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Original Article

Assessment of left ventricular ejection force and sympathetic skin response in normotensive and hypertensive subjects: A double-blind observational comparative case–control study

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ABSTRACT

Background: Pathophysiology of essential hypertension remains obscure. Correlation among ventricular ejection force, sympathetic activity, and hypertension is less clearly narrated in hypertensive subjects.

Aims and objectives: To assess correlation among ventricular ejection force, sympathetic activity, and hypertension in hypertensive subjects, and to be compared with normotensive subjects.

Methods: This is a case–control study to assess left ventricular ejection force (LVEF) and sympathetic skin response, in normotensive (group 1; control), and hypertensive subjects (group 2; cases). 100 cases were selected. Subjects having stages 1 and 2 hypertension were categorized in groups 2A and 2B, respectively. LVEF was calculated by using echocardiography observing aortic acceleration time (AT) and peak systolic velocity. Comparison among groups was done by using one-way ANOVA.

Results: Both groups were comparable. In group 2, 60 cases had stage 1 hypertension and 40 had stage 2 hypertension. Significantly short AT and significantly high LVEF were found in hypertension (groups 2A and 2B) ($p < 0.0001$). Sympathetic activity was high in group 2A ($p < 0.0001$). Stroke volume (SV) was high in group 2B ($p < 0.0001$).

Conclusion: Stage 1 hypertension is a stage of increased sympathetic activity, leading to increased LVEF and hypertension (resetting of baroreceptors); stage 2 hypertension is a stage of normal sympathetic activity, increased LVEF, increased SV, and hypertension (possibly a stage of shift of renal equilibrium curve/renal output curve and blood pressure to a newer level).

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1. Introduction

Essential hypertension[1] affecting 95% of hypertensive patients has no identifiable cause.[2–4] According to Joint National Committee report (JNC 7), blood pressure ≥140/90 mmHg is hypertension.[5] Various risk factors associated with hypertension are obesity,[6] salt sensitivity,[7] genetics,[8] obstructive sleep apnea,[9] insulin resistance,[10] sympathetic over activity,[11,12] etc. Despite awareness of multiple risk factors, pathophysiology of hypertension remains ambiguous. In normotensive subjects, sympathetic stimulation results in increase in heart rate, cardiac contractility (ejection force), and peripheral resistance,[13] but in hypertensive subjects, correlation among sympathetic activity, cardiac contractility and hypertension is less clearly illustrated. Therefore, the main aim of the study was to assess any correlation among these factors in hypertensive subjects and to be compared with normotensive subjects, in a case–control manner.

2. Methods

This is a double-blind comparative observational exploratory case–control study to assess left ventricular ejection force (LVEF), sympathetic nervous system activity, and stroke volume (SV) in normotensive (group 1; control group) and hypertensive subjects (group 2; cases). All the cases were newly diagnosed, i.e. no previous history of treatment of hypertension. Arbitrarily, 100 controls and an equal number of hypertensive cases were opted for the study. Informed written consent and approval of institutional ethical committee was taken. In group 2, subjects having stage 1 hypertension were categorized in group 2A while stage 2 hypertension was categorized in group 2B. Cases and controls were randomly selected from medical Out Patient Department (OPD) of Mittal Hospital and Research Centre, Pushkar Road, Ajmer, Rajasthan, India. Recruitment was done from January 2015 to March 2015. In both the groups, the age group was 35–40 years; all participants were male. Cases having coronary artery disease, thyroid disease, diabetes, left ventricular hypertrophy, aortic valvular disease, and history suggestive of neuropathy, which could affect echocardiographic findings/sympathetic skin response (SSR), were excluded. Assessment was done only once, i.e. at the time of first examination (0 month). The following parameters were examined

(1) Complete examination including body mass index (BMI), resting pulse rate, and respiratory rate
(2) Left ventricular ejection force (LVEF)
(3) Sympathetic skin response (SSR)
(4) Stroke volume (SV)

Left ventricular ejection force – This was assessed with the help of echocardiography by applying Newton's second law of motion.[14] This law states that force is equal to the product of mass and acceleration. Ventricular ejection force does not require estimation of ventricular volume and is independent of ventricular configuration. Five-chamber transthoracic view was used with the help of image-directed continuous wave Doppler echocardiography[15,16] (GE Vivid S6 with probe frequency 1.7 MHz). Aortic peak systolic velocity (PSV), aortic acceleration time (AT)/time to peak velocity interval (TTP), time–velocity integral during the acceleration phase of the cardiac cycle (TVI_{ac}), and heart rate were measured. TVI_{ac} represents the area under the Doppler envelope from the beginning of systole to PSV (Fig. 1). Three consecutive cardiac cycles were examined and their mean was used for analysis. The diameter of aortic valve was measured from frozen real time images during systole by using leading edge to leading edge method. The mass of blood accelerated across aortic valve over a time period was calculated by multiplying the density of blood, which is 1.055, by the cross-sectional area (CSA) and TVI_{ac}. The acceleration component was calculated by dividing the PSV by TTP. LVEF was calculated by using a formula $(1.055 \times CSA \times TVI_{ac}) \times (PSV/TTP)$.[17,18]

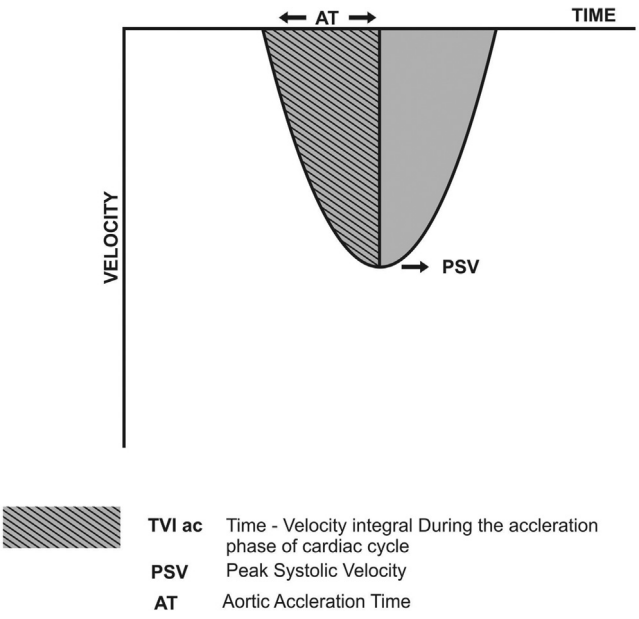

Fig. 1 – Aortic flow.

Sympathetic skin response was done with standard protocol in supine, relaxed, semi-darkened room with ambient temperature control at 22–24 °C in the upper limbs. In this process, standard surface electromyography electrodes (Recorder and Medicare system model Aleron 401) were applied with conducting jelly to the palm and dorsum of the hand, with a reference electrode on the forearm. Hand grip and cold pressor were used as provocative methods. Skin potential changes during and between the tests were analyzed by a computer. Latency was measured from the onset of stimulus artifact to the beginning of response. Amplitude was recorded peak to peak (Fig. 2).[19–21]

All readings of echocardiography and SSR were recorded by a senior resident and a senior technician.

Stroke volume was measured in transthoracic 4-chamber view by subtracting ESV (end systolic volume) from EDV (end diastolic volume).

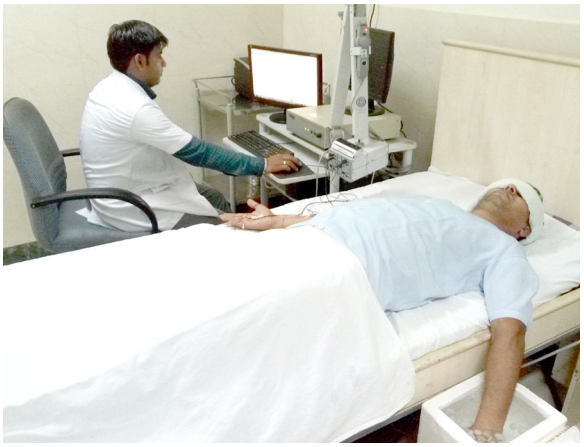

Fig. 2 – Sympathetic skin response.

2.1. *Data analysis*

Collected data were entered in Microsoft Excel spreadsheet and then analyzed by using SPSS 20.0 software. Comparison between groups 1 and 2 was done by using Mann–Whitney *U* test and among group 1, group 2A, and group 2B, it was done by using one-way ANOVA and post hoc analysis done by Tukey's test.

3. Results

Both groups 1 and 2 were matched according to age, sex, and BMI. Pulse rate and respiratory rate were within normal range in all groups (Table 1). In group 2, 60 cases were having stage 1 hypertension and 40 were having stage 2 hypertension. Significantly short AT was found in all stages of HTN ($p < 0.0001$, group 1 vs. group 2A and 1 vs. group 2B) (Table 2; Fig. 3a–c). LVEF was significantly high in groups 2A and 2B ($p < 0.0001$, group 1 vs. group 2A and group 1 vs. group 2B) (Table 2, Fig. 4). Significantly high sympathetic skin response was there in group 2A (group 1 vs. group 2A, $p < 0.0001$) (Table 3; Fig. 5a–c). Stroke volume was significantly high in group 2B ($p < 0.0001$, group 1 vs. group 2B) (Table 2).

Doppler images of aortic flow.

Group 1	Slow/curved acceleration/Long AT, low PSV	Fig. 3a
Group 2A	Sharp acceleration/Short AT, high PSV, pointed peak	Fig. 3b
Group 2B	Sharp acceleration/Short AT, high PSV, broad based	Fig. 3c

Sympathetic skin response images.

Group 1	Long latency, low amplitude, dome	Fig. 5a
Group 2A	Short latency, high amplitude, spike	Fig. 5b
Group 2B	Long latency, low amplitude, dome	Fig. 5c

4. Discussion

Pathophysiology of essential hypertension remains elusive. Various risk factors found to be associated with essential hypertension are obesity, salt sensitivity, genetics, sympathetic overactivity, etc. In normotensive subjects, increase in sympathetic activity results in increased cardiac contractility (cardiac ejection force)[13]; but in hypertension, the correlation of sympathetic activity and cardiac contractility is not well established; therefore, the current study was planned to assess LVEF and sympathetic activity in a observational case–control manner in 100 cases of essential hypertension and equal

Table 1 – General examination.

Groups	Age (years), mean	Sex	BMI (kg/m^2), mean	Pulse rate, mean	Respiratory rate, mean
Group 1 ($n = 100$)	38	Male	22.6	80	14
Group 2A ($n = 60$)	39	Male	22.8	82	14
Group 2B ($n = 40$)	39	Male	22.4	78	15

Table 2 – Cardiac contractility data.

	PSV/VMAX (m/s)	CSA (10^{-4} m^2)	AT/TTP (10^{-3} s)	TVI_{ac} (10^{-2} m)	SV (10^{-3} L)	LVEF (10^{-3} N)
Group 1 ($n = 100$)	1.176 ± 0.070	3.76 ± 037	92 ± 7.8	6.8 ± 0.43	42.54 ± 4.4	0.35128 ± 0.05
Group 2 ($n = 100$)	1.452 ± 0.11	3.95 ± 0.26	50 ± 4.9	8.0 ± 1.8	53.31 ± 6.4	1.01379 ± 0.38
Group 2A ($n = 60$)	1.363 ± 0.038	3.97 ± 0.30	53 ± 2.7	6.7 ± 0.27	43.23 ± 3.7	0.72383 ± 0.06
Group 2B ($n = 40$)	1.586 ± 0.024	3.90 ± 0.17	44 ± 1.6	10.8 ± 1.2	60.48 ± 1.9	1.44871 ± 0.20
p value			<0.0001			<0.0001
Group 1 vs. group 2 *p* value			<0.0001			<0.0001
Group 1 vs. group 2A *p* value			<0.0001			<0.0001
Group 1 vs. group 2B						

AT/TTP, aortic acceleration time/time to peak velocity interval; CSA, cross-sectional area; LVEF, left ventricular ejection force; PSV/VMAX, peak systolic velocity; SV, stroke volume; TVI_{ac}, time velocity integral during the acceleration phase of cardiac cycle.

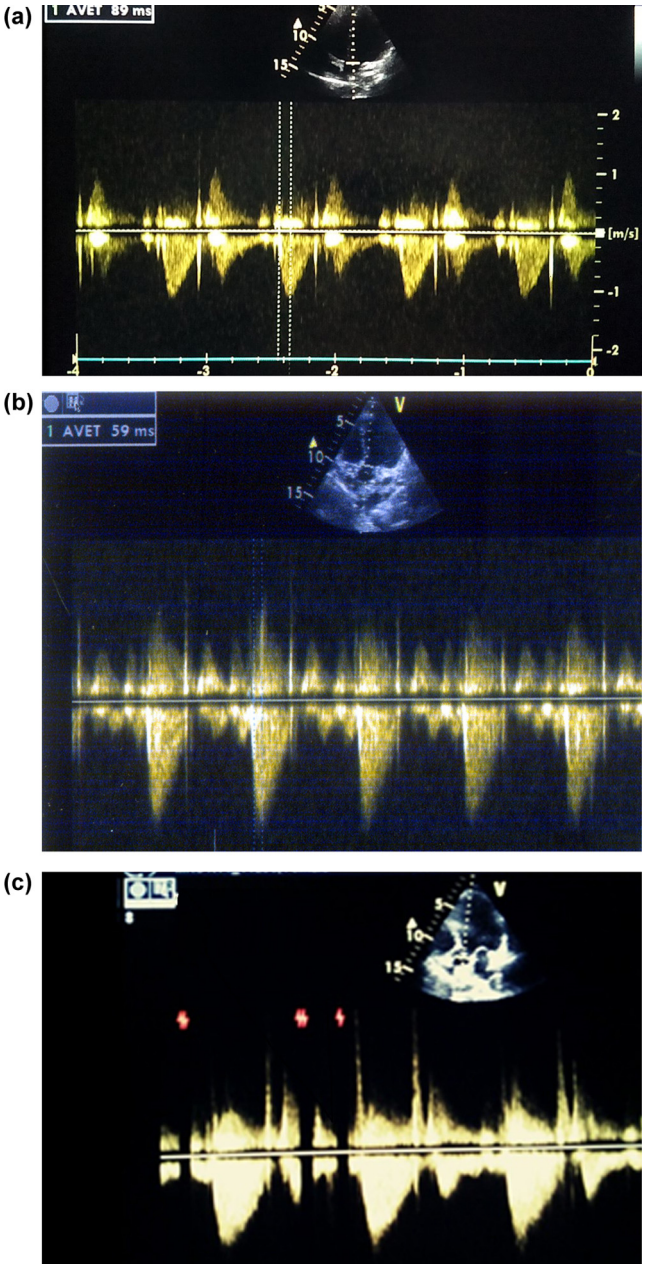

Fig. 3 – Doppler images of aortic flow: (a) group 1, (b) group 2A, and (c) group 2B.

number of nonhypertensive controls. Nonhypertensive controls were grouped as group 1 and hypertensive cases were grouped as group 2. In group 2, stage1 and stage 2 hypertensive cases were categorized as group 2A and group 2B, respectively. The cases were examined only once at 0 month. The study was conducted at Mittal Hospital and Research Centre, Pushkar road, Ajmer, Rajasthan, India.

All groups were matched according to age, sex, and BMI. Among vital parameters, resting pulse rate and respiratory rate were within normal range in all groups (Table 1).

Findings of the study are divided into two subheadings.

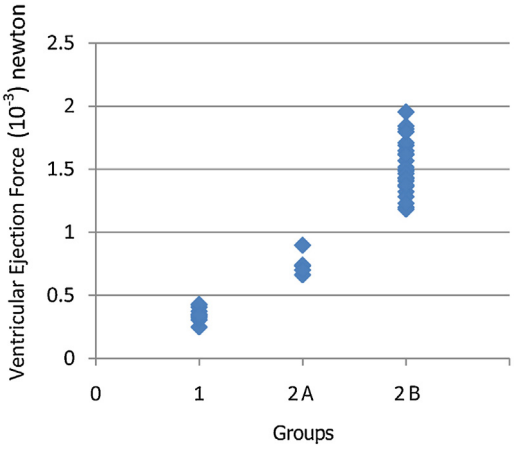

Fig. 4 – Ventricular ejection force.

4.1. *Cardiac findings (Table 2; Fig. 3–c)*

In Doppler aortic flow, three types of flow patterns were present. In normotensive slow curved acceleration, in stage 1, hypertension sharp acceleration was with pointed peak, and in stage 2, hypertension sharp acceleration was with a broad base (Fig. 3a–c).

In statistical findings, in group 1 vs. 2A, significantly short AT ($p < 0.0001$), significantly high PSV ($p < 0.0001$), and significantly high ventricular ejection force ($p < 0.0001$) was observed in group 2A. There was no significant difference in stroke volume ($p > 0.05$). Overall findings suggest that in group 2A (stage 1 hypertension) there was statistically significant high LVEF and insignificant difference in stroke volume as compared to group 1 (normotensive).

In group 1 vs. 2B – significantly short AT ($p < 0.0001$), significantly high PSV ($p < 0.0001$) and significantly high ventricular ejection force ($p < 0.0001$) was there in group 2B. There was significant difference in stroke volume ($p < 0.0001$). Overall findings suggest that in group 2B (stage 2 hypertension) there was statistically significant high LVEF and significant difference in stroke volume as compared to group 1 (normotensive).

In group 2A vs. 2B – significantly short AT ($p < 0.0001$), significantly high PSV ($p < 0.0001$), and significantly high ventricular ejection force ($p < 0.0001$) was there in group 2B. There was significant difference in stroke volume ($p < 0.0001$). Overall findings suggest that in group 2B (stage 2 hypertension) there was statistically significant high LVEF and significant difference in stroke volume as compared to group 2A (stage 1 hypertension).

As a whole in group 1 vs. group 2 statistically significant high LVEF in group 2 as compared to group 1 (Fig. 4). Description about LVEF in hypertension is not clear in JNC 7 and JNC 8.[1,22]

4.2. *SSR assessment (Table 3; Fig. 5a–c)*

In SSR, there was short latency, high amplitude, spike response in group 2A, as compared to long latency, low

Table 3 – Sympathetic skin response data.

SSR right/left upper limb	Group 1 (mean ± SD)	Group 2A (mean ± SD)	Group 2B (mean ± SD)
Hand grip			
Latency (s)	2.77 ± 0.22	1.01 ± 0.14	2.72 ± 0.23
Amplitude (10^{-3} V)	1.24 ± 0.17	6.63 ± 0.88	1.26 ± 0.28
Cold pressor test			
Latency (s)	2.81 ± 0.23	0.80 ± 0.16	2.86 ± 0.20
Amplitude (10^{-3} V)	1.11 ± 0.27	6.63 ± 1.16	1.24 ± 0.32
Interpretation	Normal baseline sympathetic activity	High baseline sympathetic activity	Normal baseline sympathetic activity
p value: Group 1 vs. 2A			
Hand grip latency	<0.0001		
Hand grip amplitude	<0.0001		
Cold pressor latency	<0.0001		
Cold pressor amplitude	<0.0001		
p value: Group 1 vs. 2B			
Hand grip latency	0.47		
Hand grip amplitude	0.95		
Cold pressor latency	0.36		
Cold pressor amplitude	0.54		
p value: Group 2A vs. 2B			
Hand grip latency	<0.0001		
Hand grip amplitude	<0.0001		
Cold pressor latency	<0.0001		
Cold pressor amplitude	<0.0001		

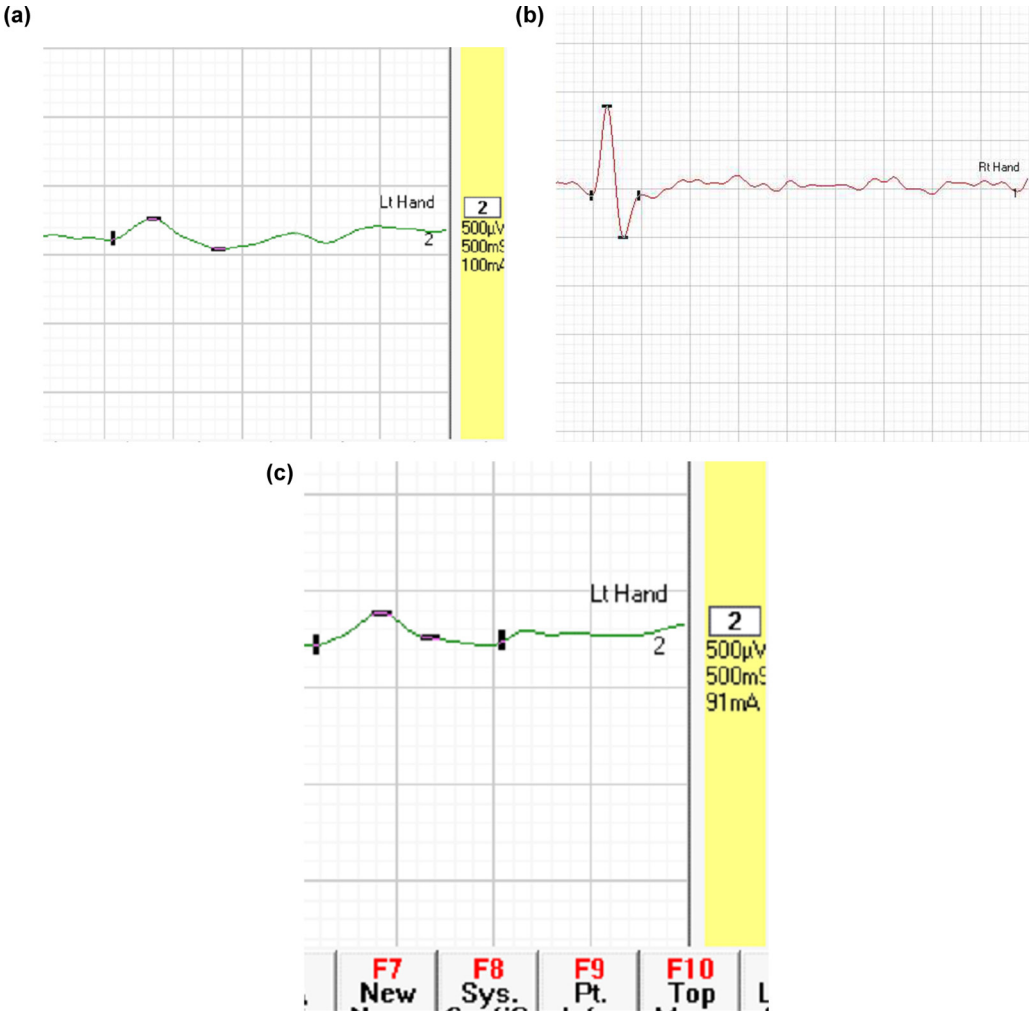

Fig. 5 – Sympathetic skin response images: (a) group 1, (b) group 2A, and (c) group 2B.

amplitude, and dome-like response in group 1 and group 2B (Fig. 5a–c).

There was statistically significant difference in latency and amplitude in group 1 vs. group 2A and group 2A vs. group 2B ($p < 0.0001$) (Table 3). Thus, overall findings suggest increased sympathetic activity in group 2A (stage 1 hypertension). Short latency and high amplitude suggestive of high sympathetic activity is also present in previous studies.[19–21]

This sympathetic activity is basal sympathetic activity/basal sympathetic tone.[13] Normally, sympathetic system is continuously active and there is basal secretion of epinephrine and norepinephrine[23] at a very low rate. This tone/secretion is sufficient to maintain blood pressure at normal level even in the absence of direct sympathetic stimulation. Basal tone is different from overt/direct sympathetic stimulation, which results from direct stimulation of sympathetic nervous system and adrenal medulla leading to increase in pulse rate, sweating, etc.[13] In the current study, overt sympathetic stimulation is not present, because resting pulse rate is within normal range in both groups 2A and 2B (Table 1).

In summary, curved aortic acceleration represents normotensive state and normal sympathetic activity; sharp

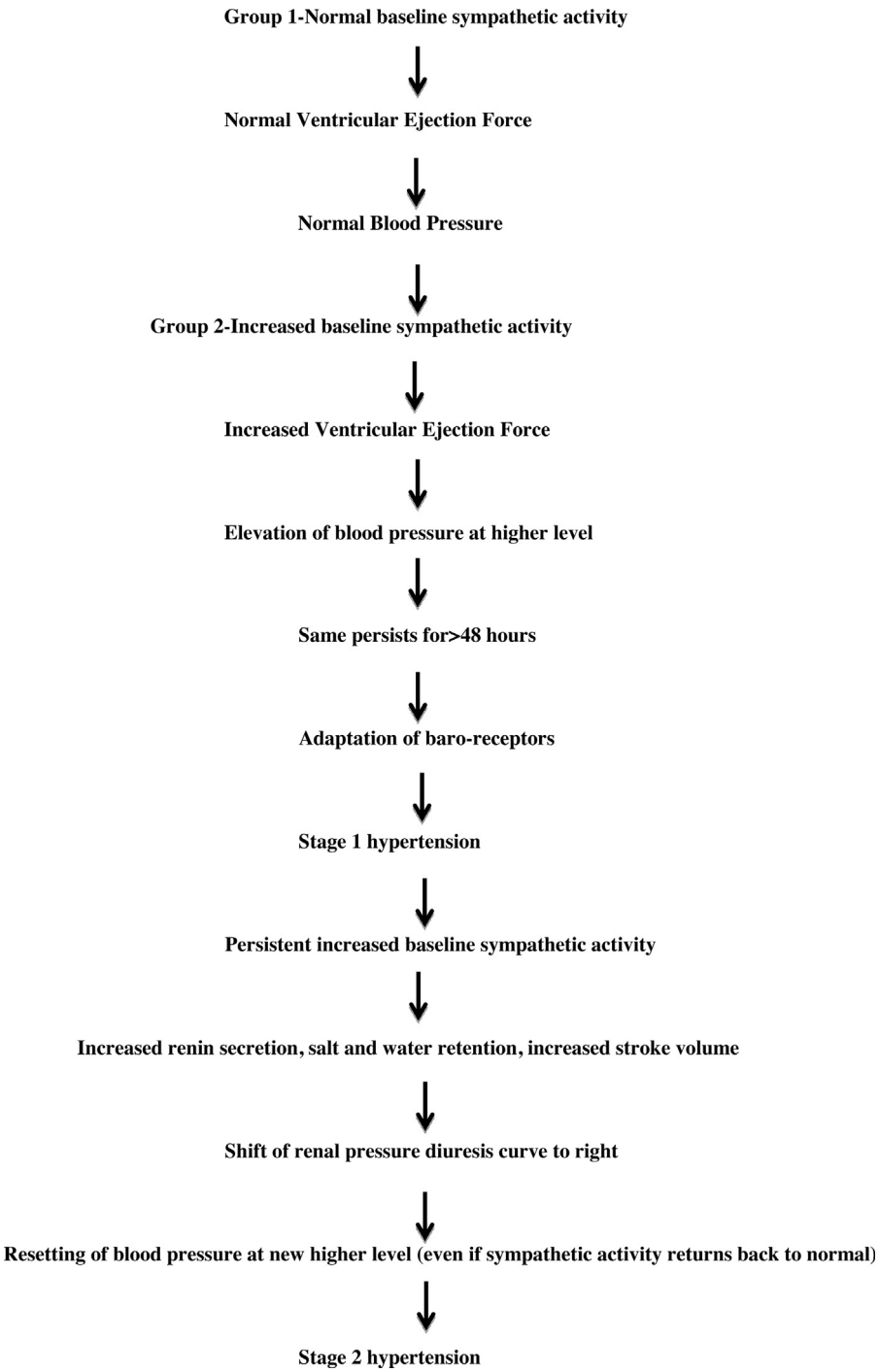

Fig. 6 – Flow chart – development of hypertension in study population (hypothesis of the study).

acceleration and pointed peak exhibits high sympathetic activity and stage 1 hypertension; sharp acceleration and broad base denote stage of high-stroke volume and stage 2 hypertension.

The possible mechanism of hypertension in the study population seems to begin from normal baseline sympathetic activity (group 1; normotensive), followed by increase in baseline sympathetic activity, resulting in increased LVEF, without significantly affecting stroke volume; and this increased ejection force leads to stage 1 hypertension (group 2A) ''Beginning of hypertension from normotensive state'' (Fig. 6).

At this stage of early blood pressure regulation mechanisms, baroreceptors come into play and try to bring the blood pressure back to normal; but if this situation persists for >48 h, early mechanism fails and there is resetting of receptors at a newer level.[24] Late mechanism includes renal mechanism, in which kidneys increase salt and water excretion (pressure diuresis) proportionately to increase the blood pressure known as renal urinary output curve but, increase in sympathetic activity opposes this effect by increase in renin secretion,[24] salt and water retention, shift of renal equilibrium curve/renal output curve to a newer level, impaired renal fluid excretion, and increase in stroke volume resetting of arterial pressure to a newer level[24] (stage 2 hypertension) (now even if sympathetic activity comes back to normal, blood pressure remains set at this newer level).

5. Conclusion

In all stages of hypertension, LVEF is high, which primarily starts from increase in basal sympathetic activity.

However, further studies like community-based observational and cohort study are required to reach to a final conclusion.

Conflicts of interest

The authors have none to declare.

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Mittal Hospital, Ajmer.

Author's contribution

Dr Tarun Saxena contributed in the design of study and writing of the manuscript; Dr Sanjay Patidar also contributed to analysis of data and writing of the manuscript; Manjari Saxena contributed to collection of data and writing of the manuscript.

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