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Letter to the Editor · Open Access ·

Unusual circadian hypertension associated with polydipsia

Jürgen M Bohlender[1,*], Jürg Nussberger[2]

[1]*Department of Nephrology, Hypertension and Clinical Pharmacology, Inselspital, Bern University Hospital, Freiburgstr. 4, Bern, Switzerland*

[2]*Department of Medicine, Division of Angiology and Hypertension, Centre Hospitalier Universitaire Vaudois (CHUV), Rue du Bugnon 46, Lausanne, Switzerland*

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Healthy people are usually capable of handling a large variability of water and sodium intake efficiently by adjusting urinary volume up to 50-fold and osmolality up to 35-fold without notable changes of blood pressure (BP). This is accomplished by the rapid and variable secretion of antidiuretic hormone controlling renal free water clearance and a variable renal sodium excretion under the powerful control of the renin-angiotensin-aldosterone system.[1] Both mechanisms and others, e.g., neuronal, maintain a normal salt and water homeostasis and help protect the brain and other organs against deleterious volume changes. Therefore, drinking large amounts of fluids normally does not lead to significant BP rises and polydipsia is not a usual cause of acute or chronic hypertension to be considered in the routine workup of hypertensive patients.[2]

However, there are exceptions to such theories. In the following, we present an unusual case of circadian hypertension associated with polydipsia that was successfully treated by restriction of daily drinking volume and discuss its potential pathophysiological and clinical implications. Although chronic polydipsia may be rare, it may occasionally be a modifiable etiologic factor contributing to BP elevations and treatment resistance of high blood pressure particularly when volume handling is impaired by concomitant disease.

A 76 year old female patient was referred to the local hypertension clinic for evaluation of persistent uncontrolled hypertension despite antihypertensive combination therapy. A diagnosis of primary hypertension had been made four years earlier when she suffered an ischemic stroke in the vertebrobasilar territory as a sequel of cerebral microangiopathy present on contrast-enhanced magnetic resonance imaging (MRI) of the brain and precerebral arteries. Antihypertensive drug treatment was thereafter initiated. A control MRI exam in January 2016 found stable cerebral leukoencephalopathy Fazekas grade 2, prominent Virchow-Robin spaces and unchanged mild reduction of brain volume.[3] She was a retired clerk and still managed her household independently. Her medical history comprised degenerative osteochondrosis of the cervical and lumbar spine, glaucoma, a partial thyroidectomy for goiter, and surgical treatments for cataract, non-metastatic carcinoma of the breast without recurrence and other minor conditions. Furthermore, she had had an episode of symptomatic urolithiasis about 12 years ago.

She complained about lower back pain, difficulties with walking, mild sensory deficits of her hands and left leg, mild neurogenic vertigo after her last stroke and frequent nocturia up to eight times but she denied dyspnea, chest pain, orthostatic dizziness or headaches. Her antihypertensive treatment was a combination pill containing perindopril 2.5 mg and hydrochlorothiazide (HCT) 6.25 mg once at noon with a second pill at 4 pm when systolic BP still exceeded 160 mmHg. She took L-thyroxine 75 μg, clopidogrel 75 mg and betahistin 16 mg in the morning and used levobunolol and latanoprost solutions to treat her eyes. Upon examination, she showed abnormal gait corresponding to a residual syndrome after stroke and slight bilateral ankle edema but no other notable abnormalities. Her body mass index was 24.5 kg/m^2.

In 2016, BP self-determinations with an automated device showed high systolic blood pressure around 160–180 mmHg and sometimes up to 220 mmHg in the afternoon. Two weeks before attending the clinic, she started meticulous BP recordings four times daily at about 5 am, 11 am, 4 pm and 8 pm that revealed striking and unusual circadian BP changes. In the morning she was normotensive. Systolic BP then rose to about 160 mmHg or higher and remained above 140 mmHg until the evening despite the intake of perindopril with HCT in the afternoon. Diastolic BP fol-

***Correspondence to:** juergen.bohlender@bluewin.ch

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lowed this pattern. Heart rate stayed normal (Figure 1). The abnormal daytime BP rise with hypertension in the afternoon persisted when she took amlodipine 5 mg instead of perindopril with HCT in the afternoon.

Further questioning revealed that she started drinking large amounts of tap and mineral water in the morning and continued this during the whole day (about 2 L until noon with a total of usually > 3.5 L/day). She forced herself to this drinking pattern ever since 2004, when she had been advised to maintain a high drinking volume in order to prevent a relapse of renal calculi.

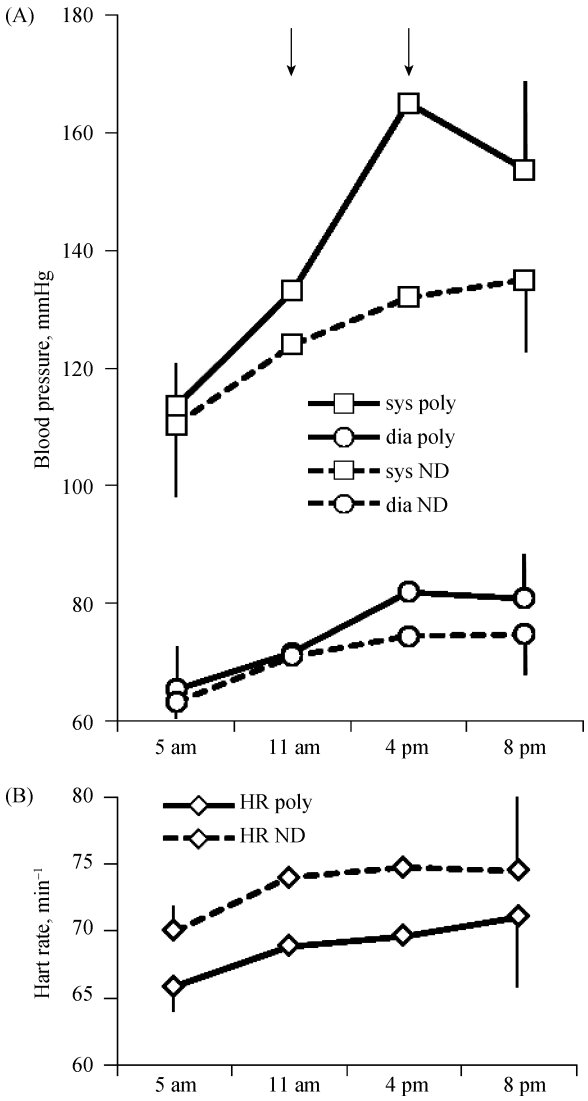

Figure 1. Circadian blood pressure (A) and heart rate profiles (B) before and after cessation of polydipsia. The results of the patient's blood pressure self-measurements averaged over a period of 15 consecutive days with poly diptic behavior (solid lines) and one week after reduction of her daily drinking volume to normal are shown (dotted lines, average of six consecutive days). Values represent mean ± SD. Arrows indicate the approximate time points when perindopril plus hydrochlorothiazide was usually taken during the period of polydiptic behavior. BP: blood pressure; dia: diastolic; HR: heart rate; ND: normal daily drinking volume; poly: polydipsia; sys: systolic.

An ultrasound exam of her kidneys was unremarkable and excluded renal artery stenosis. Transthoracic echocardiography showed mild concentric left ventricular hypertrophy with normal ejection fraction. Extended laboratory tests were performed on the first visit and after stopping antihypertensive medication for 2 weeks on the second visit including determinations of plasma renin and aldosterone and of 24 h urinary electrolytes, metanephrins, glucocorticoid and mineralocorticoid metabolites. Furthermore, on the first visit she was asked to reduce her daily drinking volume to < 2 L. On the second visit, 24 h urinary volume was 1.2 L and Na excretion 112 mmoL/24 h. Estimated glomerular filtration rate (eGFR) had increased from 50 to 76 mL/min between the visits[4] Our laboratory results otherwise did not reveal any significant abnormality that could explain the circadian BP pattern. Plasma Na and K, and blood levels of brain natriuretic peptide N-terminal pro-fragment and of thyroid stimulating hormone were normal. Remarkably, after reduction of the daily drinking volume her circadian BP pattern spontaneously normalized without further afternoon hypertension (Figure 1). The result was confirmed by 24 h ambulatory BP measurement (not shown). Nocturia had also decreased to 1–2 times.

Our case appeared unique, because a distinct circadian BP pattern with hypertension in the afternoon was associated with daytime polydipsia. We performed a PubMed literature search using the words "polydipsia", "drinking volume", "water", "overload" and "hypertension" or "blood pressure" and combinations of these terms. However, we were unable to find a similar case description with circadian episodic hypertension induced by polydipsia comparable to our patient.[5]

We concluded retrospectively, that impaired volume handling may have played a central role, because reduction of fluid intake was the only intervention before spontaneous normalization of the circadian BP pattern. Termination of the converting enzyme inhibitor readily explained the improvement of serum creatinine and eGFR on the patient's second clinic visit. Her antihypertensive medication facilitated nocturnal BP normalization but the characteristic periodic BP changes persisted when no antihypertensive drugs were taken. Since all other drugs remained unchanged, they were also excluded as a primary cause together with abnormal adrenal glucocorticoid and mineralocorticoid secretion and abnormal blood thyroxine levels. Interestingly, the amount of ingested liquid was apparently sufficient to trig-

ger hypertension but it did not lead to significant plasma electrolyte abnormalities. This clearly distinguished our case from others where polydipsia was associated with hyponatremia.[6]

The periodic BP changes induced by polydipsia could have been related to an impaired capacity of the kidneys to excrete the accumulated volume during daytime with frequent nocturia. Our patient had mild renal insufficiency. Furthermore, nocturia decreased after polydipsia was stopped. One possible explanation therefore would be defective volume and/or osmolality sensing by central or peripheral mechanisms. Alternatively, an abnormal regulation of the renin-angiotensin-aldosterone system, an abnormal secretion of antidiuretic hormone or an altered sensitivity of the kidneys to its action could have fostered the diurnal BP rise by complex and yet unclear interactions.[1,7]

However, the volume hypothesis of hypertension has recently been challenged as an oversimplistic model.[8] Taken alone, it would not provide an exhaustive explanation for our patient's recurrent daily hypertension in the afternoon. Her rapid BP rise in the morning strongly suggested that enhanced sympathetic nervous output with arterial vasoconstriction was also involved. She had microangiopathic leukoencephalopathy on cerebral imaging. This pathology could have been associated with enhanced sensitivity of the brain to small changes of plasma osmolality or with periodic brain swelling from polydipsia causing and sympathetic nervous system activation.[9] Furthermore, she had had a cerebral vascular accident in the vertebrobasilar territory supplying the brain stem. Her partial thyroidectomy could have affected the innervation of the carotid bodies. Thus, a dysfunctional central baroreflex would represent another viable hypothesis.[10]

We were finally unable to provide a simple and unifying pathophysiological explanation for our patient's remarkable circadian hypertension induced by polydipsia. She later refused any further investigations after her BP had normalized. Nevertheless, we believe that there were several coincident factors that contributed to the unusual circadian hypertension involving hormonal, renal and neuronal mechanisms.

Psychogenic polydipsia is often encountered in patients with mood disorders or psychiatric illness and may cause severe electrolyte disturbances and hyponatremia.[6,11] There is also still popular believe that elderly people should drink frequently to avoid dehydration or renal failure when using non steroidal antirheumatic drugs and analgesics. The reason for polydipsia in our case was a previous episode of painful urolithiasis. The clinical presentation was unusual because polydipsia caused striking circadian BP oscillations with recurrent hypertension, sleep disturbances and avoidable antihypertensive treatment. The case highlights the potential risks and harms of polydipsia for BP regulation and secondary hypertension when co-morbidity exists that alters volume handling or neuronal BP control.

Excessive fluid intake is not always evident or spontaneously reported during the routine workup of hypertensive patients unless specifically considered and asked for. Physicians should therefore be aware of this occasional risk factor when faced with unexplained BP elevations and apparent treatment resistant hypertension.

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