Obesity, Salt Intake, and Renal Perfusion in Healthy Humans

Lisa E. Porter, Norman K. Hollenberg

Abstract—Renal perfusion rises as obesity develops during short-term overfeeding in animal studies. In humans, the assessment is complicated by the need to normalize renal perfusion for body size. We made use of the fact that radioactive xenon washout measures renal perfusion per unit of tissue mass to address this issue by comparing 45 moderately obese and 147 lean healthy potential kidney donors. All were disease free. The rationale for involving kidney donors reflects the fact that the xenon method for measuring renal perfusion demands injection of the xenon directly into the renal artery, which can be accomplished during the arteriogram that is a necessary part of potential kidney donor evaluation. In 21 obese subjects (body mass index [BMI], 29.1±0.9) in balance on a 10-mmol sodium intake, renal perfusion (352±16 mL·100 g⁻¹·min⁻¹) was significantly higher than predicted from findings in the 95 lean control subjects (313±3 mL·100 g⁻¹·min⁻¹; P=0.035) after adjustment for age. With a high sodium intake (200 mmol), however, renal perfusion was not significantly different in 24 obese subjects (BMI, 28.8±0.7; 323±13 mL·100 g⁻¹·min⁻¹) in comparison to 52 lean controls (341±10 mL·100 g⁻¹·min⁻¹) after adjustment for age. Systolic and diastolic blood pressures were similar in obese and age- and gender-matched lean control subjects. Renal vasodilation was seen in association with sustained obesity in humans. While the mechanisms of obesity-related vasodilation are unclear, the dependence on sodium intake in this study is consistent with a role for the renin-angiotensin system. The findings are not in accordance with a reduction in renal perfusion reported in healthy obese humans in whom measured renal perfusion was indexed for body size. (Hypertension. 1998;32:144-148.)

Key Words: sodium □ renin □ renal blood flow

Growing recognition that obesity often plays a causal or complicating role in the pathogenesis of hypertension and type 2 diabetes mellitus has led to widespread interest in mechanisms that might link obesity with altered renal function. Renal perfusion rises as obesity develops during short-term overfeeding in dogs and rabbits. In dogs, the increase in RBF occurs without an increase in kidney weight, so perfusion increases per unit of tissue mass. Kidney weight increases in rabbits, however, and the rise in RBF with overfeeding is not significant when adjusted for kidney mass. Renal perfusion determination in humans is complicated by the widely perceived need to index RBF to some measure of body size. During human development, for example, renal mass, perfusion, and function increase as the body grows from infancy to the adult state. Moreover, in adults, renal mass does vary with body mass. Thus, the need to normalize or index renal perfusion for body size has been intuitively as obvious. Standard practice has been to use a body surface area of 1.73 m², a convention that is the subject of substantial recent analysis. Depending on whether normalization for body surface area was used, renal perfusion could be less than anticipated or exceed expectation. Thus, at the moment there is no information in humans on either the appropriate adjustment of renal perfusion for body mass or the consequence of increase of obesity for renal perfusion.

To address these issues, we took advantage of the fact that radioactive xenon (133Xe) transit through the kidney provides a measure of blood flow per unit of tissue mass. Because blood flow is registered as milliliters per 100 grams per minute with this method, no further adjustment for kidney size or body size is necessary. This method requires injection of the tracer directly into the renal artery, which we accomplished in potential kidney donors at the time of the renal arteriogram that is required for kidney donation. Although morbid obesity was considered a contraindication to kidney donation, subjects with moderate obesity did undergo donor evaluation and arteriography, which made it possible to assess the influence of obesity on renal tissue perfusion in otherwise healthy humans. Also, because of our recent observation that obesity blunts the renal vascular response to Ang II and also interacts significantly with a common variant of the AGT gene to exert an even greater blunting effect, we examined the influence of salt intake on renal perfusion in obese and lean kidney donors.

Methods

RBF studies with 133Xe were carried out at the time of angiography in 192 potential kidney donors who ranged in age from 18 to 63 years. The “lean” comparison group included 147 subjects whose body weight was within 20% of ideal according to Metropolitan Life
Selected Abbreviations and Acronyms

AGT = angiotensinogen
Ang = angiotensin
BMI = body mass index
NHANES = National Health and Nutrition Examination Surveys
PRA = plasma renin activity
RAS = renin-angiotensin system
RBF = renal blood flow

In 21 obese subjects on low salt intake, age-adjusted renal perfusion (352±16 mL · 100 g⁻¹ · min⁻¹) was significantly higher than that in age-matched lean subjects (313±3 mL · 100 g⁻¹ · min⁻¹; P=0.035) (Figure 1). The 6 overweight subjects, reflected in a borderline high BMI between 25 and 26.9, had a somewhat higher RBF than did the lean controls, but this was not significant (P=0.6). Those with frank obesity (BMI between 27 and 35) had significantly higher RBF than controls (P=0.013, n=13). The 5 subjects in whom renal perfusion exceeded the 95% confidence interval were all 31 years of age or younger, significantly younger than the obese group (P<0.01). With high salt intake, however, renal perfusion was not significantly different in 24 obese subjects (323±13 mL · 100 g⁻¹ · min⁻¹) compared with lean controls (341±10 mL · 100 g⁻¹ · min⁻¹) (Figure 2).

Baseline PRA levels in obese and matched lean subjects on low salt intake were not significantly different (2.7±0.4 and 3.2±0.3 µg · h⁻¹ · L⁻¹, respectively; P=0.112). Similarly, basal PRA measured at the time of arteriography was identical in the lean control (1.5±0.6 µg · h⁻¹ · L⁻¹) and obese (1.5±0.5 µg · h⁻¹ · L⁻¹) subjects on a high salt diet (Table 3).

### Results

Baseline systolic and diastolic blood pressures and levels of serum creatinine, fasting blood sugar, and 24-hour urine sodium were not significantly different in obese subjects compared with those in age- and gender-matched lean controls on either the low or high salt diet (Tables 1 and 2).

<table>
<thead>
<tr>
<th>Index</th>
<th>Obese (n=19)</th>
<th>Lean (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.4±2.0</td>
<td>33.4±2.0</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>11:8</td>
<td>11:8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.6±3.2</td>
<td>170.7±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>86.1±3.7</td>
<td>64.5±3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.1±0.9</td>
<td>22.0±0.4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>119±2</td>
<td>117±3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±3</td>
<td>75±2</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>85.75±3.54</td>
<td>89.28±3.54</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>(0.97±0.04)</td>
<td>(1.01±0.04)</td>
</tr>
<tr>
<td>Fasting blood sugar, mmol/L</td>
<td>5.05±0.11</td>
<td>4.88±0.17</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>(91±2)</td>
<td>(88±3)</td>
</tr>
<tr>
<td>Mean 24-h urinary Na, mEq/24 h</td>
<td>27±5</td>
<td>24±5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index</th>
<th>Obese (n=18)</th>
<th>Lean (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41.3±3.4</td>
<td>41.4±3.4</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>9:9</td>
<td>9:9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.2±3.3</td>
<td>170.4±3.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85.8±3.9</td>
<td>61.7±3.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.8±0.7</td>
<td>21.4±0.4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>121±4</td>
<td>116±3</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>75±2</td>
<td>72±3</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L</td>
<td>97.24±4.42</td>
<td>85.75±3.54</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>(1.10±0.05)</td>
<td>(0.97±0.04)</td>
</tr>
<tr>
<td>Fasting blood sugar, mmol/L</td>
<td>4.77±0.17</td>
<td>5.11±0.11</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>(86±3)</td>
<td>(92±2)</td>
</tr>
<tr>
<td>Mean 24-h urinary Na, mEq/24 h</td>
<td>177±14</td>
<td>177±12</td>
</tr>
</tbody>
</table>
Discussion

Our goal was to determine how perfusion per unit of renal tissue mass is influenced by sustained obesity in humans. We found renal vasodilation resulting in increased perfusion per unit of renal tissue mass in obese humans on low salt intake, but not when studies were performed in subjects on high salt intake. These results did not reflect differences in the degree of obesity in the low and high salt groups. The difference in body weight between obese and lean averaged 21.6 kg with the low salt diet and 24.1 kg with the high salt diet. Sodium intake was controlled because it is a major determinant of RBF, at least in part by way of the RAS.11 The specific salt intake–based difference in our results, however, was not anticipated. This difference in the effect of salt intake can be considered “hypothesis generating” and may provide insight into the mechanism of obesity-associated renal vasodilation as discussed below.

Cut points to define obesity are problematic, since cardiovascular risk increases with BMI in a continuous manner. This has led to a range of definitions of obesity, with somewhat arbitrary cut points. Many investigators have used the NHANES II criteria defining “overweight” as a BMI $\geq$ the 85th percentile for a population aged 20 to 29 years (BMI, 27.8 and 27.3 for males and females, respectively); and “severely overweight” as a BMI $\geq$ the 95th percentile (BMI, 31.3 and 32.3, respectively).17 These criteria are lax. Increased risk for CHD has been demonstrated in women with BMIs as low as 2318 and is seen in the Framingham offspring population in men and women with BMIs over 24.5.19 In this study we used a BMI of 25 as the boundary in accordance with the 1985 US weight guidelines, which defined a desirable BMI range between 19 and 24.13 The Canadian Expert Group on Weight Standards were also in accordance.14

A potential limitation, limiting generalizability, but also a strength of our study was the utilization of a relatively homogeneous, very healthy population. Because these individuals were being considered for kidney donation, only those determined by exhaustive diagnostic evaluation to be free of disease and at low risk underwent arteriography. For the same reason, we were unable to study severely obese subjects. In a random sample of obese patients in the community, one would expect a higher blood pressure level and higher fasting blood sugar. In less healthy obese subjects, increased body mass may exert a different effect on renal perfusion.

Obesity-associated vasodilation has been demonstrated in animals in relatively short-term overfeeding experiments. Dogs fed a high fat diet for 6 weeks had increased cardiac output, decreased systemic vascular resistance, and increased blood flow to the kidney and gastrointestinal tract.2 Similar results were seen in rabbits after 8 to 12 weeks of high fat intake.3 In both normotensive and hypertensive obese humans, RBF was higher than in lean controls,7,20 but when renal perfusion in humans was normalized to body surface area, RBF fell with increasing BMI.6 By using the radioxenon technique for measuring RBF, we were able to eliminate considerations about either body size or kidney size as relevant variables. Renal perfusion was not reduced in obese humans, providing further evidence of the inadequacy of normalizing RBF to body surface area.

Both the RAS and the actions of insulin have been considered candidates in obesity-associated hemodynamic changes, but the mechanisms remain unclear and all discussion must be considered speculative. The fact that we found a salt intake–based difference in the effect of obesity on RBF confirms, at least in part, the interesting possibility of a role for the RAS. Measurement of PRA levels in this study and elsewhere has not clarified this role. PRA has been shown to

| TABLE 3. Baseline PRA Levels in Obese and Lean Subjects |
|-----------------|-----------------|
| PRA, $\mu g \cdot h^{-1} \cdot L^{-1}$ |
| **Index** | **Obese** | **Lean** |
| Low salt | $2.7 \pm 0.4$ (n=13) | $3.2 \pm 0.3$ (n=9) |
| High salt | $1.5 \pm 0.5$ (n=7) | $1.5 \pm 0.6$ (n=9) |
be unchanged or increased in association with obesity\textsuperscript{21,22} and may decrease with weight loss.\textsuperscript{23,24} We found no significant difference in PRA levels between obese and lean subjects in the present study. This study was prompted in part by our recent finding that obesity is associated with a blunted RBF response to infused Ang II.\textsuperscript{3} In that study, designed to assess the effect of AGT gene polymorphisms on Ang II–mediated control of the renal circulation, obesity was found to be a strong predictor of blunted renal response.\textsuperscript{3} The diminished response seen in many hypertensive subjects was to a major degree accounted for by their higher BMI. One possibility that we have considered is that this blunted response in hypertension reflects downregulation of renal Ang II receptors by chronically elevated intrarenal Ang II levels.\textsuperscript{25} Down-regulation of renal Ang II receptors could also explain the failure of our obese subjects to reduce their RBF appropriately in the setting of low salt intake. Plasma AGT levels have repeatedly been shown to be strongly positively correlated with BMI.\textsuperscript{26–28} AGT mRNA is expressed abundantly in adipocytes.\textsuperscript{29,30} Expression varies with fasting and refeeding in both normal rats and obese mice.\textsuperscript{29} Plasma AGT concentration has been shown repeatedly to vary directly with BMI in a variety of populations\textsuperscript{26–28} and extended to the demonstration of an association between AGT gene polymorphisms and body fat distribution in men.\textsuperscript{31}

Our finding that the effect of obesity on renal perfusion was dependent on sodium intake may be relevant to the complex relationship between body weight and sodium sensitivity. When adolescents were changed from a high salt to a low salt diet, only the obese group had a significant change in blood pressure.\textsuperscript{32} Weight loss resulted in a loss of BP sodium sensitivity even though ideal body weight was not attained, suggesting that caloric excess rather than body weight per se may determine sodium sensitivity. This has important implications in extrapolation of results from short-term overfeeding studies in animals to obese humans, who have likely been overweight for a relatively long time. The fact that the high renal perfusion rates were found primarily in young subjects (<31 years) in this study may be relevant to the same issue.

Higher insulin levels associated with obesity also may contribute to vasodilation. Hyperinsulinemic/euglycemic clamp studies in normal humans revealed decreased forearm vascular resistance and increased blood flow despite an increase in sympathetic nerve activity.\textsuperscript{33} Peripheral vasodilation was also demonstrated during chronic insulin infusions in normal dogs.\textsuperscript{34} However, insulin infusions in dogs that were insulin-resistant secondary to obesity failed to cause vasodilation,\textsuperscript{1} and in obese humans, leg blood flow increased with insulin infusion but at a much slower rate than in lean humans.\textsuperscript{35} Fasting insulin levels in obese humans were not correlated with RBF.\textsuperscript{1} This lack of response in insulin-resistant individuals is interesting in the light of the apparent effect of age in the present study: the increase in RBF in the obese was most prominent in the younger subjects (Figure 1). If we assume that the younger subjects had been overweight for a shorter period of time, then it follows that they were less insulin resistant and therefore more susceptible to the vasodilatory effects of insulin. An alternative explanation for this apparent age effect could be that very long-term and sustained obesity eventually leads to a decline in renal function—a possibility of some importance given the contribution of obesity to hypertension and to diabetes mellitus.

We believe that the findings in this study have two broad implications. First, the renal vasodilation documented during short-term weight gain caused by overfeeding in animal models can be identified in moderately obese humans in the steady state and is not the product of short-term overfeeding. Moreover, the degree of vasodilation varied with the state of sodium balance, implicating RAS activation, possibly at the tissue level. Finally, efforts to index renal perfusion to body surface area may result in a systematic underestimation of renal perfusion in the obese, an observation with ramifications for interpretation of studies on the renal circulation in hypertension and in non–insulin-dependent diabetes mellitus.

Acknowledgments

This research was partially supported by National Institutes of Health grants T32 HL-07609, NCRR GCRC M01RR026376, P01AC00059916, and 1P50 ML53000-01. We are grateful to Diana Capone for her assistance in the preparation and submission of this manuscript.

References

Renal Perfusion in Obesity


Obesity, Salt Intake, and Renal Perfusion in Healthy Humans
Lisa E. Porter and Norman K. Hollenberg

Hypertension. 1998;32:144-148
doi: 10.1161/01.HYP.32.1.144

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/32/1/144

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/