The Effect of Upright Tilt on Nifedipine-Induced Natriuresis

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Calcium channel blockers are antihypertensive agents with diuretic actions. Yet edema occurs in some patients receiving long-term treatment with these drugs. As with other vasodilators, stimulation for fluid retention could result from systemic vasodilation. We speculated that the upright posture could enhance sodium retention. To test this hypothesis, we studied the effect of upright tilt in 10 patients before and after the oral administration of 20 mg nifedipine. Before nifedipine upright tilt caused a 41% drop in the sodium excretion rate, from 0.27 ± 0.04 to 0.16 ± 0.03 meq/min (p < 0.05). Fractional sodium excretion decreased by 46%, from 2.4 ± 0.5 to 1.3 ± 0.3% (p < 0.01). Urinary volume and renal plasma flow also decreased (p < 0.05). Plasma renin activity (PRA) rose by 46% (p < 0.005). With the patients in the supine posture nifedipine increased the sodium excretion rate to 0.49 ± 0.09 meq/min (p < 0.05). Fractional sodium excretion was 3.1 ± 0.6 meq/min (p = 0.2). The natriuresis took place despite a full in mean blood pressure and a significant rise in PRA (up 115% from prenifedipine supine values, p < 0.005). Renal plasma flow also increased (p < 0.01). The upright tilt caused a reversal of the nifedipine-induced natriuresis. The sodium excretion rate dropped to 0.23 ± 0.05 meq/min and fractional sodium excretion to 13 ± 0.2% (both not different from control). This drop in natriuresis occurred while mean blood pressure was at its lowest and PRA was 254% above the initial levels (p < 0.005). The glomerular filtration rate and renal plasma flow also dropped to prenifedipine upright values. The upright posture may boost sodium-retaining stimuli arising from calcium antagonist-induced vasodilation. These joint actions may offset the direct natriuretic action of these drugs. (Hypertension 1992;19[suppl II]:II-22-II-25)
\( p \)-aminohippurate (PAH) before and after the oral administration of 20 mg nifedipine. The patients were studied in four sequential periods: 1) control supine, 2) control upright (after a 90° tilt to an upright posture), 3) postnifedipine supine (30 minutes after taking the drug), and 4) postnifedipine upright. Three 20-minute clearance studies were done during each period.

At the end of each clearance study, urinary sodium and urine volume were measured and replaced by intravenous fluid administration during the next 20-minute study. In three of the 10 patients the posture sequence was reversed; that is, we studied them first upright and then supine. Because the results did not differ from those of the other group, we report all patients as a single population.

Clearance of inulin and PAH was measured during diuresis induced by the oral administration of 20 ml water/kg body wt. A priming bolus of inulin (50 mg/kg) and PAH (8 mg/kg) was administered diluted in 5% dextrose solution over about 5 minutes. This priming bolus was followed by a continuous infusion of inulin (0.5 mg/kg/min) and PAH (0.25 mg/kg/min) in 5% dextrose solution by means of a constant infusion pump (Harvard Apparatus, South Natick, Mass.). The patients remained supine during a 45-minute equilibration period. Urine samples were obtained through a bladder catheter.

Mean blood pressure, urinary sodium excretion \( (U_{Na^+}V) \), fractional sodium excretion \( (FE_{Na^+}) \), GFR, ERPF, filtration fraction (FF), and renal vascular resistance were calculated for each 20-minute study. The control and postnifedipine results in each position were obtained through a bladder catheter.

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### Statistical Methods

Data are presented as mean±SEM. The significance of the differences in measured values between periods was evaluated by analysis of variance (ANOVA). When the results of ANOVA were significant, we applied the paired t test to compare the results in the supine and upright posture for both the control and postnifedipine periods. Critical values were obtained by the Bonferroni method. A probability level of greater than 0.05 (two-tailed test) was regarded as nonsignificant.

### Results

#### Control Studies

Despite a constant water intake, upright tilt caused a 41% drop in urinary volume \( (p<0.05) \); \( U_{Na^+}V \) decreased by 41%, also \( (p<0.05) \). \( FE_{Na^+} \) decreased by 46% \( (p<0.05) \), whereas PRA increased by 46% \( (p<0.005) \). Mean blood pressure was unchanged. ERPF declined by 15% \( (p<0.05) \). As expected, renal vascular resistance also rose by 16% \( (p<0.05) \). Upright tilt during control studies caused no changes in the plasma sodium concentration, GFR, or FF.

#### Postnifedipine Studies

Before the upright tilt nifedipine increased \( U_{Na^+}V \) by 81% \( (p<0.05) \) despite a significant fall in mean blood pressure and a rise in PRA (up 115% from control supine values, \( p<0.005 \)). ERPF rose \( (p<0.01) \) as renal vascular resistance fell \( (p<0.005) \). Urinary volume, \( FE_{Na^+} \), and GFR showed nonsignificant upward trends. FF and the plasma sodium concentration did not change.

When the patients were tilted to an upright posture, both \( U_{Na^+}V \) and \( FE_{Na^+} \) dropped toward control upright values. Mean blood pressure fell further \( (p<0.05) \), and PRA rose 254% over the control supine value \( (p<0.005) \). GFR and ERPF also dropped to control upright values. The plasma sodium concentration and FF did not change.

### Discussion

These studies show that nifedipine-induced diuresis can be prevented by an upright tilt. As long as the
patients were standing erect, the administration of this vasodilator made no difference in sodium excretion.

Most vasodilator drugs induce renal sodium retention. The mechanisms by which this phenomenon occurs relate to systemic hemodynamic changes leading to a drop in renal perfusion pressure and enhancement of both the renin-angiotensin system and the sympathetic nervous system.14

CCB are powerful vasodilators, and as such they should induce sodium retention. However, many studies have shown that CCB can actually enhance natriuresis.9,10,15,16 This effect is easy to reproduce in laboratory animals7,17 or in the metabolic unit, where the patient is usually sitting or lying on a bed. The results are different when ambulatory patients are evaluated during their day-to-day activities. Here the data are controversial.12,18 The absence of plasma volume expansion has been regarded as evidence against sodium retention. However, plasma volume may be normal during therapy while extracellular fluid volume is increased.8 In such cases edema may be present.

When side effects have been looked at, a substantial incidence of edema has been found, particularly around the ankles.19 In a study of nisoldipine, edema was present in 20% of the patients, and in one half treatment had to be withdrawn.20 In a study of nitrendipine, 21% of the patients dropped out because of edema.21 It has been postulated but not proved that arteriolar vasodilation causes translocation of fluid into the interstitial space around the ankles.22 To this notion it has been necessary to add the effect of gravity in the dependent parts. The hypothesis may be valid, but if so, venous return should decrease not only because of the fluid lost into the interstitial space but also because vasodilation itself increases vascular capacitance. As a result, cardiopulmonary receptors should increase the activity of the renin-angiotensin system. Increased renin secretion also results from blockade of calcium entry into the juxtaglomerular cells.23 CCB-induced renin secretion2,23 can directly and indirectly stimulate tubular sodium reabsorption,24 thereby antagonizing the natriuretic effects of the drug.

The upright posture is known to boost neurogenic activity and renin secretion.25,26 Both effects may induce a decline in sodium and water diuresis. Thus, we speculated that standing up could enhance the renin response to a blood pressure drop and peripheral fluid entrapment, thereby opposing the direct natriuretic effect of nifedipine. Our results support this notion.

The posture-induced drop in urinary volume and sodium excretion coincided with a mild drop in mean blood pressure and a rise in PRA. The hypertensive effect of nifedipine increased PRA. This did not prevent the natriuresis in the supine posture. When the patients were tilted up mean blood pressure dropped to its lowest levels, and this was associated with a further rise in PRA and the already described reversal of natriuresis. Thus, we believe that the renin-angiotensin system may have contributed at least in part to this phenomenon.

The sympathoadrenal system could be the other pressor system involved in the response to upright tilt after nifedipine administration. In other clinical settings associated with systemic vasodilation the upright tilt has been shown to increase sympathetic activity.28

In our control upright studies renal vascular resistance rose. As a result, ERPF decreased. However, because the fall in GFR was not significant, the lower \( U_{Na} \cdot V \) must relate at least in part to a tubular effect.

This notion is supported by the higher \( F_{E_{Na}} \).

The drop in blood pressure after nifedipine administration did not prevent renal vasodilation in the supine posture. That is, there was a departure from normal autoregulation. These renal responses were also reversed in the upright posture when PRA was highest and mean blood pressure lowest. Under these more drastic hemodynamic conditions the disrupted mechanisms of sodium excretion and autoregulation are displaced toward the usual relation with renal perfusion.

In summary, we have shown that the upright posture abolishes the natriuretic effect of acute nifedipine therapy. However, the clinical significance of these findings remains to be determined.

References


**KEY WORDS**

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