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Introduction - Hypertension and renal function

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- Kidney is one of main targets of hypertensive (HT) process
- Close and often reciprocal association renal dysfunction and loss BP control

Introduction - Renal Blood Flow (RBF)

1. reduced in most patients with HT, sometimes already in borderline hypertensives or offspring of borderline hypertensives

2. falls steeply as MBP increases from 110 to 140 mmHg fall steeper with aging for hypertensive than normotensive

3. RBF/kidney mass is decreased = renal vascular changes rather that parenchymal alterations responsible for changes in renal perfusion patterns

Introduction – Renal fraction and renal resistance

Renal fraction (% fraction of cardiac output supplied to the kidneys):

- ✈ normal in young HT but declines faster with aging
- ✈ generally reduced in HT
- ✈ decreases more than cardiac output with aging in HT

Thus rise in renal vascular resistance = early and progressive marker essential HT

Introduction - Glomerular filtration rate (GFR)

- Decline in RBF usually not matched with by concurren treduction in GFR
- GFR usually normal in uncomplicated HT despite fall RBF

→ Glomerular filtration fraction increased in essential HT

= effective filtration pressure increased in non-ischeamic glomeruli (transmission of HT in glomerular capillaries and post glomerular vasoconstriction)

Introduction - Beta-blockers

- Frequent parallelism between renal and systemic hemodynamics (r = +/-0.50)
- But discrepancies between type of beta blockers
- Propranolol decrease RBF by 14 % and cardiac output by 33%
- Thus, at least part of RBF response independent of CO

Introduction - Nebivolol

beta$_1$-selective adrenergic receptor antagonist

direct vasorelaxant effect that involves facilitation of NO release from the endothelium

dual mechanism of action : maintenance of cardiac output and decrease in peripheral vascular resistance

→ suggest favourable effects on renal hemodynamics:
could preserve RBF
possibly through NO release

Introduction – Renal Nitric oxide (NO)

- Basal NO production prevents excessive renal vasoconstriction and favors excretion of sodium and water

- Inhibition of NO increase renal vascular resistance, decreases GFR and urinary sodium excretion

Introduction – Renal Nitric oxide (NO)

- Animal evidence of enhanced L-arginine/NO pathway in kidney

Kakoki M et al.(Hypertension 1999 Jan;33(1 Pt 2):467-71)

- Study vasodilatory beta-blockers on renal perfusion pressure (RPP) and NO release in rat kidney
- Nebivolol cause dose-dependent reduction in RPP and increase in NO release
- Metergoline (5-hydroxytryptamine (5-HT)1/2 antagonist) and NAN-190 (5-HT1A antagonist) almost completely abolished vasorelaxation and NO release caused by nebivolol.

Results suggest several beta-blockers exert their vasodilatory action through the 5-HT1A receptor/NO pathway

Introduction – Renal Nitric oxide (NO)

Whether renal NO plays a role in human essential HT is controversial:

- similar decrements in RBF with systemic L-NAME in HT and normotensives
- contrasts with forearm blood flow studies = suggests regional differences in NO bioavailability within various vascular beds

(van den Meiracker et al, Nephron 2002, Jacobi et al J. Hypertens 2002)

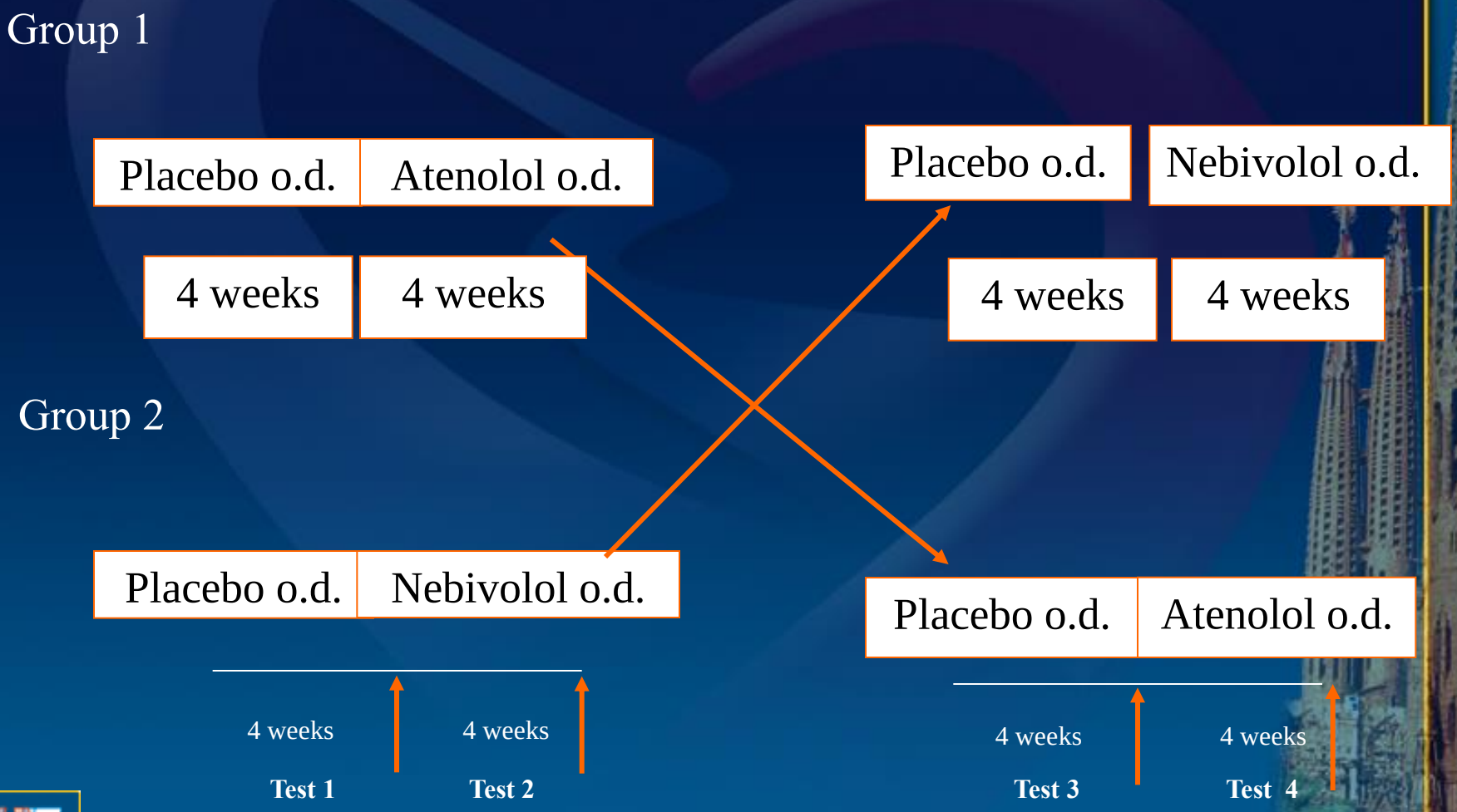
First study on chronic renal hemodynamic effects of Nebivolol vs. Atenolol in human hypertensives

- To test the hypothesis that Nebivolol has more favourable renal haemodynamic effects than Atenolol

- 14 patients 50+/-8 yrs mild to moderate essential HT defined as:
  - Median of 3 consecutive diastolic BP measurements of ≥ 95 mmHg and ≤ 115 mmHg in sitting position with 1 min. between 2 measurements

  - No antihypertensive medications for at least 4 weeks prior to randomisation

Study design



Measurements

After the end of 4 w. of placebo therapy and at the end of 4 w. of active therapy with Nebivolol (5 mg) and Atenolol (50 mg).

- Heart rate (HR)
- Blood pressure (BP)
- Cardiac output (CO) and stroke volume (SV=CO/HR) according to ASE

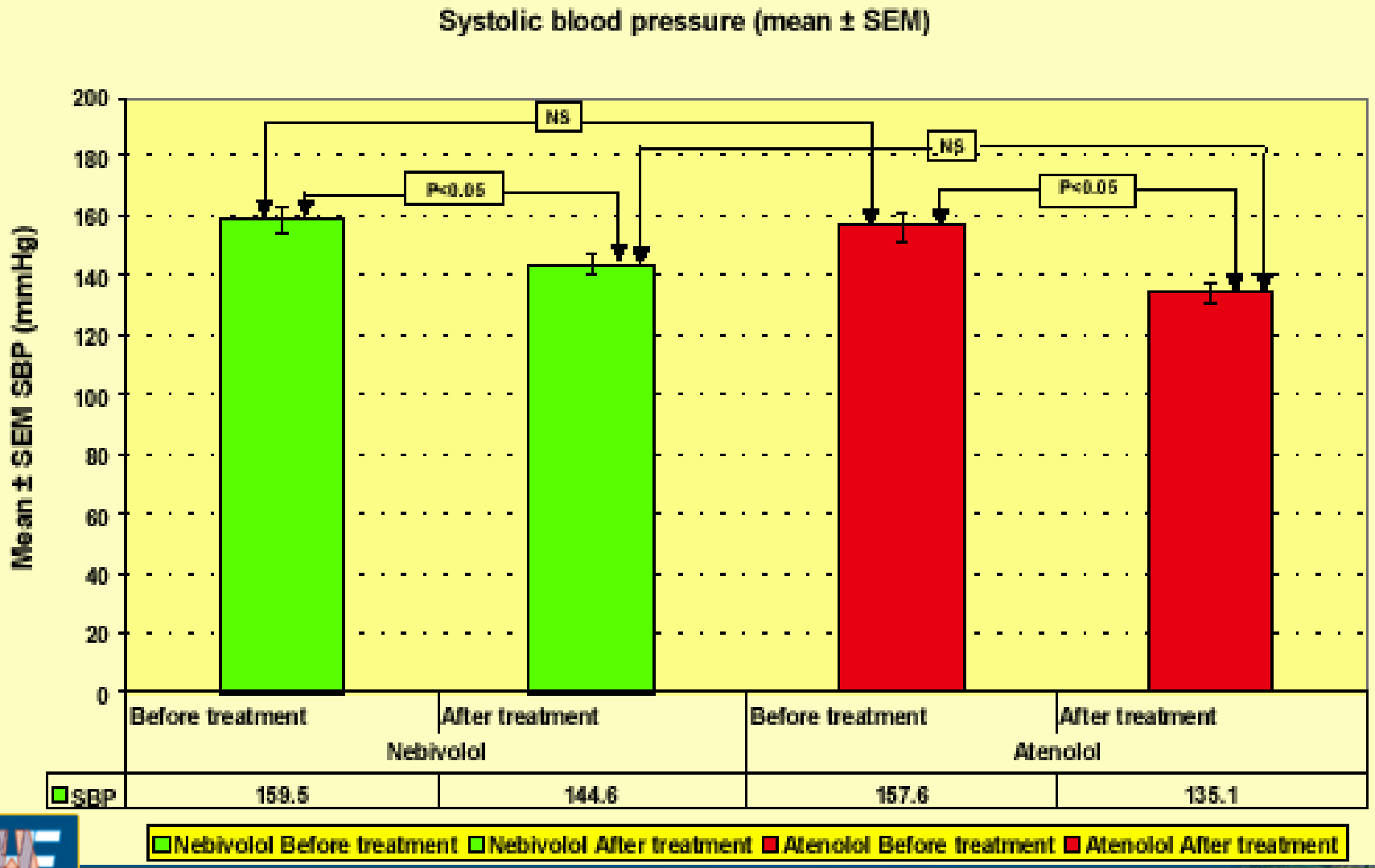
- Renal blood flow (RBF, [^{123}] iodohippurate:17μCi intravenous (i.v) bolus followed by constant infusion of 0.34μCi/mm)

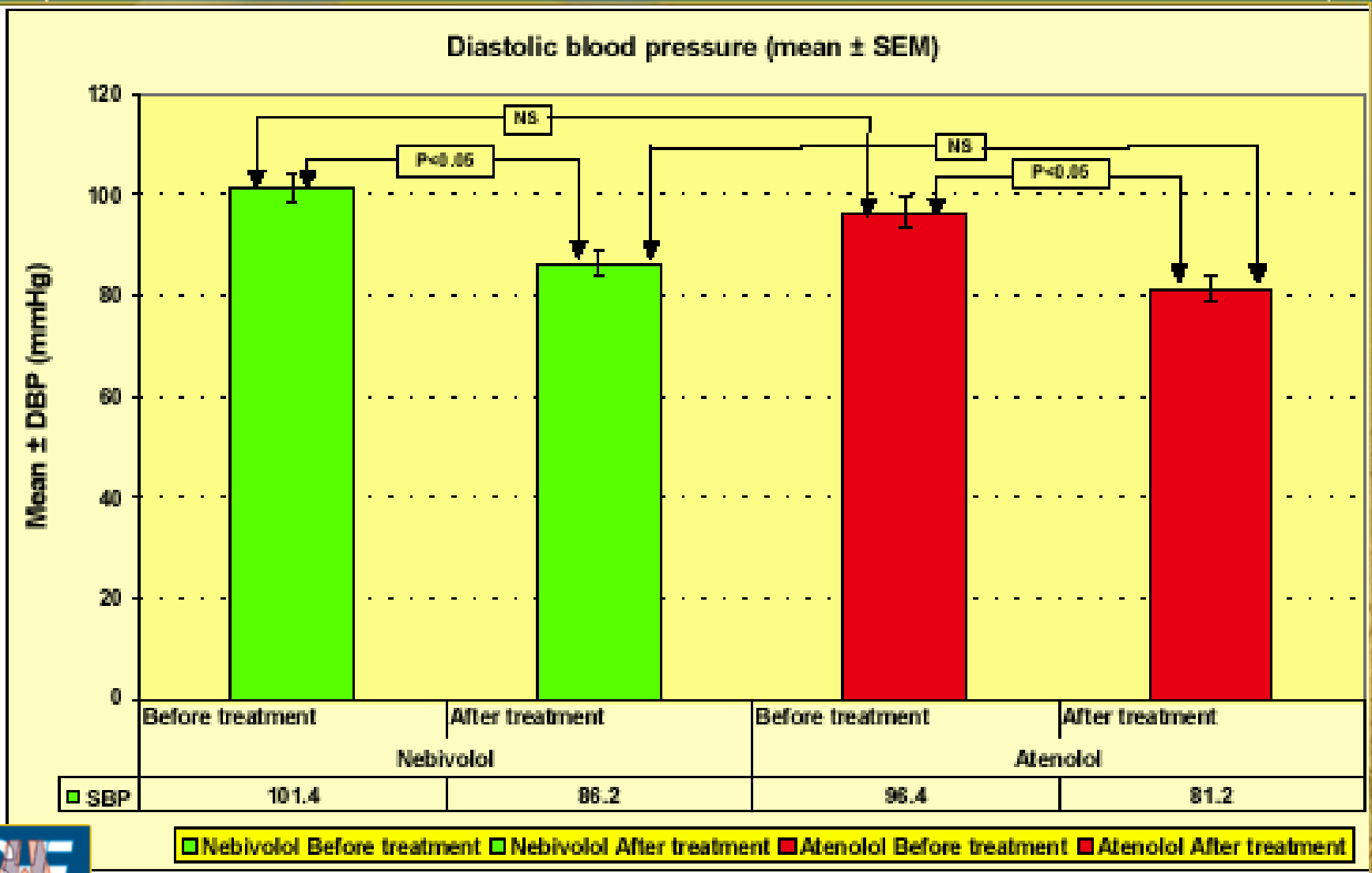
- Glomerular filtration rate (GFR, I^{51} CrEDTA (20μCi i.v bolus followed by a constant infusion of 0.15μCi/mm)

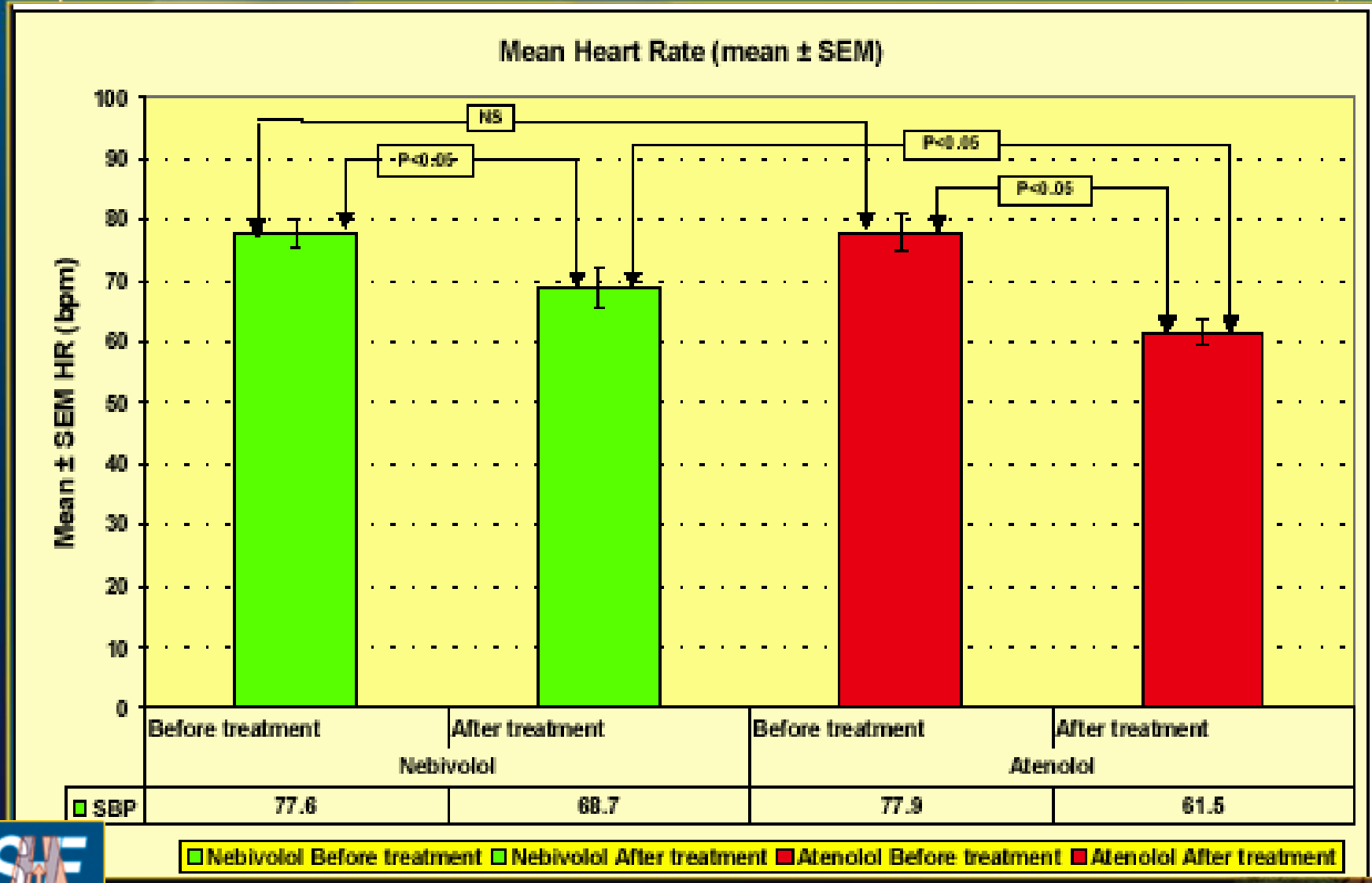
Intervention

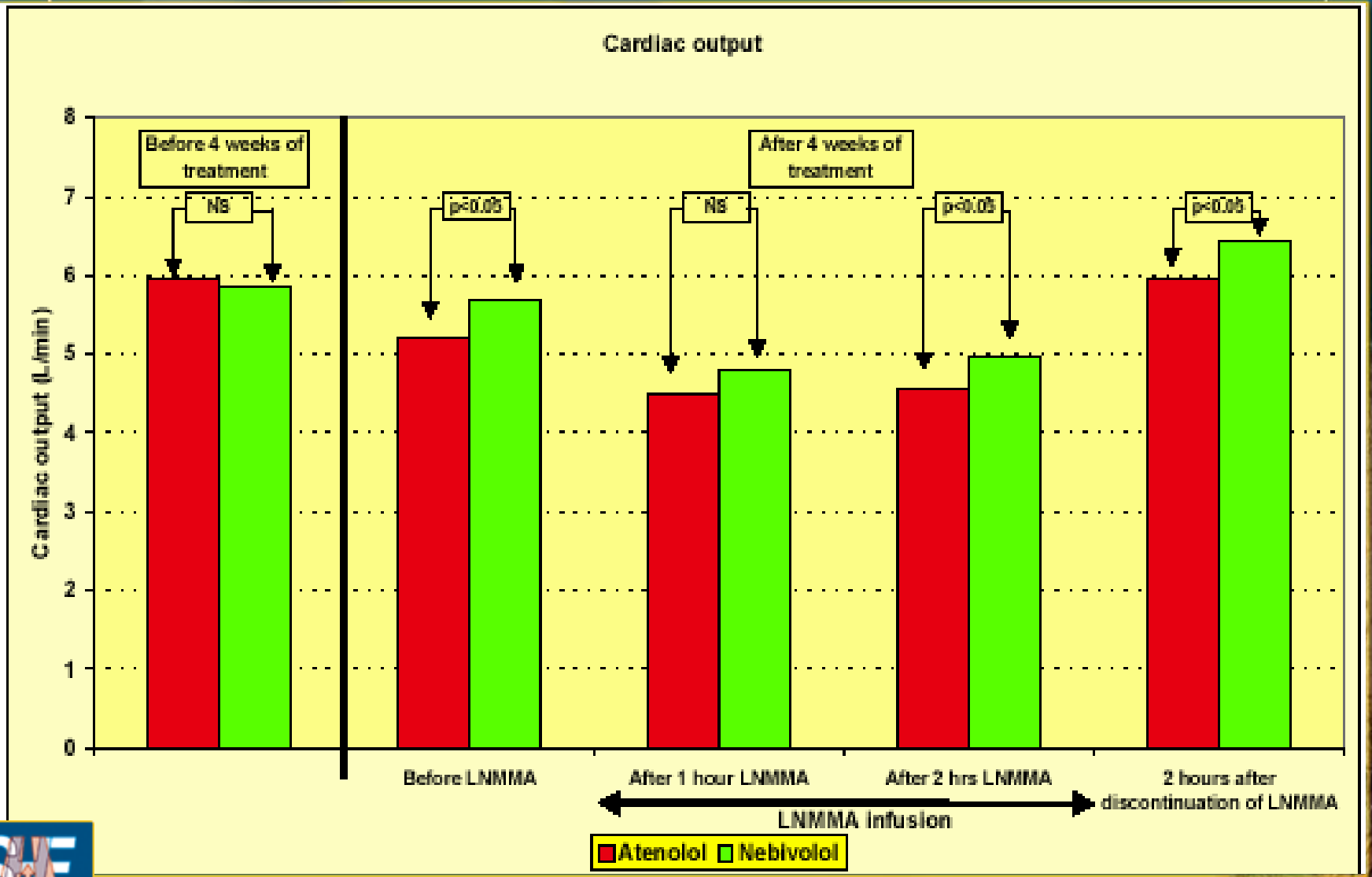
- LNMMA (Clinalfa) 3 mg/kg i.v. priming dose plus 3 mg/kg/h during 2h
- At each visit (4-8-12-16 week)

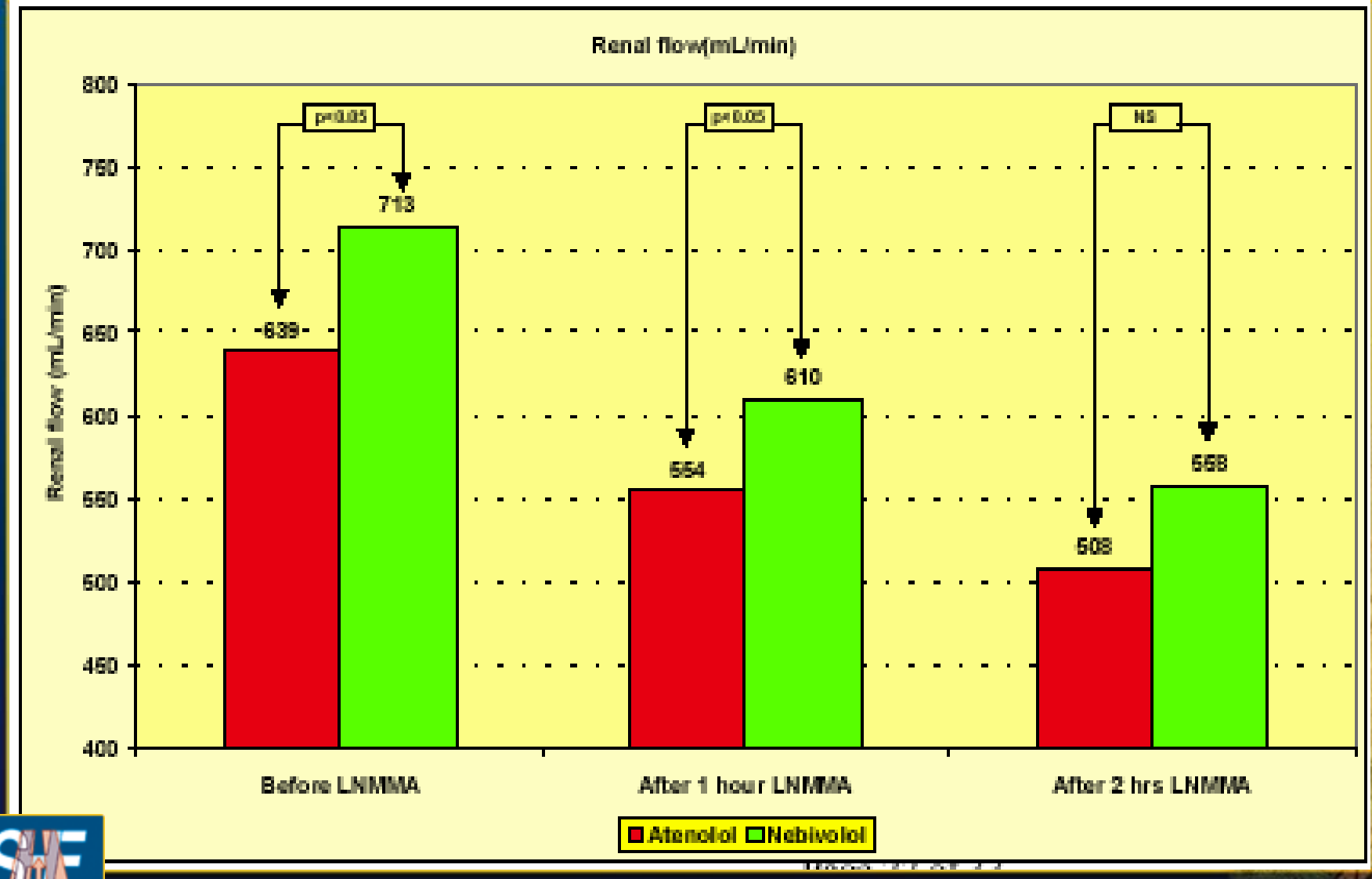
RESULTS:

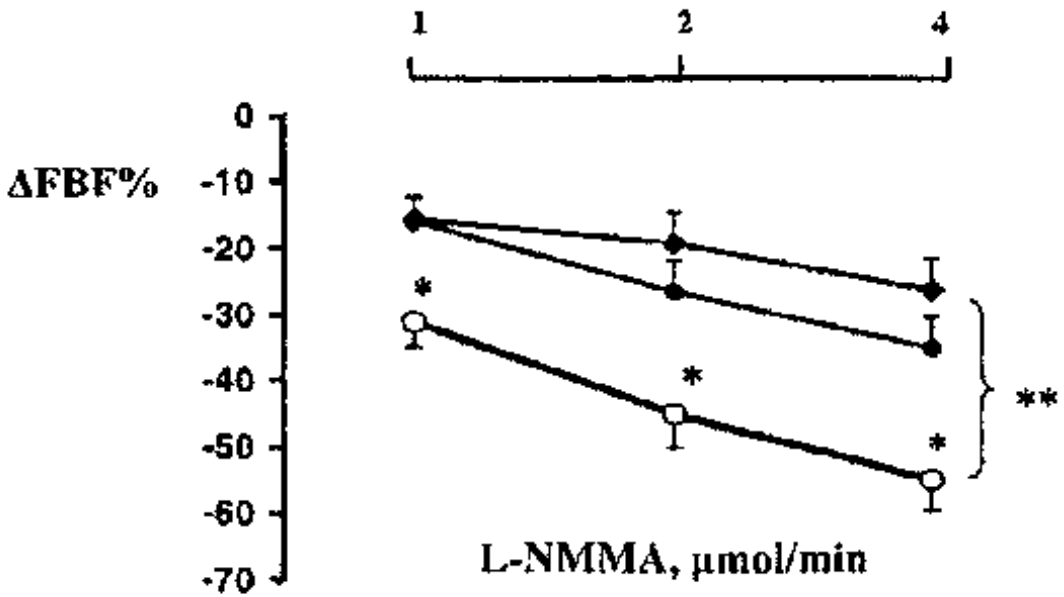

Systolic blood pressure (mean ± SEM)
Mean ± SEM SBP (mmHg)
200
180
160
140
120
100
80
60
40
20
0
NS
P<0.05
NS
P<0.05
Before treatment
After treatment
Before treatment
After treatment
Nebivolol
Atenolol
SBP
159.5
144.6
157.6
135.1
Nebivolol Before treatment
Nebivolol After treatment
Atenolol Before treatment
Atenolol After treatment


Diastolic blood pressure (mean ± SEM)
Mean ± DBP (mmHg)
120
100
80
60
40
20
0
NS
P<0.05
NS
P<0.05
Before treatment
After treatment
Before treatment
After treatment
Nebivolol
Atenolol
SBP
101.4
86.2
96.4
81.2
Nebivolol Before treatment
Nebivolol After treatment
Atenolol Before treatment
Atenolol After treatment


Mean Heart Rate (mean ± SEM)
Mean ± SEM HR (bpm)
100
90
80
70
60
50
40
30
20
10
0
NS
P<0.05
P<0.05
P<0.05
Before treatment
After treatment
Before treatment
After treatment
Nebivolol
Atenolol
SBP
77.6
68.7
77.9
61.5
Nebivolol Before treatment
Nebivolol After treatment
Atenolol Before treatment
Atenolol After treatment


Cardiac output
Cardiac output (L/min)
0
1
2
3
4
5
6
7
8
Before 4 weeks of treatment
NS
After 4 weeks of treatment
p<0.05
NS
p<0.05
p<0.05
Before LNMMA
After 1 hour LNMMA
After 2 hrs LNMMA
2 hours after discontinuation of LNMMA
LNMMA infusion
Atenolol
Nebivolol


Renal flow(mL/min)
Renal flow (mL/min)
800
750
700
650
600
550
500
450
400
p<0.05
p<0.05
NS
639
713
554
610
508
558
Before LNMMA
After 1 hour LNMMA
After 2 hrs LNMMA
Atenolol
Nebivolol

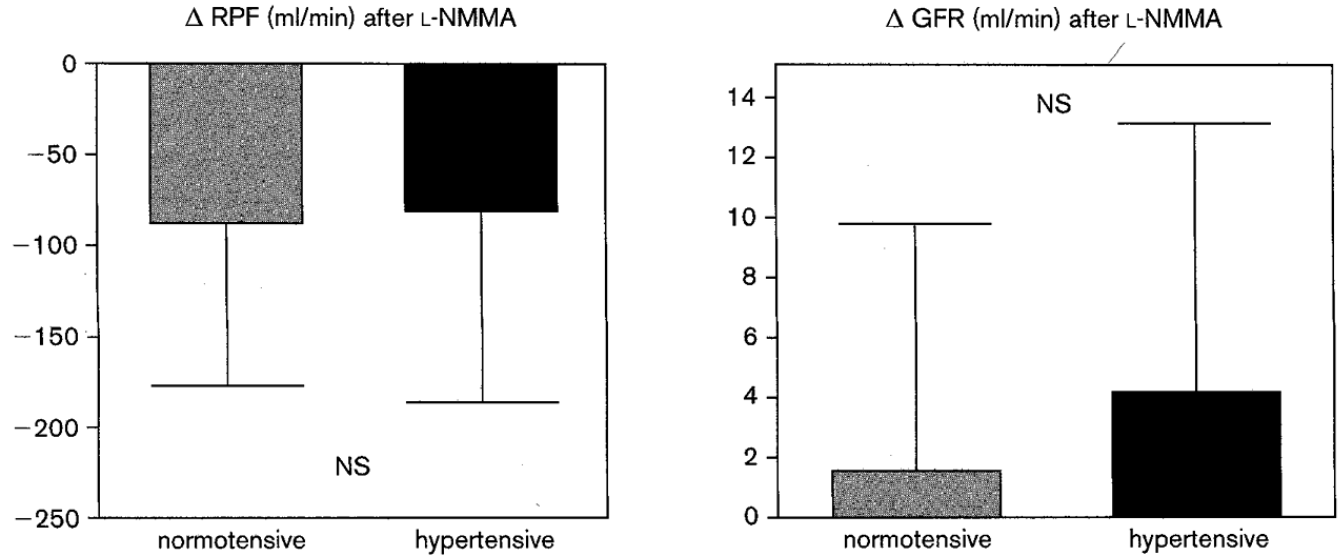


Percentage changes in FBF from baseline preceding each drug infusion for 3 dose levels of acetycholine, sodium nitroprusside, and L-NMMA after placebo (♦), nebivolol (○), and atenolol (●) therapy. Values are mean±SEM. *$P<0.05$ and **$P<0.001$ for differences between treatments.

N. Tzemos, Circulation 2001;104:511-514

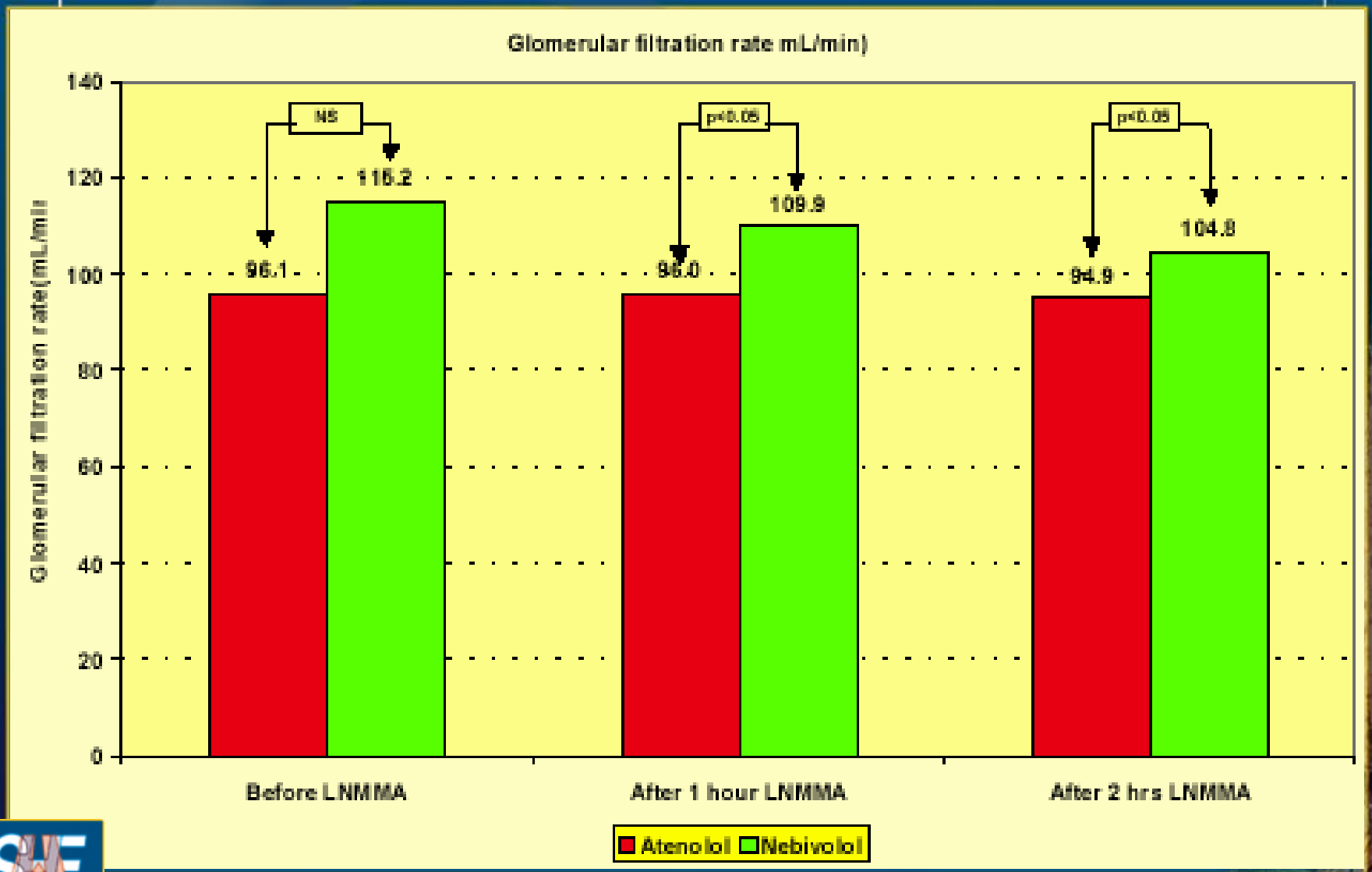
Renal bioavailability of NO not decreased in human HT

		Normotensive subjects ($n = 32$)	Hypertensive subjects ($n = 39$)	P-value control versus patients
Δ MAP	L-NMMA 3 mg/kg	5.3 ± 6.3 **	6.0 ± 6.1 **	NS
Δ HR	L-NMMA 3 mg/kg	−5.8 ± 3.9 **	−4.1 ± 3.8 **	NS



Impact of L-NMMA on systemic and renal hemodynamics. (x ± SD; * $P < 0.05$; ** $P < 0.001$ from baseline; MAP, mean arterial pressure; HR, heart rate; RPF, renal plasma flow; GFR, glomerular filtration rate); L-NMMA, N^G-monomethyl-L-arginine.

J. Jacobi et al, J Hypertens 2002;20:525-530.


Glomerular filtration rate mL/min)
Glomerular filtration rate(mL/min)
140
120
100
80
60
40
20
0
NS
p<0.05
p<0.05
96.1
115.2
96.0
109.9
94.9
104.8
Before LNMMA
After 1 hour LNMMA
After 2 hrs LNMMA
Atenolol
Nebivolol

Conclusion:

Hypertension = Importance of Renal Function

- **Effects on**
  - **RBF**
  - **Renal fraction**
  - **Renal resistance**
  - **GFR and GF fraction**
- **Renal effects of NO: animals vs. humans**
- **Effects of Beta-blockers**