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Motor performance, reward-based Y-maze behaviour and regional brain histological abnormalities in a Goldblatt renovascular hypertension rat model: an exploratory controlled study

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Abstract

Background: Chronic hypertension is associated with cerebrovascular injury and cognitive decline, including impairment of hippocampus-dependent learning and memory. However, motor performance, reward-based spatial behaviour and regional brain histology have rarely been assessed together in renovascular hypertension models. This exploratory controlled study evaluated these outcomes after unilateral renal artery constriction using the Goldblatt model.

Results: Mean arterial pressure was higher in hypertensive than control rats (155.5 ± 18.2 versus 95.1 ± 4.1 mmHg; mean difference, 60.4 mmHg; 95% confidence interval, 47.2–73.6; $p < 0.001$). Falls or stops were more frequent among hypertensive rats at 30 cm/s (4/5 versus 1/5), 45 cm/s (5/5 versus 1/5) and 60 cm/s (4/5 versus 2/5). Y-maze completion-time distributions differed between groups (exact $p = 0.042$). One of 10 hypertensive rats versus 6 of 10 controls found the reward within 5 minutes, whereas 3 of 10 hypertensive rats versus 1 of 10 controls did not find it within 20 minutes. Histological abnormalities were recorded in 2 of 6 frontal-lobe, 5 of 6 basal-ganglia and 5 of 6 cerebellar readings. Animal-level correlations between behavioural and histological findings could not be examined.

Conclusions: Goldblatt renovascular hypertension was associated with poorer treadmill performance and delayed reward finding in the Y-maze. The delayed maze performance may indicate impaired hippocampus-dependent spatial function, although motor slowing and other non-cognitive influences cannot be excluded. Basal-ganglia and cerebellar abnormalities were anatomically compatible with the motor deficits, but the absence of treatment-group and animal identifiers and the lack of hippocampal tissue precluded causal or correlational inference. Larger studies incorporating validated cognitive tasks and quantitative, animal-linked neuropathology are warranted.

Background

Hypertension is a leading modifiable risk factor for stroke and is increasingly recognised as a contributor to cognitive impairment and dementia (1–5). Sustained elevation of arterial pressure alters the cerebral circulation through vascular remodelling, endothelial dysfunction, oxidative stress, inflammation and impaired autoregulation (1, 2). These processes can reduce cerebrovascular reserve and promote blood-brain barrier dysfunction, small-vessel disease, infarction and neurodegeneration.

Experimental models allow examination of functional outcomes and tissue changes under controlled conditions. The Goldblatt model produces renovascular hypertension by reducing renal perfusion and activating the renin-angiotensin system (6, 7). It differs mechanistically from the spontaneously hypertensive rat and should be identified as an induced renovascular model.

Hypertension-related injury may affect several neural systems. The hippocampus is central to spatial learning and memory and may be vulnerable to hypertension-related vascular and neuronal injury. In a two-kidney, one-clip mouse model, hypertension impaired long-term memory and reduced CA1 dendritic complexity and adult hippocampal neurogenesis (8). Frontal cortical networks contribute to executive

and voluntary motor function, the basal ganglia support movement selection and learning, and the cerebellum is central to balance, coordination and motor adaptation (9–12). Delayed maze performance may therefore raise a hypothesis of hippocampal-dependent dysfunction, whereas treadmill deficits may implicate motor networks; neither task is anatomically specific in isolation.

This exploratory study evaluated MAP, treadmill performance, reward-based Y-maze performance and histological observations in the frontal lobe, basal ganglia and cerebellum after Goldblatt renal artery constriction. We hypothesised that hypertensive rats would show higher MAP and poorer neurobehavioural performance than normotensive controls. We also examined whether the regional histological pattern provided anatomically plausible context for the behavioural findings.

Methods

Study design and setting

This exploratory controlled animal experiment was conducted in the Physiology and Anatomy laboratories at the University of Zimbabwe Faculty of Medicine and Health Sciences. Healthy male Sprague-Dawley rats with no visible signs of illness were followed for 12 weeks in two groups: Goldblatt-induced hypertensive rats and normotensive controls.

Animals, allocation and sample size

The surviving study dataset contained 20 healthy Sprague-Dawley rats with no visible signs of illness, with 10 animals in each group for blood-pressure and Y-maze assessments. Treadmill records were available for a subset of five rats per group. We had six sets of regional histology readings. No a priori sample-size calculation was done, because non-probability consecutive sampling was employed.

Induction of renovascular hypertension

Hypertension was induced by unilateral renal artery constriction using the Goldblatt method (6, 7). Under anaesthesia that included xylazine, the renal region was surgically exposed, the kidney was identified, and the renal artery was constricted with suture material. The available record did not contain verifiable doses, routes, details of the second anaesthetic agent, perioperative analgesia or physiological monitoring. Animals recovered in a designated chamber, and all were reported to survive the procedure. The normotensive group did not undergo renal artery constriction.

Blood-pressure assessment

Blood pressure was measured non-invasively with a BIOPAC tail-cuff system. Measurements were undertaken during the 12-week follow-up. The preserved animal-level dataset contained one MAP value per rat, after repetitive cuff measurements.

Treadmill assessment

Five rats from each group were tested on a motorised rat treadmill at 30, 45 and 60 cm/s. The recorded endpoint was a fall or stop during the observation period, classified as occurring before 5 min, after 10 min or after 15 min. Grip, endurance and gait were also observed, including toe dragging, shuffling and impaired foot coordination.

Y-maze assessment

All rats underwent a reward-based Y-maze task. Rats were deprived of food for 48 hours before rewarded Y-maze testing to increase motivation to locate the food reward; water remained available ad libitum. Because prolonged food deprivation may affect stress, metabolism, and locomotor activity, Y-maze outcomes were interpreted as reward-directed spatial performance rather than as an isolated measure of hippocampal function. During familiarisation, each rat was guided to food pellets in one arm and allowed to explore for approximately 20 min. The rat was then removed for approximately 20 min before being returned to locate the reward without guidance. Time to reward location was recorded in five categories (≤ 5, > 5–10, > 10–15, > 15–20 and > 20 min), together with descriptive observations of exploration and inactivity.

Histological assessment

At study completion, animals were killed and the brains removed. Sections from the frontal lobe, basal ganglia region and cerebellum were examined by light microscopy; the hippocampus was not included in the reported sampling. Eighteen slides were reported, six per region. The available histology table contained six matched sets of regional readings but did not retain treatment-group or individual-animal identifiers. Fixation, embedding, section thickness, staining, magnification, field-selection method, assessor blinding and diagnostic criteria were not documented; consequently, histological findings were treated as descriptive observations and were not compared between groups or correlated with behavioural outcomes.

Outcome measures

No single primary outcome was prespecified. Outcomes were MAP, treadmill falls or stops, Y-maze time to reward, qualitative gait observations and regional histological observations. Y-maze latency was treated as a reward-based spatial-performance measure rather than a hippocampus-specific endpoint.

Statistical analysis

Animal-level MAP values were summarised as mean ± standard deviation and range and compared between groups with a two-sided Welch t-test. The mean difference and 95% confidence interval were calculated. The 2 × 5 Y-maze table was compared using a two-sided Fisher-Freeman-Halton exact test, calculated by enumeration under fixed marginal totals. Treadmill and histology data were summarised as counts because only aggregate records were available. No behaviour-histology correlation was attempted because individual-animal and treatment-group identifiers were absent from the histology

data. Analyses used Python 3.11 with SciPy 1.16. Statistical significance was defined as $p < 0.05$, but all analyses were exploratory.

Ethical approval

The Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals approved the study (JREC/225/2024; 26 March 2024). Anaesthesia was used during surgery, and carcasses were disposed of by incineration after study completion.

Results

Blood pressure

MAP was substantially higher in hypertensive rats than in normotensive controls (155.5 ± 18.2 vs 95.1 ± 4.1 mmHg). The mean between-group difference was 60.4 mmHg (95% CI 47.2-73.6; Welch $t = 10.22$, $df = 9.93$; $p < 0.001$). Hypertensive MAP values ranged from 134 to 185 mmHg; control values ranged from 88 to 103 mmHg (Table 1).

Table 1 Mean arterial pressure by experimental group

Group	n	MAP, mean ± SD (mmHg)	Range (mmHg)
Normotensive control	10	95.1 ± 4.1	88-103
Goldblatt hypertensive	10	155.5 ± 18.2	134-185

MAP, mean arterial pressure; SD, standard deviation. Welch's t-test: mean difference 60.4 mmHg (95% CI 47.2-73.6), $p < 0.001$.

Treadmill performance

Hypertensive rats had more falls or stops at each treadmill speed. At 30 cm/s, 4/5 hypertensive rats and 1/5 controls fell or stopped. Corresponding counts were 5/5 versus 1/5 at 45 cm/s and 4/5 versus 2/5 at 60 cm/s (Table 2). Recorded gait observations in the hypertensive group included reduced grip, toe dragging, shuffling and impaired foot coordination. Because the same animals were assessed repeatedly and animal-level paired records were unavailable, no inferential test was performed.

Table 2 Falls or stops during treadmill testing

Speed	Group	n	<5 min	After 10 min	After 15 min	Total
30 cm/s	Hypertensive	5	0	1	3	4
30 cm/s	Control	5	0	0	1	1
45 cm/s	Hypertensive	5	0	2	3	5
45 cm/s	Control	5	0	0	1	1
60 cm/s	Hypertensive	5	4	0	0	4
60 cm/s	Control	5	0	0	2	2

Values are numbers of rats whose first recorded fall or stop occurred in the stated interval. Categories reproduce the surviving aggregate study table.

Y-maze performance

Reward-location times were shifted toward longer intervals in the hypertensive group (exact p = 0.042; Table 3). Six of ten control rats found the reward within 5 min compared with 1/10 hypertensive rats. Three hypertensive rats did not find the reward within 20 min compared with one control rat. Reduced exploration and periods of inactivity were also recorded in the hypertensive group. These observations show poorer reward-based Y-maze performance but do not, by themselves, localise the deficit to the hippocampus.

Table 3 Time to locate the food reward in the Y-maze

Time interval	Normotensive control, n	Hypertensive, n
≤5 min	6	1
>5-10 min	2	1
>10-15 min	0	0
>15-20 min	1	5
>20 min	1	3

Two-sided Fisher-Freeman-Halton exact test for the 2 × 5 table, p = 0.042.

Histological observations

The six available sets of histology readings described abnormalities in 2/6 frontal-lobe, 5/6 basal-ganglia and 5/6 cerebellar observations (Table 4). Findings included infarct-like foci in the frontal lobe; oedema, degeneration and focal gliosis in the basal ganglia; and oedema or gliosis in the cerebellum. The

hippocampus was not represented. Because treatment-group and individual-animal identifiers were absent, these observations cannot be attributed to hypertension, compared with controls or correlated with treadmill or Y-maze performance.

Table 4 Recorded histological observations by brain region

Record	Frontal lobe	Basal ganglia	Cerebellum
1	Normal	Degeneration and oedema	Normal
2	Normal	Focal periventricular gliosis	Focal gliosis
3	Few infarct-like foci	Oedema and degeneration	Focal gliosis and oedema
4	Normal	Oedema	Gliosis
5	Normal	Focal gliosis	Gliosis adjacent to a vessel
6	Infarct-like foci	Normal	Gliosis adjacent to a vessel

The source table did not retain treatment-group identifiers. Terminology is reproduced conservatively from the recorded light-microscopy observations.

Discussion

In this exploratory Goldblatt model, renal artery constriction produced a large MAP separation between hypertensive and control rats. Hypertensive animals also performed less well on the treadmill and took longer to find the Y-maze reward. The treadmill pattern suggests motor-system dysfunction, whereas delayed reward finding raises the possibility of impaired hippocampal-dependent spatial function. The predominance of recorded abnormalities in the basal ganglia and cerebellum provides qualitative anatomical coherence with the motor findings. However, the absence of group and animal linkage and the lack of hippocampal sampling prevent a valid between-group or behaviour-histology correlation.

The blood-pressure findings support successful induction of renovascular hypertension. The mean MAP difference exceeded 60 mmHg, with no overlap between the recorded group ranges. This is consistent with the Goldblatt mechanism, in which renal hypoperfusion activates the renin-angiotensin system and raises systemic pressure. (6,7). However, only a single preserved MAP value per animal was available, so the trajectory and stability of hypertension across the 12 weeks could not be quantified.

Poor treadmill performance in the hypertensive group was evident across all three speeds. The observed toe dragging, shuffling, and impaired foot coordination could reflect dysfunction within interconnected cortical, basal-ganglia and cerebellar motor systems. (9,11). At a systems level, the high frequency of recorded basal-ganglia and cerebellar abnormalities is therefore qualitatively concordant with the motor phenotype. This is anatomical plausibility rather than an observed correlation: the histology records cannot be assigned to hypertensive or control rats or paired with individual treadmill results. The small

treadmill subset, lack of baseline performance, absence of blinded scoring and unavailable animal-level repeated measures further preclude firm estimates of effect or localisation.

Y-maze reward finding was also delayed in hypertensive rats. The hippocampus is central to spatial learning and memory, and Y-maze performance can be sensitive to hippocampal function. (10). In a two-kidney, one-clip hypertensive mouse model, long-term memory impairment occurred alongside reduced CA1 dendritic complexity and adult hippocampal neurogenesis. (8). Against this background, the shift toward longer reward-location times in the present study is consistent with possible hypertension-related hippocampal dysfunction, but it does not establish it. The reward-based protocol was not a validated hippocampus-specific assay, the hippocampus was not examined histologically, and latency can be altered by locomotor impairment, motivation, stress, sensory function and food deprivation. (10). The concurrent treadmill deficit therefore makes motor slowing an important alternative explanation. Future studies should combine validated spontaneous-alternation or spatial-recognition protocols with independent measures of locomotion and motivation.

The recorded oedema, degeneration, gliosis and infarct-like foci are biologically compatible with hypertensive cerebrovascular injury. Chronic hypertension can impair autoregulation, damage small vessels and promote blood-brain barrier disruption, ischaemia and neuroinflammation. (1,2,13). The basal-ganglia and cerebellar findings could plausibly contribute to the treadmill phenotype, while frontal-lobe injury could affect executive and goal-directed components of maze performance. This pattern-level convergence strengthens the rationale for a shared neurological effect but is not evidence of causation or a statistical correlation in this dataset. Direct linkage requires group-labelled, same-animal histology, standardised staining, quantitative regional scoring, scale bars and blinded assessment.

The direction of the behavioural findings is consistent with clinical evidence linking midlife hypertension to later cognitive impairment and dementia. (5,14) . Translation should be cautious because this was an induced renovascular model with limited phenotyping. Its value lies in generating testable hypotheses about the relationship between sustained blood-pressure elevation, motor performance and reward-based spatial behaviour.

Strengths and limitations

A strength of the study was assessing blood pressure and two functional domains within the same experimental model. Reanalysis of the preserved animal-level MAP values also allowed reporting of the magnitude and uncertainty of the between-group difference. Important limitations included the small convenience sample; the absence of a documented sample-size calculation, randomisation, sham surgery, and blinding; incomplete animal and perioperative details; and the use of aggregate behavioural records. The 48-h food-deprivation period may have influenced welfare and motivation. Histology lacked group and individual-animal identifiers and key processing details; the hippocampus was not sampled, and no quantitative morphometry or immunohistochemistry was performed. These limitations reduce

reproducibility and prevent direct correlation of regional pathology with treadmill or Y-maze performance.

Implications for future research

A confirmatory experiment should prespecify a primary outcome and sample-size calculation, randomise animals, include a sham-operated group, document analgesia and welfare monitoring, and blind behavioural and histological assessors. Retain repeated blood-pressure and behavioural measurements at the animal level. Validated cognitive tasks should be paired with automated locomotor and motivation measures. Quantitative neuropathology should include hippocampal subfields (CA1, CA3 and dentate gyrus) as well as frontal, basal-ganglia and cerebellar regions, using markers of neuronal injury, astroglial and microglial activation, vascular remodelling and blood-brain barrier integrity. Preserving same-animal identifiers would then permit prespecified correlations between regional injury scores and behavioural performance.

Conclusion

Goldblatt renal artery constriction produced marked hypertension and was associated with poorer treadmill performance and delayed Y-maze reward finding in this exploratory rat study. Together, these findings suggest motor-network dysfunction and possible impairment of hippocampal-dependent spatial function. Regional histological abnormalities, particularly in the basal ganglia and cerebellum, were anatomically compatible with the motor phenotype. Nevertheless, we cannot draw a behaviour-histology correlation or a histological conclusion about the hippocampus because group and animal identifiers were unavailable and the hippocampus was not sampled. The findings justify a larger, prospectively designed study with rigorous bias control, validated cognitive testing and quantitative, animal-linked neuropathology.

Abbreviations

CI
confidence interval
JREC
Joint Research Ethics Committee
MAP
mean arterial pressure
SD
standard deviation.

Declarations

Ethics approval and consent to participate

The Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals approved the animal study (JREC/225/2024; 26 March 2024). Consent to participate was not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data extracted from the source dissertation and analysed in this manuscript are included within the article. Additional source records, where available, may be requested from the corresponding author.

Competing interests

The authors declare no competing interests.

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Authors' contributions

KM conducted the experiment, collected the data, performed the initial analysis and prepared the source dissertation. TC reanalysed the preserved quantitative data and drafted and critically revised the manuscript. All authors reviewed and approved the final manuscript and agree to be accountable for the work. TM supervised the research process and assisted with dissection and sample preparation.

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Authors' information

Not applicable.

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