blockade (BQ123) and during dual ET_A + ET_B receptor blockade (BQ123+788). Hatched bar indicates period of antagonist infusion.

Conclusions

The study demonstrates that dual ET_A + ET_B receptor blockade enhances insulin sensitivity in patients with IR and cardiovascular disease. The data show that ET-1 contributes to IR and that this negative effect is antagonised by dual ET_A + ET_B receptor blockade.