Potassium Supplementation Improves the Natriuretic Response to Central Volume Expansion in Primary Aldosteronism

Paolo Coruzzi, Massimo Gualerzi, Gianfranco Parati, Lorenzo Brambilla, Valerio Brambilla, Marco Di Rienzo, and Almerico Novarini

Potassium depletion induced by dietary potassium restriction is known to cause sodium retention, while potassium supplementation is known to increase urinary sodium excretion. However, the ability of potassium deficiency to affect mineralocorticoid-induced sodium retention in aldosterone-producing adenoma (APA) subjects has not been extensively investigated, neither in baseline conditions nor when facilitating natriuresis through a physiological manoeuver such as central blood volume expansion. With the aim of testing the hypothesis that potassium supplementation would attenuate the mineralocorticoid-induced sodium retention, in 7 APA patients elevation of serum potassium was obtained by infusion of isosmotic potassium chloride (KCl) at a constant rate of 36 mmol/h for a 2-hour period for 5 consecutive days. The same patients were also submitted to acute central volume expansion by head-out water immersion (WI) associated with either low or normal serum potassium levels. The assessment of natriuresis in baseline condition and during WI was also performed in 10 age-matched control subjects. Central hypervolemia by WI induced a significant natriuretic response in APA hypokalemic subjects; on the other hand, in the same APA subjects giving potassium supplementation, WI-induced urinary sodium excretion was significantly higher ($P < .001$) than that obtained during WI at normal potassium intake (hypokalemic condition). Blood pressure responses and hormonal profiles were almost superimposable during the 2 WI experiments performed at different serum potassium levels. By confirming that amelioration of hypokalemia attenuates mineralocorticoid-induced sodium retention, this study also suggests that potassium intake may represent an important determinant of mineralocorticoid escape.

THE RENAL ESCAPE from the sodium-retaining effect of aldosterone is a hallmark of primary aldosteronism; the mechanisms known to contribute to the escape from mineralocorticoids include (1) increased renal interstitial hydrostatic pressure, (2) endogenous release of renal autacoids, (3) decreased sympathetic activity, and (4) increased atrial natriuretic peptide (ANP) levels.[1]

Mineralocorticoid excess may produce sodium retention, potassium depletion and hypokalemia,[2,3] and the recent demonstration that even mild potassium depletion produces striking alterations in urinary sodium excretion of normotensive and hypertensive subjects[4,5] seems to suggest a possible role of potassium in modulating the response that leads to escape.

Another physiological mechanism involved in modulating sodium excretion is central blood volume shift, through the stimulation of volume sensitive cardiopulmonary receptors. While it is well known that a central blood volume shift represents a physiological stimulus able to elicit a natriuretic effect,[1] little information is available on the possible role of cardiopulmonary receptors stimulation in regulating sodium escape of primary hyperaldosteronism with or without potassium supplementation. Our study was specifically designed to investigate the above 2 issues, namely (1) the role of central volume expansion in regulating urinary sodium excretion in primary hyperaldosteronism, and (2) whether potassium supplementation may attenuate the mineralocorticoid-induced sodium retention, in patients affected by an aldosterone-producing adenoma (APA), and whether this is the case in control conditions and during central volume expansion. To this aim, 7 APA patients were submitted to acute central volume expansion by head-out water immersion (WI) associated with either low or normal serum potassium levels, the latter obtained through potassium chloride intravenous supplementation.

WI was selected as a means for obtaining volume expansion because it induces a volume stimulus similar to that of an isotonic saline infusion without altering plasma composition. Its usefulness and safety in testing the effects of central volume sihft in APA patients is further supported by reports that potassium deficiency is a contraindication for intravenous isotonic saline administration and that diagnostic testing with saline infusion should be undertaken only when serum potassium levels are above 3.5 mmol/L.[3,6]

METHODS

Subjects

Seven patients (3 men, 4 women) with confirmed primary aldosteronism (obtained through clinical and radiological evaluation) and 10 control subjects matched for age and body weight were included in the study. Their ages ranged from 29 to 65 years. The patients did not exhibit any clinical evidence of cardiovascular disease and their renal function (creatinine clearance and proteinuria) was normal. In all patients surgical confirmation of APA was obtained at the end of the study. The patients had their antihypertensive medications (invariably represented by calcium and alpha blockers) discontinued at least 2 weeks before the test. The protocol was approved by our institution's Ethics Committee and all participants gave their informed consent.

From the Dipartimento di Scienze Cliniche, Fondazione Don C. Gnocchi-ONLUS, University of Parma, Parma; Istituto Scientifico Ospedale S. Luca, IRCCS-Istituto Auxologico Italiano, Milano; and LaRC, Centro di Bioingegneria, Fondazione Don C. Gnocchi, Politecnico di Milano, Milano.

Submitted February 25, 2003; accepted July 8, 2003.

Address reprint requests to Paolo Coruzzi, MD, Dipartimento di Scienze Cliniche-University of Parma, Fondazione Don C. Gnocchi-ONLUS, Piazzale dei Servi 3-43100 Parma, Italy.

0026-0495/03/5212-0024$30.00/0
doi:10.1016/j.metabol.2003.07.019

Experimental Protocol

Each patient was studied on 2 separate occasions while receiving a diet containing either 120 mmol/d sodium and 80 mmol/d potassium for 5 days (hypokalemic condition) only or 120 mmol/d sodium and 80 mmol/d potassium with intravvenous potassium chloride (KCl, 72 mmol/d) supplementation (normokalemic condition). Elevations of serum potassium were produced by infusions of isosmotic KCl at a constant rate of 0.6 mmol/min (36 mmol/h) for a 2-hour period for 5 consecutive days using a Braun infusion pump (Braun Melsungen, Germany); serum potassium levels were monitored daily and normal values (>4 mmol/L) were invariably obtained after 5 days of intravenous KCl supplementation.

Body weight, blood pressure, and 24-hour urinary sodium, potassium, and creatinine excretion were also monitored throughout each study period.

Water Immersion Studies

After the completion of the 2 diet periods at either normal (80 mmol/d) or high (152 mmol/d) potassium intake, each APA subject was submitted twice to acute extracellular volume expansion by WI, thereby acting as his or her own control. WI was performed as follows: at 8 AM after an overnight fast and fluid deprivation (lasting 10 hours), an antecubital vein was catheterized for blood sampling; the subjects voided, received 200 mL of water to drink then sat quietly outside the immersion tank for 2 hours at a room temperature between 26 ± 0.4 and 27 ± 0.4°C (preimmersion study). The oral water load was repeated hourly throughout the study. Each subject then stepped into the immersion tank and sat on an adjustable chair with water reaching the level of the neck at costant temperature (34 ± 0.5°C). Both arms were kept out of water, supported in the horizontal position. Subjects were asked to remain in the tank for 2 hours (immersion study) and stepped out of it at hourly intervals to void urine.

At the end of each hour of the test, before subjects stood to void, blood was drawn for serum potassium, hematocrit, creatinine, plasma renin activity (PRA), plasma aldosterone (PA), and ANP determination. The pooled 2-hour urine volumes were measured and the urinary concentrations of creatinine, sodium, and potassium were determined.

Both in basal conditions and during WI, arterial blood pressure was measured in seated position with a noninvasive fully automated monitor (Spacelabs model 90207, Redmond, WA) every 10 minutes, with the instrumented arm kept in the same position before and during WI; arterial blood pressure was also measured every 10 minutes from the contralateral arm with the auscultatory technique through a standard mercury manometer.

Blood for PRA, PA, and ANP measurements was drawn with chilled plastic syringes and then placed immediately into chilled plastic tubes containing EDTA and aprotinin. The plasma was separated in a refrigerated centrifuge at 4°C. Samples were frozen and stored at −20°C until assayed.

Ten control normal subjects (age ranging from 25 to 60 years) were also placed on a 120-mmol/d sodium and 80-mmol/d potassium diet. When sodium equilibrium was achieved, a WI study was then performed and urine collected for sodium, potassium, and creatinine determination before and at the end of the 120-minute immersion.

Laboratory Procedures

PRA (Renin-kit, Liso-phase, Sclavo, Milan, Italy) and PA (Coat-A-Count Aldosterone, Diagnostic Products Corp, Los Angeles, CA) were determined by radioimmunoassay (RIA); plasma ANP was measured by RIA after extraction from 2-mL samples, as previously reported in detail.[7]

Serum and urinary sodium and potassium were measured by internal standard flame photometry; serum and urinary creatinine were measured with a Technicon Autoanalyzer (Rome, Italy).

Table 1. Clinical and Biochemical Data in Seven APA Subjects After 5 Days of Normal (80 mmol/d) and High (152 mmol/d) Potassium Intake

Variable	80 mmol/d K^+ Intake	152 mmol/d K^+ Intake
Body weight (kg)	73.5 ± 3	73.4 ± 3
Mean arterial pressure (mm Hg)	118 ± 2	117 ± 2
Serum potassium (mmol/L)	3.1 ± 0.1	4.4 ± 0.1*
Urinary sodium excretion (mmol/d)	110 ± 8	112 ± 8
Plasma renin activity (ng/L · s)	0.07 ± 0.08	0.12 ± 0.02
Plasma aldosterone (pmol/L)	1,415 ± 194	1,553 ± 222
Atrial natriuretic peptide (pg/mL)	31 ± 3	34 ± 3*

NOTE. Values are mean ± SE. Significant difference compared with values noted on day 5 with the 80-mmol K^+ diet.
*$P < .008$.

Statistics

Values are given as means ± SE. Statistical evaluation of the differences between-conditions was performed by the Student's *t* test for paired values or where appropriate, by nonparametric Friedman test. A *P* value less than .05 was taken as the minimal level of statistical significance throughout the study.

RESULTS

APA Patients

Effects of potassium loading in baseline conditions. In comparison to normal potassium intake (80 mmol/d), high potassium intake (152 mmol/d) did not produce any significant change in baseline levels of mean arterial pressure (118 ± 2 and 117 ± 2 mm Hg, respectively; *P* = not significant [NS]), creatinine clearance, PRA, PA, or ANP in APA patients.

Furthermore, whereas potassium supplementation produced a significant elevation of serum potassium levels (from 3.1 ± 0.1 to 4.4 ± 0.1 mmol/L; $P < .008$), no significant changes were found in the body weight and urinary sodium excretion (110 ± 8 and 112 ± 8 mmol/d, respectively) of APA subjects (Table 1).

Effects of WI (before and during potassium loading). Figure 1 shows that urinary sodium excretion during the preimmersion period was 104 ± 8 μmol/min and reached a peak value of 211 ± 14 μmol/min ($P < .0001$) during WI in APA subjects undergoing normal potassium diet (cumulative sodium loss of 25 mmol/2 h); there was also a significant increase in urinary potassium excretion in these subjects during WI from 43 ± 6 to 67 ± 9 μmol/min; $P < .02$ (cumulative potassium loss of 8 mmol/2 h).

After restoration of normokalemia, preimmersion urinary sodium excretion values of APA subjects giving potassium supplementation were identical to those obtained during the basal period of the study with normal potassium intake (106 ± 6 μmol/min), thereby demostrating a satisfactory sodium equilibrium state after the modest sodium loss induced by the previous WI. Sodium excretion markedly increased during WI with potassium supplementation (339 ± 20 μmol/min; $P < .0001$) and this natriuretic event was significantly higher than

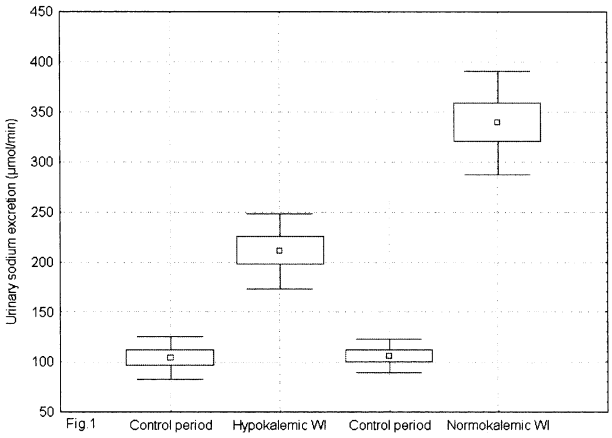

Fig 1. Natriuretic response in 7 APA patients, in baseline condition (control period), and during head-out WI. Data obtained either in the hypokalemic or in the normokalemic condition are shown separately.

that observed during WI at normal potassium intake ($P <$ .0007).

In APA patients there was also a significant increase ($P <$ .02) in urinary potassium excretion, with respect to baseline.

No differences in serum potassium, hematocrit, creatinine clearance, or mean arterial pressure were observed between baseline and WI conditions, at normal or high potassium intake. During normal potassium intake, WI induced a slight but not significant decrease of PRA in APA subjects (from 0.07 ± 0.008 to 0.05 ± 0.08 ng/L · s, P = NS); a similar suppression of PRA was obtained in the same subjects during WI at high potassium intake (from 0.12 ± 0.02 to 0.09 ± 0.02 ng/L · s, P = NS).

During potassium supplementation, the evidenced increase of PA (from 1,415 ± 194 to 1,533 ± 222 pmol/L) was not statistically significant; similarly, a nonsignificant reduction of PA (from 1,415 ± 194 to 1,220 ± 250 pmol/L, P = NS) was found during WI plus normal potassium intake and a similar reduction of PA was also obtained during WI at high potassium intake in APA patients (from 1,553 ± 222 to 1,387 ± 194 pmol/L, P = NS).

WI induced a significant increase of ANP plasma levels under either normal or high potassium intake from 31 ± 3 to 55 ± 6 pg/mL ($P <$ .005), and from 34 ± 3 to 59 ± 5 pg/mL ($P <$ .004), respectively (Table 2).

Control Subjects

WI induced a significant increase in urinary sodium excretion (from 107 ± 8 to 213 ± 10, $P <$ .0001) also in the 10 normal control subjects. This WI-induced natriuretic response did not significantly differ from that obtained in APA hypokalemic patients (P = NS) undergoing WI without potassium supplementation, while this natriuretic event was significantly lower when compared to that observed during WI in normokalemic APA subjects. WI also induced a significant suppression of PRA and PA ($P <$ .01 and $P <$ .001, respectively), while there was a significant increase in circulating levels of ANP ($P <$ .001) in normal control subjects.

No significant differences in mean arterial pressure and creatinine clearance were observed between baseline and WI conditions.

DISCUSSION

The present study provides important insights into the mechanisms involved in regulating natriuresis in APA patients by assessing for the first time the natriuretic effect of a central blood volume expansion obtained through head-out WI before and after potassium supplementation. First, our data show that isotonic-isooncotic volume expansion by WI is a potent stimulus for a significant natriuretic response which, in hypokalemic APA patients, was identical to that obtained in normal subjects. Moreover, a comparison between the natriuretic response obtained in control and APA subjects submitted to WI disclosed an "exaggerated" natriuretic response only when APA subjects were given potassium supplementation. The activation of cardiopulmonary receptors by WI-induced central blood volume shift and by the resulting increase in atrial stretch[8] may thus represent an important mechanism responsible for the central circulatory modulation that facilitates sodium escape in APA patients,[1] thereby overriding the continued sodium-retaining effects of mineralocorticoids excess.

Second, our demonstration that amelioration of hypokalemia through intravenous potassium supplementation, although unable in itself to increase natriuresis in these patients, potentiates the natriuretic response induced by central volume expansion by WI, provides clear-cut evidence in favor of the hypothesis that potassium intake is a critical determinant of the escape from mineralocorticoids in hyperaldosteronism, at least when associated with another potent natriuretic stimulus.

The mechanisms whereby WI affects renal sodium handling include (1) increased renal interstitial hydrostatic pressure,[8,9] (2) endogenous release of renal autacoids and dopamine,[10,11] (3) decrease of sympathetic renal nerve activity,[12] and (4) increased ANP plasma levels[7,13]; all of these mechanisms are known to contribute to the escape from mineralocorticoids.

Our study was not specifically designed to address all of the complex mechanisms involved in the potentiating effects of high potassium intake on WI-induced natriuresis. However, a few possibilities deserve to be discussed, as several factors may play a role in the modulation of sodium excretion by increased serum potassium levels.

Potassium salts are known to have a direct natriuretic action and therefore a nonspecific effect of potassium in antagonizing

Table 2. MAP, PRA, PA, and ANP Values Before and During Water Immersion at Either Normal or High Potassium Intake

Variable	Hypokalemic WI	Normokalemic WI
MAP (mm Hg)	B 118 ± 2	B 117 ± 2
	WI 119 ± 2	WI 117 ± 2
PRA (ng/Ls)	B 0.07 ± 0.008	B 0.12 ± 0.02
	WI 0.05 ± 0.008	WI 0.09 ± 0.02
PA (pmol/L)	B 1,415 ± 194	B 1,553 ± 222
	WI 1,220 ± 250	WI 1,387 ± 194
ANP (pg/mL)	B 31 ± 3	B 34 ± 3
	WI 55 ± 6*	WI 59 ± 5†

NOTE. Values are mean ± SE.
Significant difference from B (before): *$P <$ .005, †$P <$ .004.

the mineralocorticoid-induced sodium retention could reasonably be suggested. However, this does not seem to be the case in our subjects, as the 24-hour natriuretic responses, obtained during either normal or high potassium intake, were almost superimposable. Changes in blood pressure or in the plasma levels of hormones physiologically involved in regulating natriuresis in humans might also play a role. However, our study failed to disclose any significant change in systemic arterial pressure or any alteration in the plasma concentrations of the various hormones that may affect urinary sodium excretion. Indeed our present data indicate that potassium-induced modulation of mineralocorticoid escape during WI occurs independently of changes in systemic arterial pressure, the renin-angiotensin-aldosterone system, and circulating ANP.

These results should not be surprising, since it has been demonstrated that sodium escape cannot be explained solely by the pressure natriuresis mechanism[14] and no significant differences in ANP plasma levels have been reported during administration of fludrocortisone with or without potassium supplementation.[15] Moreover, in agreement with our findings, a previous study failed to show any major contribution of decreased renin activity and angiotensin II levels to sodium escape.[16]

Thus, other mechanisms might also be involved in the potentiation of WI-induced natriuresis by restoration of normokalemia, including (1) a profound reduction in renal vascular resistance,[17] (2) an increased sensitivity of the kidney to the natriuretic effect of ANP, [18] and (3) an increased sensitivity of high- and possibly low-pressure receptors.[19,20]

In summary, central volume expansion by WI increased natriuresis in APA patients and such an WI-induced natriuretic effect was markedly enhanced by correcting hypokalemia through high potassium intake, a manoeuver that significantly enhanced WI-induced natriuresis also as compared to that observed during WI in normal control subjects. This facilitation of natriuresis occurred independently of changes in systemic arterial pressure, in the activity of renin-aldosterone system, and in the circulating levels of ANP. Our study thus suggests that potassium intake, in association with other factors, may be an important determinant of mineralocorticoid-induced sodium retention as well as mineralocorticoid escape in APA subjects; the precise mechanism involved in determining such an effect, however, remains to be clarified and should be addressed in future studies.

REFERENCES

1. Gonzales-Campoy JM, Romero JC, Knox FG: Escape from the sodium-retaining effects of mineralocorticoids: Role of ANF and intrarenal hormone systems. Kidney Int 35:767-777, 1989
2. Weinberger MH, Grim CE, Hollifield JW, et al: Primary aldosteronism: Diagnosis, localization, and treatment. Ann Intern Med 90:386-395, 1979
3. Young WF, Hogan MJ, Klee GG, et al: Primary aldosteronism: Diagnosis and treatment. Mayo Clin Proc 65:96-110, 1990
4. Krishna GG, Chusid P, Hoeldtke RD: Mild potassium depletion provokes renal sodium retention. J Lab Clin Med 109:724-730, 1987
5. Coruzzi P, Brambilla L, Brambilla V, et al: Potassium depletion and salt-sensitivity in essential hypertension. J Clin Endocrinol Metab 86:2857-2862, 2001
6. Espiner EA, Tucci JR, Jagger PI, et al: Effect of saline infusion on aldosterone secretion and electrolyte excretion in normal subjects and patients with primary aldosteronism. N Engl J Med 277:1-7, 1967
7. Coruzzi P, Novarini A, Musiari L, et al: The antinatriuretic effect of dopaminergic blockade during volume expansion is independent of circulating atrial natriuretic factor. Clin Sci 77:479-484, 1989
8. Epstein M: Renal effects of head-out water immersion in humans: A 15-year update. Physiol Rev 72:563-621, 1992
9. Coruzzi P, Musiari L, Biggi A, et al: Role of renal hemodynamics in the exaggerated natriuresis of essential hypertension. Kidney Int 33:875-880, 1988
10. Epstein M, Lifschitz M, Hoffmann DS, et al: Relationship between renal prostaglandin E and renal sodium handing during water immersion in normal man. Circ Res 45:71-80, 1979
11. Coruzzi P: Escape from the sodium-retaining effects of mineralocorticoids: Is there a role for dopamine? J Clin Endocrinol Metab 78:455-458, 1994
12. Mano T: Sympathetic nerve mechanisms of human adaptation to environment: Findings obtained by recent microneurographic studies. Environ Med 34:1-35, 1990
13. Epstein M, Loutzenhiser R, Friedland E, et al: Relationship of increased plasma atrial natriuretic factor and renal sodium handling during immersion-induced central hypervolemia in normal humans. J Clin Invest 79:738-745, 1987
14. Knox FG, Burnett JC Jr, Kohen DE, et al: Escape from the sodium-retaining effects of mineralocorticoids. Kidney Int 17:263-276, 1980
15. Krishna GG, Kapoor SC: Potassium supplementation ameliorates mineralocorticoid-induced sodium retention. Kidney Int 43:1097-1103, 1993
16. Biollaz J, Durr J, Brunner HR, et al: Escape from mineralocorticoid excess: The role of angiotensin II. J Clin Endocrinol Metab 54:1187-1193, 1982
17. Davis CL, Briggs JP: Effect of reduction in renal artery pressure on atrial natriuretic peptide-induced natriuresis. Am J Physiol 252: F146-F153, 1987
18. Gaillard CA, Koomans HA, Rabelink TJ, et al: Enhanced natriuretic effect of atrial natriuretic factor during mineralocorticoid escape in humans. Hypertension 12:450-456, 1988
19. Saum WR, Ayachi S, Brown AM: Actions of sodium and potassium ions on baroreceptors of normotensive and spontaneously hypertensive rats. Circ Res 41:768-774, 1977
20. Skrabal F, Aubock J, Hortnagi H, et al: Effects of moderate salt restriction and high potassium intake on pressor hormones, response to adrenaline and baroreceptor function in man. Clin Sci 59:S157-S160, 1980