



Case Study

Supine Hypertension and Extreme Reverse Dipping Phenomenon Decades after Kidney Transplantation: A Case Report

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ABSTRACT

Background: Supine hypertension, a consequence of autonomic neuropathy, is a rarely recognized pathological condition. Reported diseases in the background are pure autonomic failure, multiple system atrophy, Parkinson's disease, diabetes and different autoimmune disorders.

Methods: In our case report we present a case of supine hypertension which developed in a patient decades after kidney transplantation. The patient was followed for 25 months and we demonstrate the effect of the modification of antihypertensive medications.

Results: At the time of the diagnosis supine hypertension appeared immediately after laying down (office sitting Blood Pressure (BP): 143/101 mmHg; office supine BP: 171/113 mmHg) and on Ambulatory Blood Pressure Monitoring (ABPM) extreme reverse dipping was registered (daytime BP: 130/86 mmHg, nighttime BP: 175/114 mmHg). After the modification of the antihypertensive medications, both office supine BP (office sitting BP: 127/92 mmHg; office supine BP: 138/100 mmHg) and on ABPM nighttime BP improved markedly (daytime BP: 135/92 mmHg, nighttime BP: 134/90 mmHg).

Conclusion: In conclusions, our case report points out that autonomic neuropathy-caused supine hypertension and extreme reverse dipping can develop in chronic kidney disease, after kidney transplantation. The modification of the antihypertensive medications can slowly restore this pathological condition.

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1. INTRODUCTION

Neurogenic supine hypertension, a consequence of autonomic neuropathy is defined as the elevation of Blood Pressure (BP) above 140 mmHg systolic and/or 90 mmHg diastolic values, measured after at least 5 min in clinostatic position [1]. Reported diseases in the background are pure autonomic failure, multiple system atrophy, Parkinson's disease, diabetes and different autoimmune disorders. Neurogenic supine hypertension can be present in up to 50% of patients with neurogenic orthostatic hypotension; however, it is rarely recognized [2]. A recent review paper and a consensus document recommend treatment options, which are both nonpharmacological and pharmacological, but due to the absence of strong evidence these are based on expert opinion and generally, the treatment is unsolved [2,3].

In the following we present a case of supine hypertension which developed in a patient decades after kidney transplantation. This case was presented in a rudimentary form as a poster in Artery 19 Conference in Budapest, Hungary [4].

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2. CASE REPORT

A male patient in his age of 54 with the complaint of moderately elevated BP came to our office on 23rd October, 2017. Important data in his history was kidney transplantation in 1985 due to glomerulonephritis and since that time he was in regular nephrology care with stage 3b chronic kidney disease. He had chronic hypertension since 1981 and chronic lumboschialgia since 2010. His other comorbidities were hyperuricemia, hypercholesterolemia and gastroesophageal reflux disease. Due to angina complaints coronarography was carried out in 2016 and multiple non-significant narrowing of the anterior descending coronary artery were found without intervention necessity. As drug adverse reaction he had angiotensin-converting-enzyme inhibitor-caused angioedema and calcium-channel blocker-caused ankle edema, both in 2015.

His current medications were: mycophenolate 2 × 500 mg; tacrolimus 1 × 2 mg; prednisolone 1 × 5 mg; doxazosin 2 × 2 mg; furosemide 1 × 40 mg; prazosin 2 × 2 mg; bisoprolol 2 × 2.5 mg; urapidil 1 × 30 mg (morning); allopurinol 3 × 100 mg; rosuvastatin 1 × 5 mg; famotidine 1 × 40 mg. The patient was included into a screening program, which is ongoing in our family medicine praxis aiming to evaluate the cardiovascular risk of patients with

hypertension (number of ethical approval: ETT TUKEB 570/2014). Within this program BP is measured twice on both sides in sitting and twice on the left side in supine position (Omron M3 device, Omron Corporation, Japan) and 24-h BP, arterial stiffness and central hemodynamics are also registered with Ambulatory Blood Pressure Monitoring (ABPM) (Mobil-O-Graph device, I.E.M. GmbH, Germany). This device besides that provides validated 24-h BP results [5] also gives validated estimates of pulse wave velocity [6], central hemodynamic parameters [7] and others, like stroke volume, which was recently validated [8].

Besides moderately elevated sitting office BP (143/101 mmHg, HR: 68/min), when the patient's BP was measured in supine position, we noticed a sudden marked increase (supine BP: 171/113 mmHg, HR: 58/min). Schellong test was also performed and it showed orthostatic hypotension (31/14 mmHg decrease). It is an accepted method in German-speaking and in some related countries to diagnose both orthostatic hypertension and autonomic neuropathy. Schellong test is performed as follows:

- first, the blood pressure and the heart rate is measured in lying position, after at least 10 min of rest;
- next, blood pressure is measured in upright position after 1, 5 and 10 min. The highest decrease in blood pressure registered is considered, and the upper limit of normality for orthostatic hypotension is 20 mmHg systolic and/or 10 mmHg diastolic fall. For autonomic neuropathy the upper limit of normality is 30 mmHg systolic BP decrease.

While the mean 24-h BP increased slightly and the mean daytime BP was normal in ABPM, extreme reverse dipping phenomenon was found at night at our patient, which was unknown until that time (Table 1 and Figure 1). His nighttime mean BP was 45/28 mmHg

higher than the daytime mean BP. Antihypertensive medication was changed: urapidil and doxazosin were stopped and valsartan–hydrochlorothiazide was started (in the morning 40 mg/6.25 mg, in the evening 80 mg/12.5 mg) and the patient was sent for different examinations to discover the background of this phenomenon. Ultrasound of the transplanted kidney did not visualize compression of the renal artery in supine position; on echocardiography left ventricular hypertrophy was found. In 09 January 2018, a specialist in a Neuropathy Outpatient Clinic diagnosed moderate autonomic neuropathy; during Schellong test the systolic BP decreased 28 mmHg in vertical position. In deep breathing test the heart rate difference between the average of the largest accelerations during inspiration and the average of the largest decelerations during expiration was only 2 beats/min. Other tests of the autonomic neuropathy were normal (Valsalva ratio: 1.27, 30/15 ratio: 1.22).

After half year (15 May 2018), on control ABPM both the supine hypertension and the extreme reverse dipping phenomenon were attenuated, but still present. On the day of this control visit benfotiamine plus pyridoxine (200–200 mg daily, respectively) were started by a rheumatologist, because of chronic back pain and this therapy continued during the follow-up. In the summer of 2018 valsartan–hydrochlorothiazide was changed to telmisartan–hydrochlorothiazide (40 mg/12.5 mg, once in the morning) by the nephrologist because of the valsartan scandal. On the 1-year-visit (ABPM control date: 06 November 2018) the supine BP was still elevated, telmisartan–hydrochlorothiazide doses was modified to 2 × 20 mg/6.25 mg. In the next ABPM control (date: 30 May 2019) the supine hypertension at night was attenuated and it improved further for the last ABPM control (date: 12 November 2019), when the reverse dipping phenomenon disappeared and the nighttime BP pattern became non-dipper (Figure 1).

Table 1 | 24-h ambulatory blood pressure and central hemodynamic and office blood pressure measurements

24-h ABPM and office measurements	24 October 2017			15 May 2018			06 November 2018			30 May 2019			12 November 2019		
	Total	Day	Night	Total	Day	Night									
Systolic BP (mmHg)	140	130	175	134	129	151	126	119	156	130	123	145	135	135	134
Diastolic BP (mmHg)	93	86	114	90	86	102	86	82	102	91	88	98	91	92	90
HR (/min)	69	73	58	69	72	59	72	76	58	71	74	64	70	72	65
Mean arterial pressure (mmHg)	114	106	142	110	106	124	104	99	127	109	104	120	111	111	110
Pulse pressure (mmHg)	48	44	61	44	43	49	40	37	54	39	35	47	43	43	44
Central systolic BP (mmHg)	128	121	159	124	120	141	118	111	147	122	116	135	127	127	127
Central diastolic BP (mmHg)	93	88	113	90	87	101	87	83	103	92	89	98	92	93	91
cSys MAP-C ₂ (mmHg)	144	133	188	138	132	165	129	118	171	133	124	153	138	137	142
cDia MAP-C ₂ (mmHg)	94	88	114	90	87	102	87	83	104	92	89	99	92	93	91
Augmentation index (%)	23	20	35	21	19	29	24	21	34	20	18	25	22	22	21
Cardiac output (L/min)	4.8	4.9	4.7	4.9	5	4.8	4.6	4.6	4.7	4.8	4.7	5.1	5	5	5
Total vascular resistance (mmHg/ml)	1.4	1.3	1.8	1.3	1.3	1.4	1.3	1.8	1.3	1.4	1.3	1.4	1.3	1.3	1.3
Reflection magnitude (%)	63.8	62.3	70	63.5	62.7	63.8	62.3	70	63.5	65.5	62.2	72.6	66.8	65.2	72.6
Pulse wave velocity (m/s)	8	7.8	9.1	7.9	7.8	8	7.8	9.1	7.9	7.9	7.7	8.3	8.2	8.2	8.2
Stroke volume (ml)	70.3	68	79.7	71.7	69.3	81.2	64.7	60.5	82	69	64.5	78.8	71.6	70	77.8
Systole dipping (%)	–34.6 (Inverted)			–17.1 (Inverted)			–31.1 (Inverted)			–17.9 (Inverted)			0.7 (Non-Dipper)		
Diastole dipping (%)	–32.6 (Inverted)			–18.6 (Inverted)			–24.4 (Inverted)			–11.4 (Inverted)			2.2 (Non-Dipper)		
Office sitting BP (mmHg)	143/101			126/95			133/95			137/99			127/92		
Office sitting HR (/min)	68			76			70			68			72		
Office supine BP (mmHg)	171/113			144/100			137/100			143/102			138/100		
Office supine HR (/min)	58			62			64.5			63.5			66.5		

Dipping categories: <0% Inverted; <10% Non-Dipper; <20% Normal; ≥20% Extreme (inverted). ABPM, ambulatory blood pressure monitoring; BP, blood pressure; cSys MAP-C₂, central systolic blood pressure calculated with brachial mean arterial BP-systolic BP calibration; cDia MAP-C₂, central diastolic blood pressure calculated with brachial mean arterial BP-systolic BP calibration; HR, heart rate; PWV, pulse wave velocity.

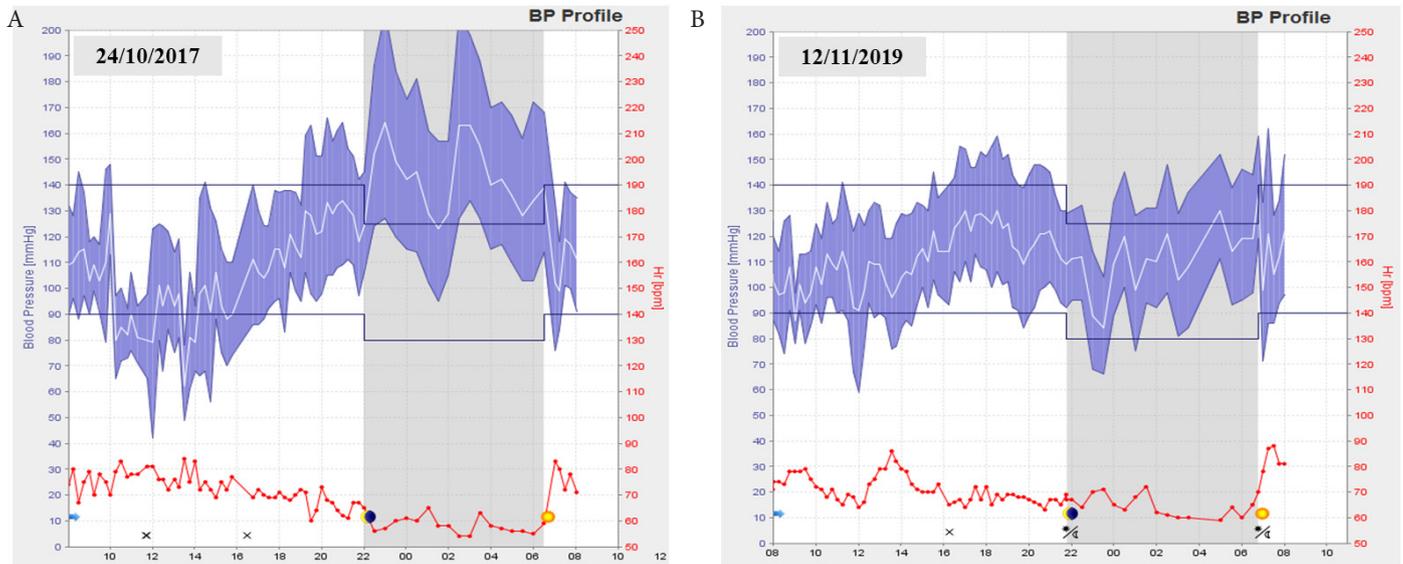


Figure 1 | 24-h ambulatory blood pressure monitoring on the first visit (A) and on the 2-years-control (B).

After the publication of Vallelonga and Maule [3], in June 2019 we applied some non-pharmacologic and also other pharmacologic possibilities at the patient, but none of them were tolerable. These were as follows:

- sleeping with the head of the bed raised about 20 cm (30°): the patient did not tolerate it because of back pain;
- having a small snack before going to sleep to induce mild postprandial hypotension: the patient did not tolerate it because of complaints connected with the treated gastroesophageal reflux disease;
- transdermal nitroglycerine patch placing from 8 p.m. to 6 a.m.: the patient did not tolerate it because of headache;
- evening administration of the short half-life losartan: it was not recommended by the nephrologist because of the less nephroprotective evidence available compared with telmisartan.

So after a couple of days of these attempts we returned for the original therapy.

In summary, supine hypertension and extreme reverse dipping were attenuated with the modification of antihypertensive medications. Benfotiamine plus pyridoxine was administered continuously during this period.

3. DISCUSSION

This is the first case report to demonstrate the presence and the attenuation of supine hypertension and extreme reverse dipping on ABPM in a patient with chronic kidney disease, decades after kidney transplantation. We suppose, that both chronic kidney disease [9] and immunosuppressive drugs [10] could have played role in the development of these pathological conditions. Autonomic neuropathy can cause both supine hypertension and reverse dipping phenomenon on ABPM besides orthostatic hypotension, which can influence the development of target organ damage [2]. Supine hypertension is a difficult condition to treat, but as it is demonstrated in our case report, the modification of the

antihypertensive medication can markedly reduce its magnitude. The long-term administration of the neuroprotective combination of benfotiamine plus pyridoxine (200–200 mg daily) might have also contributed to this improvement but there is no mechanistic data available supporting evidence to it.

There are also non-pharmacological approaches to improve this condition, which are listed nicely in two recent papers [2,3]. Our patient did care for his water and salt intake long ago due to the chronic kidney disease and in his case unfortunately no other non-pharmacological treatments were tolerable because of his other chronic diseases. His comorbidities and side effects also limited the use of other recommended pharmacological treatments (losartan or nitroglycerine patch).

In conclusion, our case report points out that autonomic neuropathy-caused supine hypertension and extreme reverse dipping can develop in chronic kidney disease, after kidney transplantation. The modification of the antihypertensive medications can slowly improve this pathological condition.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

DB and BK performed the different measurements of the patient during the visits. DB wrote the manuscript. JN planned and managed the patient's controls, made treatment decisions and critically revised the manuscript.

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