Renal functional reserve in obesity hypertension

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Introduction

Ingestion of a protein-rich meal induces an acute increase in GFR and in effective renal plasma flow (ERPF) in both animals and humans

O'Connor et al., 1976 & Bergstrom et al., 1985

Patients with type 2 diabetes lose functional renal reserve earlier in the evolution of nephropathy which has been attributed to defective nitric oxide production

Earle, Seam, Raymond et al., 2001

Impaired renal functional reserve & albuminuria can detect hypertensive patients at risk of progressive renal damage.

Losito, Fortunati Zangi et al, 1988

In healthy individuals other vasoactive mediators such as renal kallikrein and vasoactive kinins may be involved as possible mediators of glomerular filtration increment in response to protein load.

King, 1995 & Jaffe et al, 1989

There is a strong linear relationship between the rise in BMI and systolic BP, diastolic BP, and pulse pressure

Mus Spadano Coakley et al., 1999

In obesity-induced hypertension excessive renal sodium reabsorption seems to initiate the increase in blood pressure with weight gain

Hall 2000

Endothelium dependent vasodilation evoked by nitric oxide release in renal and small arteries is impaired in both essential hypertensives and obese individuals

Hyoshi Sasaki Nakagawa et al., 2003

Objective

To determine whether the interdependent effects of hypertension and obesity on renal functional reserve are different from the effects of hypertension alone.

renal haemodynamic changes (renal kallikrein and nitric oxide)
PATIENTS AND METHODS

Inclusion criteria
- systolic blood pressure ≥ 140 mmHg
- diastolic blood pressure ≥ 90 mmHg
- body mass index (weight/height²) > 30 kg/m²
- lean patients had a body mass index < 25 kg/m²

Exclusion criteria
- severe hypertension
- secondary forms of hypertension
- congestive heart failure
- renal insufficiency
- diabetes mellitus
- recent cerebrovascular disease
- myocardial infarction
- hypercholesterolemia
- liver disease
- clinical proteinuria
- obese individuals (body mass index > 40 kg/m²)

Arterial blood pressure
- mean of at least three measures taken during a 10 min period

MAP = [(2 X diastolic) + systolic] / 3

Study Protocol
- Diet Na+ 100 mEq/d
- GFR - inulin clearance ...
- RPF - [¹³¹I] PAH clearance
- Renal vascular resistance = mean ABP divided by RPF

Renal Hemodynamics Protocol
- 8.00 - 12.00 AM
- GFR - inulin clearance ...
- Inulin infusion, blood samples, urine samples
- RPF - [¹³¹I] PAH clearance
- Renal vascular resistance = mean ABP divided by RPF
Renal Haemodynamics Protocol

8-12 AM supine - two intravenous accesses
loading dose of inulin at zero (50 mg/kg)
inulin 30 mg/min for 180 min
urine samples Plasma samples Serum concentration
Renal inulin clearance NO kallikrein
GFR

Clearance (C) = \( \frac{I_c \times I_v}{S} \)

\( I_c \) - the inulin concentration in the infusion fluid
\( I_v \) - the velocity of infusion
\( S \) - the serum inulin concentration

Renal plasma flow

2 μCi/kg of \([131I]\) orthoiodohippurate in bolus
44 min
10 ml blood sample from the contralateral arm
orthoiodohippurate plasma clearance standard formula

inulin and \([131I]\) orthoiodohippurate clearances were normalized to 1.73 m² of body surface area

Renal functional reserve

= GFR (after protein load) - GFR (at baseline)

Statistics

\( \bar{x} \) = SEM

To compare baseline to protein load data
- The paired t-test and Wilcoxon signed rank test

To compare obese HT to lean HT group
- Kruskal-Wallis test and the one-way ANOVA

To compare individual data point
- Dunn’s or Bonferroni’s multiple comparison tests

\( p < 0.05 \)

RESULTS
**Table 1** Baseline clinical and laboratory parameters in obese hypertensive and lean hypertensive patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Obese hypertensive (n = 42)</th>
<th>Lean hypertensive (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50.5 ± 0.9</td>
<td>50.6 ± 2.7</td>
</tr>
<tr>
<td>Gender, male/female (%)</td>
<td>59%</td>
<td>61%</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>32.9 ± 0.3</td>
<td>22.9 ± 0.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>152.8 ± 0.6</td>
<td>151.2 ± 0.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>96.2 ± 0.6</td>
<td>97.9 ± 0.7</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>113.1 ± 1.9</td>
<td>115.7 ± 1.9</td>
</tr>
<tr>
<td>Mean eGFR, ml/min/1.73m²</td>
<td>76 ± 2.1</td>
<td>78 ± 4.3</td>
</tr>
<tr>
<td>Urinary protein, mg/24h</td>
<td>157.1 ± 12.6</td>
<td>145.8 ± 32.5</td>
</tr>
<tr>
<td>Urinary albumin, g/24h</td>
<td>21 ± 0.9</td>
<td>19 ± 0.7</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>0.98 ± 0.008</td>
<td>0.97 ± 0.006</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.41 ± 0.15</td>
<td>5.21 ± 0.54</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.26 ± 0.06</td>
<td>1.21 ± 0.07</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/l</td>
<td>1.82 ± 0.18</td>
<td>1.52 ± 0.30</td>
</tr>
<tr>
<td>Serum glucose, mmol/l</td>
<td>4.5 ± 0.13</td>
<td>4.6 ± 0.13</td>
</tr>
</tbody>
</table>

_Each are mean ± SEM. Normal UAE <30 mg/24 hr_

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**Individual changes in glomerular filtration rate**

1. **A**
   - Lean
   - Baseline
   - Protein load
   - Obese

2. **B**
   - Lean
   - Baseline
   - Protein load
   - Obese

3. **C**
   - Lean
   - Baseline
   - Protein load
   - Obese

4. **D**
   - Lean
   - Baseline
   - Protein load
   - Obese

**Note:**
- *p<0.05 (baseline vs. protein load)
- **p<0.05 (lean vs. obese)

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**Individual changes in renal plasma flow**

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**Individual changes in renal reserve**

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**Individual changes in urinary excretion of kallikrein**

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**นวัตกรรมของการควบคุม**

1. ภาวะ **GFR ซูม**
   - Urine Albumin Excretion, UAE ย้มปัสสาวะเพิ่ม
     - ค่า UAE ไน 30 mg/24 hr หรือ < 20 mg/min

2. การการห้องปฏิบัติการสรุปมูลสำคัญ ร่วมโมเดลภาวะภูมิคุ้มกันที่glomerular basement membrane หนาตัวขึ้น

3. ภาวะภาวะภาวะโรคไตวายเรื้อรัง
   - Microalbuminuria ความดันไตลดลงต่ำขึ้น UAE ช่วงต้นของโรคไตระหว่าง 30 - 299 mg/24 hr หรือ 20 – 199 mg/min

4. ภาวะภาวะภาวะโรคไตวายเรื้อรัง
   - Macroalbuminuria (Clinical albuminuria) ความดันไตลดลงต่ำขึ้น, บวม, GFR หดตัว UAE > 300 mg/24 hr หรือ > 200 mg/min

5. ภาวะภาวะภาวะโรคไตวายเรื้อรัง ตามนี้ให้ไปตรวจวัดไตเรื้อรังทันที
**DISCUSSION**

At baseline, Obese HT had higher values of the following parameters:
- Glomerular filtration rate
- Renal plasma flow
- Urinary kallikrein
- Nitric oxide

After the oral protein load, comparing obese HT to lean hypertensives
- Renal functional reserve .... was blunted
- Lower increase in .... urinary kallikrein
- Inability to elevate .... NO serum levels

In a protocol to assess the influence of obesity on renal function in normotensive and hypertensives, GFR, ERPF, urinary albumin excretion were increased in overweight individuals when compared with those of lean individuals, either normotensive or hypertensive.

(Ribstein, Cailar, Mimran et al., 1995)

Our results confirm that study at baseline, GFR and ERPF were significantly higher in obese HT compared with lean essential hypertensives.
The mechanism responsible for increased vasodilatation and GFR (at baseline) associated with obesity

- Increase tubular reabsorption of sodium at a site before macula densa (PCT + HL)
- Increase in blood pressure with weight gain
- Initiating a feedback mediated vasodilatation of afferent arterioles

With prolonged obesity, increased arterial pressure is required to maintain sodium balance, which is accompanied by glomerular hyperfiltration.

Obese patients

- Extracellular fluid volume expansion
- Integrated response of the renal endothelial and macula densa nitric oxide synthase
- Restoration of sodium and volume balance

Renal functional reserve is impaired in various renal diseases:
- Diabetic nephropathy
- Nephrotic syndrome
- Systemic sclerosis
- Essential hypertension

Early alterations in renal reserve are present in still-normotensive individuals at genetic risk for essential hypertension.

Loss of the renal functional reserve is a marker of the presence of hyperfiltration.

Renal functional reserve was not blunted in our lean hypertensive patients compared with a group of healthy human volunteers previously studied by our group.

Renal functional reserve remains a controversial issue within different populations of essential HT patients, there are responders and non-responders to protein load or amino acid infusion.

Renal functional reserve may be impaired in sodium sensitive hypertensive patients and conversely, the GFR tends to increase in response to protein load in patients with the non-sodium sensitive type of essential hypertension.

No study has addressed whether in obese HT individuals, a reduced glomerular reserve in response to a protein load is an early marker in the natural history of obesity hypertension, end-stage renal disease.

Renal functional reserve was reduced in our obese hypertensive patients indicating an already present stage of hyperfiltration, which may represent the possible pathophysiological mechanism that contributes to glomerulosclerosis & to the progression of renal insufficiency.
Why was the renal functional reserve blunted in obese hypertensive patients?

**Obesity & HT** are independently associated with **endothelial dysfunction**. Combination of both conditions seems to have **additive effects** on endothelium-dependent vasodilation.

Our obese HT showed a reduced capacity to elevate **nitric oxide** production after a protein-rich meal when compared with lean patients. This diminished capacity to elevate nitric oxide production results in a possible acceleration of the renal disease due to failure to modulate intrarenal hemodynamics.

The role of renal kallikrein and vasoactive kinins in regulating renal response to protein intake

In rats, an increasing amount of dietary protein augments the excretion of active kallikrein and prokallikrein. In rats fed a high-protein diet, GFR & RPF are lowered by **aprotinin**, a kallikrein inhibitor.

In human, despite ageing, all parameters regarding the kinin system changed significantly in the direction of increased bradykinin synthesis during a protein load.

**The mechanisms leading to early renal dysfunction in obesity hypertension** were not fully elucidated in the present study since the potential role of other vasoactive agents and proinflammatory cytokines on renal hemodynamics and glomerular damage was not evaluated.

However, this study provides **support for the hypothesis** that obese hypertensives with loss of the renal functional reserve could be more susceptible to the deleterious effects of hypertension, dyslipidemia, and dysglycemia, which frequently coexist in these patients. This can precipitate gradual nephron loss, glomerulosclerosis, and eventually, end-stage renal disease.

Thank you