Sodium, blood pressure and cardiovascular pathology: is it all volaemia?

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Keywords: dialysis; hypertension; nitric oxide; oxidative stress; renal failure; sodium

Introduction

The daily intake of salt in the western world greatly exceeds human needs, which may have adverse cardiovascular consequences, especially in patients with abnormalities in renal sodium handling. In normotensive subjects, the effects of salt intake on blood pressure appear to be relatively small [1]. However, a large subset of patients with essential hypertension responds to salt loading and restriction with pronounced changes in blood pressure, which has led to the concept of salt sensitivity [2].

Patients with end-stage renal disease are very susceptible to the adverse effects of salt, as their ability to excrete sodium is lost or greatly impaired. In these patients, sodium loading may lead to severe hypertension and left ventricular hypertrophy. It is generally accepted that in renal patients, the adverse effects of salt are predominantly due to a combined water and sodium overload due to the fact that the body tries to maintain the osmolarity of the extracellular compartment. However, in parallel to salt-sensitive patients with sodium, blood pressure and cardiovascular pathology: is it all volaemia?

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essential hypertension, the response of various neuro-
humoral mechanisms to salt loading also appears to be
disturbed in patients with end-stage renal disease [3].
There are also preliminary data showing that sodium,
independent of volume, may have an effect on blood
pressure regulation. Moreover, sodium may even have
trophic effects, independent of volume status. The goal
of this comment is to give a short overview of the effects
of sodium on blood pressure and (cardio)vascular
hypertrophy, and to extrapolate relevant findings
obtained in animal experiments and patients with
essential hypertension to patients with end-stage renal
disease.

The salt sensitivity concept

In patients with essential hypertension, there appears
to be an intra-individual variation in the blood
pressure response to salt loading and restriction.
Although there is no clear cut-off point at which
patients with essential hypertension can be dichotom-
ized, so-called salt-sensitive patients respond to salt
loading with a blood pressure increase, whereas blood
pressure does not change in salt-resistant patients [2].
The mechanisms behind salt sensitivity are still under
debate. Subclinical renal damage, leading to a reduc-
tion in nephrons [4] or impaired proximal tubular
sodium handling, have been implicated in its patho-
genesis [5]. However, the responses of various neuro-
humoral mechanisms to salt loading also appear to
differ between salt-sensitive and salt-resistant patients.
In salt-sensitive patients, the suppression of the activity
of the renin-angiotensin and sympathetic nervous
system during salt loading is blunted compared to
salt-resistant patients [6,7]. The activity of Na–K
ATPase inhibitors was also found to be increased in
animal models and humans with salt-sensitive hypo-
tension, which may lead to an increase in intracellular
calcium and hence an increase in vascular resistance
[8]. Moreover, in salt-sensitive patients with essential
hypertension, blood pressure changes after salt loading
were inversely related to changes in nitric oxide (NO)
activity, which was in turn inversely related to changes
in the endogenous NO inhibitor, asymmetric dimethy-
larginine (L-ADMA) [9]. Thus, in animal models and
humans with salt-sensitive essential hypertension, the
responses of various neurohumoral mechanisms to salt
loading appear to be disturbed.

Recent animal studies also coupled the salt-sensitivity
concept to oxidative stress [10]. Both angiotensin II and
Na–K ATPase inhibitors stimulate the production of
reactive oxygen species through the enzyme vascular
NAD(P)H oxidase. The reaction between superoxide
anions and NO results in the formation of peroxynitrite,
leading to a loss in NO bioavailability. This results in an
increase in vascular resistance, an effect that is poten-
tiated by the effects of angiotensin II [11]. Interestingly,
the pressor response to angiotensin II was reduced
in mice overexpressing the antioxidant superoxide
dismutase compared to wild-type mice [12]. Thus, at
least in animal studies, additive effects of angiotensin II
and reactive oxidant species on vascular reactivity were
observed [11,13]. Data on this subject in humans are still
scarce, although an increased oxidative stress has been
observed in patients with essential hypertension [14].

Salt and blood pressure in patients
with renal disease

In patients with advanced renal failure, the blood
pressure response to salt loading is generally aug-
mented [15], which is understandable in view of the loss
of functioning nephrons in these patients. However,
in parallel with salt-sensitive patients with essential
hypertension, the response of neurohumoral mechan-
isms to sodium loading may also be blunted. Although
levels of renin and angiotensin are often not directly
related to blood pressure in patients with advanced
renal failure, the activity of the renin–angiotensin
system was found to be inappropriately increased in
relation to the volume status and exchangeable sodium
[16,17]. Moreover, the activity of the sympathetic
nervous system is increased in patients with advanced
renal failure, as is the ratio between sympathetic nerve
activity and extracellular volume [18]. The removal of
excess water and sodium improves blood pressure
control in patients with advanced renal disease [19].
Also, a complete normalization of blood pressure
regulation has been achieved by the use of prolonged
dialysis times, such as in the centre of Tassin and in the
case of nocturnal dialysis [20,21]. Interestingly, in the
Tassin centre, volume status was not largely different
from patients from centres treated with conventional
dialysis times, whereas the normalization of blood
pressure regulation in the case of nocturnal dialysis
was achieved without a change in extracellular
volume [21]. Although sodium removal has not yet
been studied during long dialysis sessions, it may be
expected that prolonged dialysis times, certainly when
using relatively low dialysate sodium concentration,
results in enhanced sodium removal [22]. In the Tassin
centre, a strict sodium-restricted diet is also prescribed.
Therefore, it is tempting to speculate that a reduction
in exchangeable sodium, even without a change in
body water content, may improve blood pressure
regulation. This hypothesis is supported by the
preliminary data of Krautzig et al. [23], who observed
an improvement in blood pressure control in dialysis
patients with the prescription of a sodium-restricted
diet and lowering of the dialysate sodium concentra-
tion. The pathophysiologic mechanisms behind the
volume-independent effects of sodium on blood
pressure regulation are not yet known and may be
mediated through the activity of various neurohumoral
systems. However, as will be discussed below, sodium
may also have structural effects on the heart and the
vasculature, which also might influence blood pressure
control.
Does sodium influence structural modifications on the cardiovascular system, independent of blood pressure?

Evidence that sodium, independent of blood pressure, may have an effect on the vascular system first arose from the animal experiments of Tobian. In these studies, the effect of sodium loading was studied in DOCA hypertensive salt-resistant rats. Despite the fact that blood pressure remained unaltered in these animals, salt loading resulted in structural alterations of renal and cerebral blood vessels and enhanced mortality [24]. In other studies in spontaneous hypertensive rats, salt loading had no effect on blood pressure, but resulted in vascular wall thickening and an increase in collagen content [25]. In human hypertension, the trophic effects of salt loading, independent of blood pressure, are less clear. Schmieder et al. [26] observed an independent relation between urinary sodium and left ventricular mass, whereas Draaijer et al. [27] observed an increased vascular stiffness in salt-sensitive patients with borderline hypertension compared to salt-resistant patients. However, the effects of diuretics on vascular stiffness are controversial, which may be due to the fact that these drugs can also stimulate angiotensin II synthesis [25].

In dialysis patients, the effect of sodium restriction on structural cardiovascular abnormalities has not been studied. However, patients in Tassin, who are treated with long dialysis sessions with a relatively low dialysate sodium concentration that will enhance diffusive sodium removal, and are maintained on a strict sodium diet, might serve as a model for the effects of salt restriction. Interestingly, peripheral vascular resistance in Tassin patients was significantly lower compared to patients from ‘conventional’ dialysis centres and even lower compared to healthy controls [20]. Also the stiffness of the carotid artery did not differ from control subjects, although femoral artery stiffness was still increased [28]. Somewhat disappointingly, left ventricular hypertrophy remained highly prevalent even in Tassin patients [20]. On the other hand, nocturnal haemodialysis, during which sodium removal is higher compared to standard dialysis, resulted in a reduction of posterior wall and intraventricular stiffness [29]. However, both with the Tassin experience and with nocturnal dialysis, it is impossible to distinguish the effects of an enhanced sodium removal from the possible effects of an enhanced removal of other substances, such as l-ADMA, which may also have an influence on cardiovascular structure.

How are the trophic effects of sodium mediated?

Earlier studies in hypertensive animals showed that the sodium and water content of the large arteries was increased compared to normotensive animals [30]. However, sodium may also have indirect effects of vascular hypertrophy.

As mentioned previously, salt loading may contribute to an increased oxidative stress. Reactive oxidant species were found to increase proliferation of vascular smooth muscle cells, which may be mediated through a reduced NO bioavailability due to the mechanisms described previously. This effect appears to be enhanced by angiotensin, which stimulates the transcription factor NF-κB [10,11,13,31]. However, these points have not yet been settled, as the vasotrophic response to angiotensin II was not different between wild-type mice and mice with an overexpression of superoxide dismutase [12]. Thus, the trophic effects of salt loading may be mediated either by an increased logging of water sodium in the vascular smooth muscle cell, or indirectly through an increased oxidative stress, which may be enhanced by angiotensin II. At least from a theoretical point of view, the effects of sodium restriction and angiotensin blockade might be additive.

Summary

The effect of sodium on blood pressure regulation in the general population is still a topic of debate. However, at least in a large subset of patients with essential hypertension, the sensitivity of blood pressure to changes in sodium intake is increased. In patients with renal disease, there is strong evidence that salt sensitivity of blood pressure is in general increased, which may be explained both by the reduced number of functioning nephrons and by disregulation of various neurohumoral systems. Moreover, in these patients, there is circumstantial evidence that sodium, apart from volume, may have an independent effect on blood pressure regulation. Experimental and clinical studies suggest that sodium may have independent trophic effects, which may be mediated through increased oxidative stress, leading to reduced NO availability, an effect that is enhanced by angiotensin II. To elucidate the clinical importance of these mechanisms in uraemic patients, additional pathophysiologic studies are needed.

Conflict of interest statement. None declared.

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Chronic hepatitis virus infections in patients on renal replacement therapy

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The magnitude of the problem

Hepatitis B (HBV) and C (HCV) virus infections represent a major problem in dialysis patients and renal allograft recipients.