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Ahmed M. Elzanaty

Ayman Saeyeldin

Rachel Royfman

Ahmed Maraey

Mahmoud Khalil

See next page for additional authors

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Short-term Outcomes of Hypertensive Crises in Patients with Orthostatic Hypotension

Ahmed M. Elzanaty[a*], Ayman Saeyeldin[b,c], Rachel Royfman[d], Ahmed Maraey[e], Mahmoud Khalil[f], Hassan Aboul-Nour[g], Eman Elsheikh[h], Chandramohan Meenakshisundaram[a], Helmy M. Siragy[i], and Blair Grubb[a]

From the [a] Division of Cardiovascular Medicine, University of Toledo, Toledo, OH, [b] Department of internal medicine, Saint Mary's hospital, Waterbury, CT, [c] Department of Advanced heart failure and transplant, Baylor university medical center, Dallas, TX, [d] University of Toledo College of Medicine and Life sciences, Toledo, OH, [e] Department of Internal Medicine, University of North Dakota, Bismarck, ND, [f] Department of Internal Medicine, Lincoln Medical Center, New York, NY, [g] Department of Neurology, Henry Ford Hospital, Detroit, MI, [h] Department of Medicine, University of Toledo, Toledo, OH and [i] Department of Medicine, University of Virginia, Charlottesville, VA.

Abstract: Supine hypertension-orthostatic hypotension disease poses a management challenge to clinicians. Data on short term outcomes of patients with orthostatic hypotension (OH) who are hospitalized with hypertensive (HTN) crises is lacking. The Nationwide Readmission Database 2016-2019 was queried for all hospitalizations of HTN crises. Hospitalizations were stratified according to whether OH was present or not. We employed propensity score to match hospitalizations for patients with OH to those without, at 1:1 ratio. Outcomes evaluated were 30-days readmission with HTN crises or falls, as well as hospital outcomes of in-hospital mortality, acute kidney injury, acute congestive heart failure, acute coronary syndrome, type 2 myocardial infarction, aortic dissection, stroke, length of stay (LOS), discharge to nursing

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IRB Approval: This study didn't require a review by the institutional review board because of the de-identified nature of the data in the NRD.
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home and hospitalization costs. We included a total of 9451 hospitalization (4735 in the OH group vs 4716 in the control group). OH group was more likely to be readmitted with falls (Odds ratio [OR]:3.27, $P < 0.01$) but not with HTN crises ($P = 0.05$). Both groups had similar likelihood of developing acute kidney injury ($P = 0.08$), stroke/transient ischemic attack ($P = 0.52$), and aortic dissection ($P = 0.66$). Alternatively, OH group were less likely to develop acute heart failure (OR:0.54, $P < 0.01$) or acute coronary syndrome (OR:0.39, $P < 0.01$) in the setting of HTN crises than non-OH group. OH group were more likely to have longer LOS and have higher hospitalization costs. Patients with OH who are admitted with HTN crises tend to have similar or lower HTN-related complications to non-OH group while having higher likelihood of readmission with falls, LOS and hospitalization costs. Further studies are needed to confirm such findings. (Curr Probl Cardiol 2023;48:101455.)

Introduction

Orthostatic hypotension (OH) is an increasingly recognized disorder affecting more than 5% of community-based adults.[1,2] OH is defined as sustained reduction of 20 mm Hg or more of systolic blood pressure or 10 mm Hg or more of diastolic blood pressure within 3 minutes of standing.[3] There has been an increased recognition of association of OH with adverse outcomes independent of underlying etiology with some studies estimating the hazard ratios of mortality of around 1.5-2.4. Adjusting for cardiovascular risk didn't eliminate the mortality association.[4-6] The coexistence of OH and supine hypertension (OH-SH) increases with age likely due to decline in autonomic and baroreflex function.[7] Uncontrolled hypertension in the setting of OH has been associated with 2-folds increased in falls.[8] Moreover, better control of the blood pressure was hypothesized to decrease progression of OH.[9] There is no clear management consensus of patients with OH-SH with current recommendation aiming to reduce suping blood pressure using non-pharmacological and pharmacological intervention with disregard of patient's standing blood pressure values as long as they are asymptomatic.[7,10] Hypertensive (HTN) crises (urgency or emergency) are the extreme presentation of uncontrolled hypertension with a mortality rate approaching

3.7% in some studies.[11] Most of the data evaluating the outcomes and guiding management of OH-SH were based on primarily outpatient studies, with scarce information on the outcomes of HTN crises requiring hospitalization in the setting of known OH.[12] Therefore, we aimed to use a large nationwide database to evaluate short-term outcomes of such patients.

Methods

Data Source

This current study used the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) Nationwide Readmission Database (NRD) for the years 2016-2019.[13] The NRD is the largest publicly available all-payer inpatient health care readmission database in the United States. The NRD is drawn from HCUP State Inpatient Databases containing verified patient linkage numbers that can be used to track admissions across hospitals within a state while adhering to strict privacy guidelines. Unweighted, the NRD contains data from approximately 18 million discharges each year. Weighted, it estimates roughly 35 million discharges in the United States. The NRD contains both patient and hospital-level information. Up to forty discharge diagnoses and 25 procedures are collected for each patient using the International Classification of Diseases, Tenth Revision, Clinical Modification. Patients were tracked during the same year using the variable "nrd_visitlink," and time between 2 admissions was calculated using variable "nrd_daystoevent." National estimates were produced using sampling weights provided by the sponsor. All values presented are weighted estimates. This study was exempted from review by the institutional review board because of the de-identified data in the NRD.

Study Population

HTN crises hospitalizations for patients with history of OH between January 2016 and December 2019 were included. HTN crises and OH were identified using International Classification of Diseases (ICD)-10 codes (I.160, I.161, and I95.1 respectively), as utilized in prior studies.[14] Hospitalizations were excluded if patients were younger than 18, or didn't survive the index admission. December discharges of each year were excluded to allow 30-day follow-up as patients can't be tracked across multiple years. Following the HCUP data use agreement, any

variable containing ≤10 observations were not reported due to the risk of personal identification and data privacy violation.

Exposure

HTN crises (ICD-10 of I.160, I.161) outcomes in OH vs non-OH patients

Study Outcomes

The primary outcomes were 30-day readmission for HTN crises, syncope or falls. Secondary outcomes included in-hospital complication like mortality, acute coronary syndrome (ACS), acute heart failure (HF), stroke/transient ischemic attack (TIA), aortic dissection, and acute kidney injury during the index hospitalization. Other outcomes like length of stay (LOS) discharge to nursing home and total hospital costs were also evaluated. A readmission was defined as any admission within 30 days of the index HTN crises admission. If the patient was readmitted multiple times during the 30 day follow up period, only the first readmission was included in the analysis.

Statistical Analysis

Baseline characteristics of participants with and without OH were compared using a Chi-square test for categorical variables and a Student's *t* test for continuous variables on the weight-adjusted sample as appropriate. Using a logistic regression model of demographic (age, gender, primary insurance, median household income), comorbidity variables (Charlson Comorbidity Index score, congestive heart failure, and history of myocardial infarction) and hospital factors (bed size and teaching status), we estimated the propensity score and assessed for covariate balance using *t* test and standardized differences. We matched those with OH to those without OH in a greedy nearest neighbor 1:1 model with caliper set at 0.2.[15] Standardized mean difference of 5% was set as a threshold to assure covariate balance. Chi-square and univariate logistic regression were done for binary outcomes variables on matched subjects only. The final effect size is reported as the odds ratio for a binary variable or mean ± SD for continuous variable. For all analyses, we set the significant value for P at < 0.05. All statistical analyses were performed with StataCorp 17 College Station, TX: StataCorp LP).

Results

Study Cohort Characteristics

We identified a total of 413,057 hospitalization for HTN crises in our analysis. Only 1.16% of the cohort (4795 hospitalizations) were diagnosed with OH, unmatched baseline characteristics and outcomes are listed in supplemental table-1 and 2. After propensity score matching, our cohort consisted of a total of 9451 hospitalization with 4735 in the OH group vs 4716 in the non-OH group. HTN urgency was the main reason for presentation in both groups (67% in OH vs 64% in non-OH; P = 0.02). There was no difference in insurance coverage or size of treating hospital between 2 groups. Patients in the OH group were more likely to be diabetic, HTN, have parkinsonism or autonomic dysfunction, and have valvular disease. On the other hand, OH group were less likely to suffer from chronic pulmonary disease, obesity, be smoker or have a history of non-STEMI (Table 1).

Readmission Outcomes

Compared to non-OH group, OH group had similar likelihood of all-cause readmission [16.0 % vs 14.0 %, P = 0.08], being readmitted with HTN crises [2.6 % vs 1.7 %, P = 0.05], and syncope [0.2 % vs 0.1% - P = 0.53]. However, OH group were more likely to be readmitted with falls [0.8% vs 0.2%, $P < 0.01$] (Fig 1).

Secondary Outcomes

There was no noted difference between both groups with regard to in-hospital mortality [0.3% in both arms P = 0.92], stroke/TIA [2.9% vs 2.5% - P = 0.52], acute kidney injury [24.1% vs 21.7% - P = 0.08], aortic dissection [2.9% vs 3.2% - P = 0.66], posterior reversible encephalopathy [0.5% vs 0.7% - P = 0.52], cerebral edema, or retinal hemorrhage (Table 2). On the other hand, OH group were less likely to suffer from acute HF [5.5% vs 9.7%- $P < 0.01$], ACS [1.4% vs 3.5% $P < 0.01$], albeit with a higher likelihood of having type 2 myocardial infarction [2.0% vs 0.9% $P < 0.01$] (Fig 2).

Furthermore, OH group were more likely to utilize more healthcare resources with longer LOS [mean of 5.0 vs 3.3 days - $P < 0.01$], higher odds of requiring nursing home on discharge [19.9% vs 13.8% - $P < 0.01$], and a higher average hospitalization costs [10,309$ vs 8075$ $P < 0.01$].

Table 1. Baseline demographic and characteristics of patients with and without orthostatic hypotension

Characteristics	Without orthostatic hypotension (n = 4716)	With orthostatic hypotension (n = 4735)	P-value
Age (mean ± SD)	73.23 ± 11.34	73.34 ± 11.41	-
Female	2774 (59%)	2810 (59%)	$P = 0.73$
Charlson Comorbidity Index Score			
0	639 (14%)	622 (13%)	$P = 0.96$
1	786 (17%)	802 (17%)	
2	879 (19%)	836 (18%)	
≥3	2412 (51%)	2475 (52%)	
Insurance			
Medicare	3739 (79%)	3698 (78%)	$P = 0.40$
Medicaid	377 (8%)	370 (8%)	
Private	455 (10%)	503 (11%)	
Self-pay	92 (2%)	103 (2%)	
Hospital bed size			
Small	834 (18%)	778 (16%)	$P = 0.45$
Medium	1260 (27%)	1343 (28%)	
Large	2622 (56%)	2614 (55%)	
Presenting diagnosis			
Hypertensive Emergency	1488 (32%)	1358 (29%)	$P = 0.04$
Hypertensive urgency	3012 (64%)	3181 (67%)	$P = 0.02$
Comorbidities			
Congestive heart failure	1219 (26%)	1247 (26%)	$P = 0.72$
Valvular disease	465 (10%)	594 (13%)	$P = 0.01$
Pulmonary circulation disorders	257 (5%)	181 (4%)	$P = 0.02$
Peripheral vascular disorders	692 (15%)	642 (14%)	$P = 0.30$
Hypertension, uncomplicated	1178 (25%)	1409 (30%)	$P < 0.01$
COPD	1047 (22%)	920 (19%)	$P = 0.03$
Renal failure	2072 (44%)	2179 (46%)	$P = 0.18$
Obesity	650 (14%)	566 (12%)	$P = 0.09$
Autonomic	15 (<1.0%)	171 (4%)	$P < 0.01$
Lymphoma	20 (<1.0%)	22 (<1.0%)	$P = 0.80$
Liver disease	147 (3%)	123 (3%)	$P = 0.30$
Hypothyroidism	837 (18%)	1,019 (22%)	$P < 0.01$
Diabetes, complicated	1143 (24%)	1364 (29%)	$P < 0.01$
Smoking	560 (12%)	414 (9%)	$P < 0.01$
Parkinson	85 (2%)	317 (7%)	$P < 0.01$
Dementia	601 (12.7%)	648 (13.7%)	
Adrenal	<11(<1%)	<11 (<1.0%)	$P = 0.17$
STEMI	<11 (<1.0%)	<11 (<1.0%)	$P = 0.67$
NSTEMI	151 (3%)	61 (1%)	$P < 0.01$
UA	11 (<1.0%)	11(<1.0%)	$P = 0.27$

COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

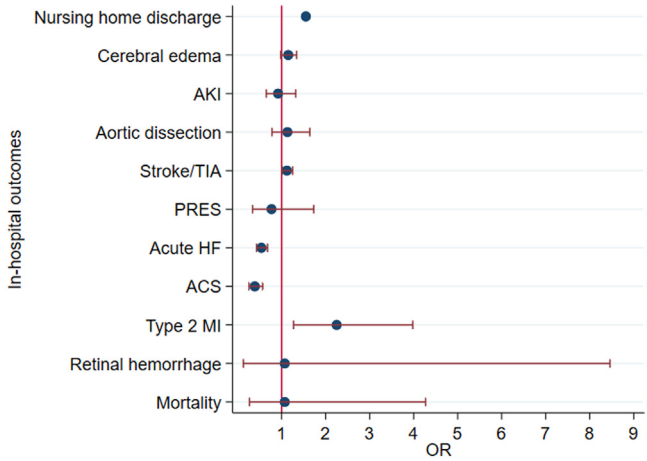

FIG 1. Forest plot showing different in-hospital outcomes of matched cohort.ACS, acute coronary syndrome; AKI, acute coronary syndrome; HF, heart failure; MI, myocardial infarction; OR, odds ratio; PRES, posterior reversible encephalopathy; TIA, transient ischemic attack. (Color version of figure is available online.)

Discussion

The interesting pathophysiology behind the syndrome of SH-OH explains how challenging the treatment paradigm can be for physicians. On one hand, SH results from abnormal baroreceptor buffering, inappropriate natriuresis, higher blood volume and residual sympathetic tone acting on hypersensitive postsynaptic adrenoreceptors.[16] On the other hand, the impaired autonomic response to blood pooling during standing leads to significant OH. Although blood pressure maybe elevated while supine, it is often normal while seated and low when standing, so the average 24-hour blood pressure may not be elevated.

In this study we focused on a particular subset of patients who presented with acute severe HTN. In our cohort, the rates of DM, essential hypertension and Parkinson's disease were significantly higher in the OH group, which is expected given the effect of these diseases on the autonomic nervous system. Patients with essential hypertension were more liable to develop OH, likely due to nocturnal natriuresis, volume depletion, and use of diuretics.[17] Hypothyroidism was also more prevalent in the OH group, possibly due to associated neuropathy and hyponatremia, with previous case reports showing reversibility with appropriate thyroid replacement therapy.[18] Interestingly, smoking was less prevalent in the OH group, part of this can be explained by prevalence of parkinsonism in

Table 2. Outcomes of patients with and without orthostatic hypotension

Outcomes	Without orthostatic hypotension (*n* = 4716)	With orthostatic hypotension (*n* = 4735)	*P*-value	Odds ratio
Inpatient outcomes				
In-hospital death	13 (<1.0%)	14 (<1.0%)	*P* = 0.92	1.07, 95% CI (0.27-4.27) *P* = 0.92
Retinal Hemorrhage	<11 (<1.0%)	<11(<1.0%)	*P* = 0.95	1.07, 95% CI (0.13-8.46) *P* = 0.95
Type 2 MI	44 (<1.0%)	98 (2%)	*P* < 0.01	2.25, 95% CI (1.27-3.98) *P* < 0.01
ACS	164 (4%)	65 (1%)	*P* < 0.01	0.39, 95% CI (0.26-0.57) *P* < 0.01
Acute HF	457 (10%)	259 (6%)	*P* < 0.01	0.54, 95% CI (0.43-0.68) *P* < 0.01
PRES	34 (<1.0%)	26 (<1.0%)	*P* = 0.52	0.77, 95% CI (0.34-1.73) *P* = 0.52
Stroke/TIA	116 (3%)	132 (3%)	*P* = 0.52	1.13, 95% CI (0.78-1.64) *P* = 0.52
Aortic dissection	150 (3%)	138 (3%)	*P* = 0.61	0.92, 95% CI (0.65-1.32) *P* = 0.66
AKI	1024 (22%)	1142 (24%)	*P* = 0.08	1.15, 95% CI (0.98-1.34) *P* = 0.08
Cerebral edema	<10 (<1.0%)	<10 (<1.0%)	*P* = 0.94	0.94, 95% CI (0.20-4.37) *P* = 0.94
Discharge to nursing home	651 (14%)	942 (20%)	*P* < 0.01	1.55, 95% CI (1.30-1.85) *P* < 0.01
Readmission outcomes				
All-cause readmission	655 (14%)	745 (16 %)	*P* = 0.08	1.16, 95% CI (0.98-1.36) *P* = 0.08
Readmitted due to hypertension	81 (2%)	121 (3%)	*P* = 0.05	1.50, 95% CI (0.99-2.27) *P* = 0.05
Readmitted due to syncope	<11 (<1.0%)	11 (<1.0%)	*P* = 0.53	1.52, 95% CI (0.41-5.66), *P* = 0.53
	11 (<1.0%)	36 (<1.0%)	*P* < 0.01	

(*continued*)

Table 2. (*continued*)

Outcomes	Without orthostatic hypotension (n = 4716)	With orthostatic hypotension (n = 4735)	P-value	Odds ratio
Readmitted due to fall				3.27, 95% CI (1.32-8.10) P = 0.01
Total cost				
Average total Cost ± SD	8075 ± 6247	10,309 ± 11,978	$P < 0.01$	Coefficient 2234.69, 95% CI (1528.13-2941.25)
Length of stay				
LOS ± SD	3.3 ± 2.6	5.0 ± 5.5	$P < 0.01$	Coefficient 1.67, 95% CI (1.36-1.98) $P < 0.01$

ACS, acute coronary syndrome; AKI, acute kidney injury; CI, confidence interval; HF, heart failure; LOS, length of stay; MI, myocardial infarction; PRES, posterior reversible encephalopathy; SD, standard deviation; TIA, transient ischemic attack.

these patients, which can affect susceptibility to dopamine mediated nicotine addiction.[19]

The prevalence of dementia in our patients was higher in the unmatched OH group (13.6% in the OH vs 5.6% in the non-OH group, $P < 0.01$). The association of OH with dementia has been reported in literature. In a study with 81 dementia cases, those with systolic pressure < or = 140 mm Hg had a significantly higher risk of dementia with Mini Mental State Examination (MMSE) of less than 24 (relative risk = 1.9, 95% confidence interval (CI), 1.2-3.2) and Alzheimer's disease (relative risk = 2.2, 95% CI, 1.2-3.8). This may be related to impairment of brain capacity to autoregulate cerebral blood flow (CBF) , with episodic hypotension leading to sustained brain changes and cognitive deficits.[20] In a another longitudinal, population-based cohort analysis of 2532 older adults in Sweden, who were followed for 12 years, OH was associated both with the development of dementia (hazard ratio 1.4, 95% CI 1.1-1.8) and with the progression from mild cognitive impairment to dementia (hazard ratio 1.5, 95% CI 1.1-2.3).[21]

Cerebral and cardiovascular complications associated with SH have been frequently assumed to be similar to essential hypertension.[22] Prior reports showed that SH maybe associated with increased LV mass[23] as well as renal impairment.[24] On the other hand, with OH, recurrent falls are common, owing to postural dizziness, syncope, weakness and visual

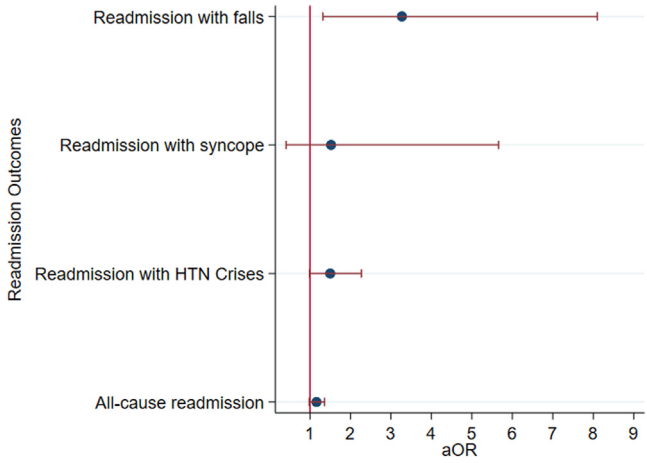

FIG 2. Forest plot showing readmission outcomes of matched cohort. (Color version of figure is available online.)

impairment.[25] In one study of older nursing home resident patients, OH was associated with an increased risk of recurrent falls (relative risk 2.6).[26] This is particularly important in patients with Parkinson's disease where there are added risks of freezing of gait, festination, and loss of postural reflexes.[27]

In our study, there was no difference in the rates of all cause readmission between both groups, albeit there was an increased readmission due to falls in the OH group (3.27, 95% CI (1.32-8.10) P = 0.01). This was associated with significantly higher LOS and higher average total cost with more than 2000$.

There was no difference in the HTN related complications including posterior reversible encephalopathy, retinal hemorrhage, stroke or TIA, Aortic dissection, cerebral edema, or renal failure. A special population with Parkinson's disease may have reports of lower stroke rate, partly because of lower tobacco use, and that these patients are usually under the regular care of a neurologist, enhancing stroke prevention measures.[28]

The rates of type 2 myocardial infarction were higher in patients with OH, which may be explained by demand ischemia due to impaired coronary perfusion during hypotensive episodes, albeit they were less likely to suffer acute HF or thrombotic ACS. Though it is difficult to ascertain the reason behind the lower cardiovascular risk given limitation of database, we hypothesis that OH patient tend to have lower average 24-hour BP than non-OH patients given the nature of the disease. The association

of elevated 24-hour BP and worst cardiovascular outcomes was previously established.[29]

Regarding pharmacologic treatment, these patients are extremely sensitive to vasodilators such as calcium channel blockers and hydralazine,[17] which are commonly used in treatment of acute severe hypertension, eventually leading to worsening of OH component. In patients with multiple system atrophy where peripheral sympathetic stimulation is preserved, sympatholytic drugs such as clonidine can lower BP,[30] conversely, in patients with peripheral autonomic degeneration, clonidine may paradoxically raise BP due to alpha-2 adrenoreceptor mediated vasoconstriction.[31]

In our analysis, there were similar outcomes between the OH and the non-OH groups, however there was more notable side effects related to OH component with increased falls leading to readmission and prolonged LOS. It is possible that these patients may tolerate elevated blood pressure better than patients in the non-OH group. Vavilala et al. discussed cerebrovascular autoregulation where the changed in MAP between 60 and 160 produced little to no effect in CBF as the brain vasculature adjust their calibers based on resistance of blood. In longstanding hypertension, the autoregulatory curve is shifted to the right and MAP $>$ 160 may not cause any increase in CBF, thus patients may tolerate markedly elevated blood pressures better.[32] It may be reasonable to propose that treatment should focus more on preventing OH while permitting some degree of supine hypertension, however understandably this can be disconcerting for patients and clinicians.

This study has several limitations. First, certain patient-level data were irretrievable for our analysis, including data on laboratory results, electrocardiograms, imaging studies, home and discharge medications. Second, the administrative nature of the database and its reliance on coding to detect diagnosis and procedures makes it prone to documentation errors. However, the NRD has been validated internally and externally in prior studies.[33] Third, given the observational nature of our analysis, there is a possibility of unmeasured bias. However, we have conducted a robust analysis to reduce allocation bias. Fourth, information about out-of-hospital mortality is not available in the NRD dataset.

More research is needed to define the magnitude of the deleterious effects of supine hypertension on cardiovascular, cerebrovascular, and renal morbidity and mortality, and to further delineate the best treatment agents for these patients.

Conclusions

We conclude that patient with OH who are admitted with HTN crises tend to have similar or lower HTN-related complications compared to non-OH group, while having higher likelihood of readmission with falls, LOS, and hospitalization costs. It is reasonable during management of these patients to focus on preventing OH symptoms while tolerating some degree of supine hypertension. Further studies are needed to validate our findings.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2022.101455.

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