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Renovascular hypertension changes cerebral hemodynamics and cardiovascular responses to increased intracranial volume

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Additional Declarations:

Table 1 is available in the Supplementary Files section.

Renovascular hypertension changes cerebral hemodynamics and cardiovascular responses to increased intracranial volume

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Authors contribution

FCM: Investigation Conductor, Formal Analysis, Writing- Original draft, Visualization; PLK Writing- Formal Analysis; Reviewing; DEB: Writing- Editing; JVM: Writing- Reviewing and Editing, Fund Acquisition; EC: Conceptualization, Writing- Original draft, Reviewing and Editing, Formal Analysis, Supervision, Fund Acquisition; DSAC: Conceptualization, Writing- Original draft, Reviewing and Editing, Formal Analysis, Supervision, Project Administration, Fund Acquisition.

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Disclosure of Potential Conflict of Interest (COI)

The authors declare that they have no conflicts of interest.

Data availability

Data will be made available upon reasonable request to the authors.

Artificial Intelligence

The authors declare that no artificial intelligence (AI) tools, large language models, or generative AI technologies were used in the drafting, revision, data analysis, or manuscript preparation of this article. Grammarly software was used to assist with English correction (https://www.grammarly.com).

Ethical Approval/Informed Consent

The authors confirm adherence to the ARRIVE guidelines (see the supplemental files – ARRIVE TABLE), and all the protocols were approved by the Ethics Committee on the Use of Animals (see the supplemental File – CEUA_16_2023)

Abstract

Background: Hypertension is a major risk factor for cardiovascular and cerebrovascular disease. Beyond its systemic effects, hypertension elevates intracranial pressure (ICP) and alters the ICP waveform morphology — specifically increasing the P2/P1 ratio, which indicates reduced intracranial compliance (ICC). The intracranial baroreflex normally triggers pressor responses to maintain cerebral perfusion pressure (CPP) during increases in ICP. However, whether this reflex is impaired in chronic hypertension remains unclear. We tested the hypothesis that 2-kidney, 1-clip (2K1C) hypertensive rats exhibit impaired intracranial baroreflex responses to increased intracranial volume.

Methods: Male Holtzman rats underwent 2K1C renovascular hypertension or sham surgery (normotensive, NT). Six weeks later, under urethane anesthesia, ICP (via an invasive sensor), mean arterial pressure (MAP), and heart rate were recorded. Two protocols were performed: (1) a bolus intracerebroventricular (ICV) infusion of 30 µL of artificial cerebrospinal fluid (aCSF) at 100 µL/min; and (2) a continuous ICV infusion of 100 µL of aCSF at 10 µL/min over 10 min. ICC was calculated from the P2/P1 ratio and the volume-pressure relationship.

Results: In NT rats, bolus infusion increased ICP and MAP, preserving CPP — confirming an intact intracranial baroreflex. In 2K1C rats, despite a similar elevation in ICP, MAP did not increase, resulting in a significant reduction in CPP and a higher P2/P1 ratio. During continuous infusion, both groups showed no change in MAP and sustained ICP elevation. However, 2K1C rats exhibited a marked decrease in CPP and a sharp increase in P2/P1, both absent in NT. The calculated ICC was significantly lower in 2K1C rats across both protocols.

Conclusions: Renovascular hypertension impairs the intracranial baroreflex: the compensatory pressor response to increased ICP is blunted, leading to reduced CPP and further deterioration of

intracranial compliance. These findings suggest that hypertensive patients may have reduced intracranial compensatory reserve, amplifying the pathological impact of transient volume fluctuations.

Keywords: hypertension, intracranial pressure, intracranial compliance, 2K1C, P2/P1

Introduction

Arterial hypertension remains one of the leading causes of cardiovascular morbidity and mortality worldwide and is a major risk factor for stroke, heart failure, chronic kidney disease, and vascular dementia [1,2]. Hypertension can also increase intracranial pressure (ICP), which has traditionally been associated with traumatic brain injury, hydrocephalus, intracranial hemorrhage, and idiopathic intracranial hypertension [3-5]. Of note are the increased baseline levels of ICP in hypertensive humans [reviewed in [6] and in rats with experimental 2-kidney, 1-clip (2K1C) renovascular hypertension [7]. In addition, in hypertension, not only ICP is elevated, but the P2/P1 ratio is also changed; in normotensive humans or rats, the P2 (tidal wave) is lower than the P1 (percussion wave) and in hypertensive states, P2 rises, and the ratio of P2/P1 is > 1 as seen in hypertensive humans or in the 2K1C rats, meaning that in hypertensive states intracranial compliance (ICC) is reduced [7-10]. In a state of low compliance, there is a greater risk of increased ICP due to increased intracranial volume [reviewed in [11]].

The relationship between ICP and cardiovascular regulation has long been recognized through the classical Cushing response, a physiological reaction characterized by hypertension, bradycardia, and bradypnea during severe increases in ICP [[12]]. The Cushing reflex was first recognized as the “last ditch” of the brain, as described by Harvey Cushing, but over the past years, more studies have suggested that this reflex is the intracranial baroreflex [13-15], which aims to maintain cerebral perfusion pressure (CPP), as seen in patients with increased ICP [14]. More recent studies have also shown that increases in ICP lead to sympathoexcitation in humans [16] and animals [15-17]. Some studies have shown that ICP-induced sympathoexcitation precedes increases in arterial pressure in humans and animals [15,16].

Over the years, chronic hypertension can dysregulate cerebral perfusion and reduce cognitive function [2,18]. The mechanisms appear to involve cerebrovascular changes (vascular remodeling, arterial stiffness, for example), disruption of the blood-brain barrier, increased neuroinflammation, and impairment of the intracranial baroreflex [2,7,18-21]. It has been suggested that ICC could serve as an early marker of cerebrovascular dysfunction [22]. Therefore, because 2K1C rats have an increased baseline ICP and a P2/P1 ratio > 1, suggesting a lower ICC [7], the present study aimed to investigate whether the intracranial reflex induced by increasing intracranial volume would be impaired in 2K1C hypertensive rats, as shown previously in 2K1C sheep [19], and the impact on the ICC. To this end, we used a bolus infusion or a continuous infusion of artificial cerebrospinal fluid (aCSF) via intracerebroventricular (ICV) injection.

Methods

Animals

Twenty-one adult male Holtzman rats (initial weight of 150-180 g) provided by the School of Dentistry – UNESP husbandry were used. Upon arrival in the animal facility of the Department of Physiology and Pathology, School of Dentistry, animals were assigned to cages and randomly allocated to the normotensive (NT) or 2K1C experimental groups by the investigator conducting the study. Animals were housed in individual stainless-steel cages with free access to a normal sodium diet (BioBase Rat Chow, Águas Frias, Brazil) and water in the animal facility and were allowed to acclimatize for 5 days before any surgery. In the animal facility, the room temperature was maintained at 23 ± 2 °C, humidity at 55 ± 10%, and with a 12:12 light-dark cycle. The Ethical Committee in Animal Use (CEUA) of the School of Dentistry – UNESP approved the experimental protocols (Proc. CEUA 16/2023). All applicable institutional and/or national

guidelines for the care and use of animals were followed. All the investigators, except Dr. Bragin, were aware of group allocation. No computer-generated sequence or other formal randomization procedure was used to determine assignment to NT or 2K1C groups. Outcome assessments and data analysis were not blinded to any investigator. To further reduce interference with data collection and analysis, the experimental protocols were performed using the same procedures and equipment for both groups.

Anesthesia and euthanasia

For 2K1C and cannulation surgeries, rats were anesthetized with ketamine [80 mg/kg of body weight (b. wt.)] combined with xylazine (7 mg/kg of b. wt.) for the surgeries. During the surgeries/procedures, the level of anesthesia was monitored by assessing the eye blink reflex and the response to paw pinch and adjusted as needed. Following the surgeries, animals received a prophylactic dose of penicillin (50,000 IU, intramuscularly) and a dose of the anti-inflammatory ketoprofen (1 mg/kg of b. wt., subcutaneously). On the day of the experiments, the animals were anesthetized with urethane (1.4 g/kg of b. wt., i.v.; Sigma-Aldrich, St. Louis, MO, USA). The dose was adjusted as needed during the procedures. At the end of the experiments, the animals were euthanized with an overdose of the same anesthetic.

Renovascular Hypertension

Under ketamine + xylazine anesthesia (see above), a laparotomy was performed, and the left kidney was exposed. The renal artery was carefully isolated and partially obstructed with a 0.2-mm silver clip to reduce renal blood flow and induce 2K1C hypertension. In the normotensive (NT) group, rats underwent the same surgical procedures (sham surgery), except

that no clip was placed in any renal artery, as previously described by our laboratory [7,23,24]. At the end of surgery, all animals received postoperative drugs, as described above.

Blood pressure recording

Under ketamine + xylazine anesthesia (see above), a polyethylene tube (PE-10 connected to a PE-50, Clay Adams, Parsippany, USA) was inserted into the abdominal aorta via the femoral artery, tunneled subcutaneously, and exposed on the back of the rat. To record pulsatile arterial pressure, mean arterial pressure (MAP), and heart rate (HR), the arterial catheter was connected to a Statham Gould (P23 Db) pressure transducer (Statham Gould, Cleveland, USA) coupled with a preamplifier (model ETH-200 Bridge Bio Amplifier, CBSciences Inc., Dover, USA) connected to a PowerLab computer data acquisition system (model PowerLab 16SP, ADInstruments, Castle Hill, Australia), with a sampling rate of 2 kHz [25]

Intracranial Pressure Recording

Intracranial pressure was recorded using an invasive ICP sensor (CODMAN 77023; Millar Instruments, Inc., Houston, TX) connected to a PowerLab computer data acquisition system (model PowerLab 16SP; ADInstruments, Castle Hill, Australia) at a sampling rate of 2 kHz based on previous studies [7]. Under urethane anesthesia (see above), the rats were adapted in a stereotaxic apparatus (Stoelting, Wood Dale, IL, USA). Then a craniotomy was performed in the right and left parietal region. A 30-gauge needle, attached to the stereotaxic apparatus, was inserted into the right lateral ventricle, enabling subsequent fluid infusion. On the left side, the ICP invasive sensor was positioned in the cerebral parenchyma. The openings were sealed with instant adhesive. The ICP waveform was continuously measured. Cerebral perfusion pressure

(CPP), P2/P1 and ICC were analyzed offline, where CPP = MAP-ICP, P2/P1 was taken from ICP waveforms. The pulsatile ICP waveform comprises three peaks: the percussion (P1), tidal (P2), and dicrotic (P3) waves. In a compliant system, P1 is higher than P2, and the P2/P1 is < 1.0 [10]; therefore, the P2/P1 ratio was used as an index of ICC, as previously demonstrated [26] and validated [11], and the increases and decreases in the P2/P1 ratio correspond, respectively, to reduced and increased ICC. ICC was also directly calculated as ICC = $\Delta V/\Delta ICP$ for a given volume injected [26].

Inclusion and Exclusion Criteria

NT rats were included in the analysis if the MAP was between 80 and 110 mmHg, and 2K1C rats were included in the analysis if the MAP was between 150 and 190 mmHg.

Statistical analysis

All data were expressed as mean ± standard error. Normality of the data was tested using the Shapiro-Wilk test. For Experiment 1 (see below for details), we use the following statistical analysis: Figure 1, within-group comparisons were performed using paired t-tests when the paired differences satisfied the normality assumption and Wilcoxon test when the normality assumption was not met; Table 1, between-group comparisons were performed using unpaired t-tests when data were normally distributed and the Mann-Whitney test when the normality assumption was not met; Figure 3A, Mann-Whitney test was used (failed normality assumption). For Experiment 2 (see below for details), we used the following statistical analysis: Figure 2, one-way repeated-measures ANOVA with Geisser-Greenhouse correction for nonsphericity, followed by Dunnett's multiple-comparisons test, comparing each post-infusion time point with

baseline. When normality was not met, we used the Friedman test followed by Dunn's multiple-comparisons test comparing each post-infusion time point with baseline; for Figure 3B, we used the Mann-Whitney test (failed normality assumption). We set the significance level at $p < 0.05$. The experimental unit was the individual animal, and each animal contributed one value per analyzed time point or condition. No sample-size calculation was performed. The number of rats per group in Experiments 1 and 2 was determined based on previous experimental studies from our laboratory using the 2K1C model and cardiovascular outcomes[7,23], using the minimum number of animals necessary to obtain interpretable data in accordance with the 3 "R" principle: replacement, refinement, reduction[27]. Graphs were generated, and statistical analyses were performed using GraphPad Prism 11.0.2. All figures were assembled under the license of BioRender.com

General Procedures

All surgical procedures and recordings were conducted in proper rooms in the animal facility of the Department of Physiology and Pathology. Two groups of rats were used for comparison in Experiments 1 and 2 (see below): NT and 2K1C, NT being the control group. The experiments started 6 weeks after the induction of hypertension or sham surgery. On the day before the experiments, animals were moved to a surgery room. Then, under xylazine+ketamine anesthesia (see Methods), the femoral vein and artery were cannulated. Following full recovery of anesthesia, animals returned to their individual cages. The next day, rats were moved to the recording room and were anesthetized with urethane (1.4 g/kg of b. wt., iv), followed by tracheostomy and connection to a mechanical ventilator (60 to 80 breaths per minute, 8 mL/kg). Then, rats were positioned in the stereotaxic frame, and a craniotomy was performed to insert a

needle into the lateral ventricle for artificial cerebrospinal fluid (aCSF) infusion. A sensor was then placed on the brain parenchyma to measure ICP. Throughout the procedure, rectal temperature was maintained between 36 and 37°C using a heating pad. At the end of the experiments, animals were euthanized with an overdose of urethane. The experiments were conducted with NT and 2K1C rats on the same day, and the order was randomized; i.e., one day, the NT experiment was conducted first, and the other day, the 2K1C experiment was conducted first.

Experiment 1: Bolus infusion of aCSF in anesthetized rats

In a group of NT and 2K1C rats, an ICV infusion of 30 µL of aCSF at 100 µL/min (approximately 18 s) was performed in urethane-anesthetized rats. After stabilization of all variables, baseline levels of MAP, HR, and ICP were measured just before the ICV infusion and at the peak of the response. CPP and P2/P1 were calculated offline at baseline and at the peak of the response. ICC was analyzed at the end of the 30 µL infusion.

Experiment 2: Continuous aCSF infusion in anesthetized rats

In another group of NT and 2K1C rats, MAP, HR, and ICP were recorded in urethane-anesthetized rats. MAP, HR, ICP, and CPP were analyzed at baseline, just before the infusion, and every 5 min for 20 min after the start of a 100 µL aCSF infusion at 10 µL/min. ICC was analyzed at the 10^{th} min of the infusion (at the end of the 100 µL infusion).

Results

Experiment 1 – Bolus infusion

As a proof of concept of central baroreceptor activation induced by increased ICP, we performed an acute (18 s) ICV infusion of 30 µl of aCSF in NT rats. Figure 1A-D shows that, compared with pre-infusion values, ICV infusion of 30 µl of aCSF increased MAP ($P = 0.0293$; Figure 1A) due to increased ICP ($P = 0.0017$; Figure 1B). CPP and the P2/P1 ratio did not change from pre-infusion levels ($P = 0.3722$ and $P = 0.2200$, respectively; Figures C and D). HR pre-infusion and post-infusion were similar (298 ± 8 and 306 ± 11 bpm; $P = 0.2433$).

In the 2K1C group, however, MAP did not change relative to pre-infusion levels ($P = 0.1058$, Figure E), whereas ICP increased further ($P = 0.0009$, Figure F). CPP decreased after the ICV infusion ($P = 0.0062$, Figure G), and the P2/P1 ratio increased ($P = 0.0220$, Figure H). HR pre-infusion and post-infusion were similar (325 ± 17 and 332 ± 19 bpm; $P = 0.1250$; non-parametric Wilcoxon test).

In Table 1, we can see that, apart from HR, all the changes, represented as delta changes, induced by the bolus infusion were much greater in 2K1C than in NT (all $P < 0.05$).

Experiment 2: continuous infusion

Figure 2A-E shows the effect of a 100-µL infusion of aCSF over 10 min on MAP, HR, ICP, CPP, and P2/P1 in NT rats. Compared with baseline, the infusion did not change MAP [$F(1.429, 8.573) = 0.7147$; $P = 0.4707$; Figure 2A] but reduced HR toward the end of the recording period (Friedman's analysis of variance; $P < 0.01$; Figure 2B). In addition, the increase in ICP during the 10-min infusion did not return to baseline until the end of the recording period [$F(1.929, 11.57) = 73.42$; $P < 0.0001$; Figure 2C]. The continuous infusion did not significantly change CPP [$F(1.782, 10.69) = 1.367$; $P = 0.2925$; Figure 2D] or the P2/P1 ratio [$F(1.148, 6.888) = 3.440$; $P = 0.1044$; Figure 2E].

Figure 2F-J shows the cerebral hemodynamic and cardiovascular changes induced by the 100-μL infusion of aCSF in 2K1C rats. Similar to NT, the infusion did not change MAP [$F(2.085, 8.339) = 0.7948$; $P = 0.4880$; Figure 2F] but reduced HR [$F(2.017, 8.069) = 4.768$; $P = 0.0427$; Figure 2G]. However, Dunnett's post hoc test did not indicate at which time point. The infusion also induced a sustained increase in ICP [$F(1.371, 5.485) = 39.84$; $P < 0.0008$; Figure 2H]. However, unlike NT rats, in 2K1C rats there was a marked decrease in CPP and a sharp increase in the P2/P1 ratio during the 10-min infusion period, respectively [$F(2.062, 8.249) = 14.18$; $P = 0.0021$; Figure 2I] and [$F(1.252, 5.010) = 18.00$; $P = 0.007$; Figure 2J].

Intracranial Compliance: Experiment 1 and Experiment 2

Calculated ICC for the NT and 2K1C rats in Experiment 1 showed that, at the same ICV volume infused, the 2K1C group had a lower ICC than NT ($P = 0.0086$; Figure 3A). A similar response occurred in Experiment 2 ($P = 0.0209$; Figure 3B).

Discussion

The data obtained show that, with bolus infusion, in NT rats the central baroreceptor and its activation effects (increase in MAP) were functioning properly, whereas this was not the case in 2K1C rats. If the infusion was done at a larger volume but at a lower rate, the major differences were marked decreases and increases, respectively, in CPP and the P2/P1 ratio in the 2K1C rats. Finally, another important difference between the two experiments was the lower ICC levels at the end of the infusion period in 2K1C compared with NT rats.

In the first protocol, the acute intracranial infusion of aCSF (30 μL in ~18 s) induced a Cushing response (except for the bradycardia): increase in ICP, MAP, and preserved CPP and

P2/P1, suggesting the activation of the intracranial baroreflex [12,15-17,28]. Conversely, in 2K1C rats, the increase in MAP was blunted despite an increase in ICP, resulting in a decrease in CPP, similar to that observed in 2K1C sheep [19]. The P2/P1 ratio is an important indicator of intracranial compliance [11,22,26]. In fact, both hypertensive patients [22] and rats [7] – and the present data – have a higher P2 value than P1, demonstrating a lower ICC even without any volume change in the intracranial compartment. In NT rats, the bolus ICV aCSF infusion did not promote relevant changes in wave morphology. However, the P2/P1 ratio was increased in 2K1C rats, indicating a compromised intracranial compliance. When ICC was calculated at the peak of the response in NT and 2K1C rats, ICC was significantly lower in 2K1C rats. With this reduction in ICC, cerebral hemodynamics cannot be adequately regulated, thereby decreasing CPP.

In the second protocol, NT and 2K1C rats were tested at a slower infusion rate (100 µL over 10 min). In both groups, similar responses were observed, including no change in MAP, and a sustained increase in ICP over the recording period. The absence of an increase in MAP in the NT rats, although not expected – as shown in Experiment 1 – is not surprising. Some of the NT animals showed a slight increase or decrease in MAP during the infusion, as has also been observed in mice [28]. Maybe at this volume and rate (a moderate infusion), it was not enough to fully activate the central baroreceptors. For the 2K1C, the same response was observed as in Experiment 1: no change in MAP even at increased ICP levels, consistent with other studies in hypertensive sheep [19]. It has been suggested that astrocytes in the ventral brainstem could act as central baroreceptors [29], and we previously showed that 2K1C rats exhibit astrogliosis in the dorsal brainstem [30]. Whether astrocytes in the ventral brainstem of 2K1C rats are functioning properly remains an open question.

Conversely, a striking difference between NT and 2K1C was observed in CPP and P2/P1 changes during the infusion. In NT, there was no significant change in CPP or P2/P1 during the infusion; in 2K1C, at the same infused volume, CPP was reduced, accompanied by a significant increase in the P2/P1 ratio. Notably, the P2/P1 ratio is already > 1 in the 2K1C rats, and the infusion further increased it. In addition, when calculating the ICC as in Experiment 1, there was a greater reduction in the 2K1C rats. Moreover, in mice with peripheral baroreceptors anesthetized (lidocaine), the same stimulus to induce an increase in ICP produced a greater response [17]. Considering that 2K1C rats have a reduced baroreflex [24], the stronger ICP increase in the 2K1C rats (~21 mmHg, vs. ~12 mmHg in NT) might be a result of the impairment of the baroreflex.

Clinical Relevance

The experimental findings in the 2K1C rat model provide a critical mechanistic translation for clinical observations in humans, demonstrating that renovascular hypertension severely impairs the intracranial baroreflex, a protective mechanism that normally triggers a pressor response to maintain CPP during volume-induced spikes in ICP [16,17]. These results directly parallel clinical data showing that human patients with hypertension exhibit a progressive loss of ICC and a high prevalence of subclinical intracranial hypertension, often regardless of whether their blood pressure is currently controlled [10,22]. Collectively, the data suggest that hypertension reduces the intracranial compensatory reserve, acting as a form of early hypertension-mediated brain organ damage that leaves the brain highly vulnerable to pathological volume fluctuations [22,31]. Therefore, monitoring ICP waveforms and maintaining strict hemodynamic control are essential

clinical strategies to preserve cerebral perfusion and mitigate the risk of long-term cerebrovascular complications.

Limitations

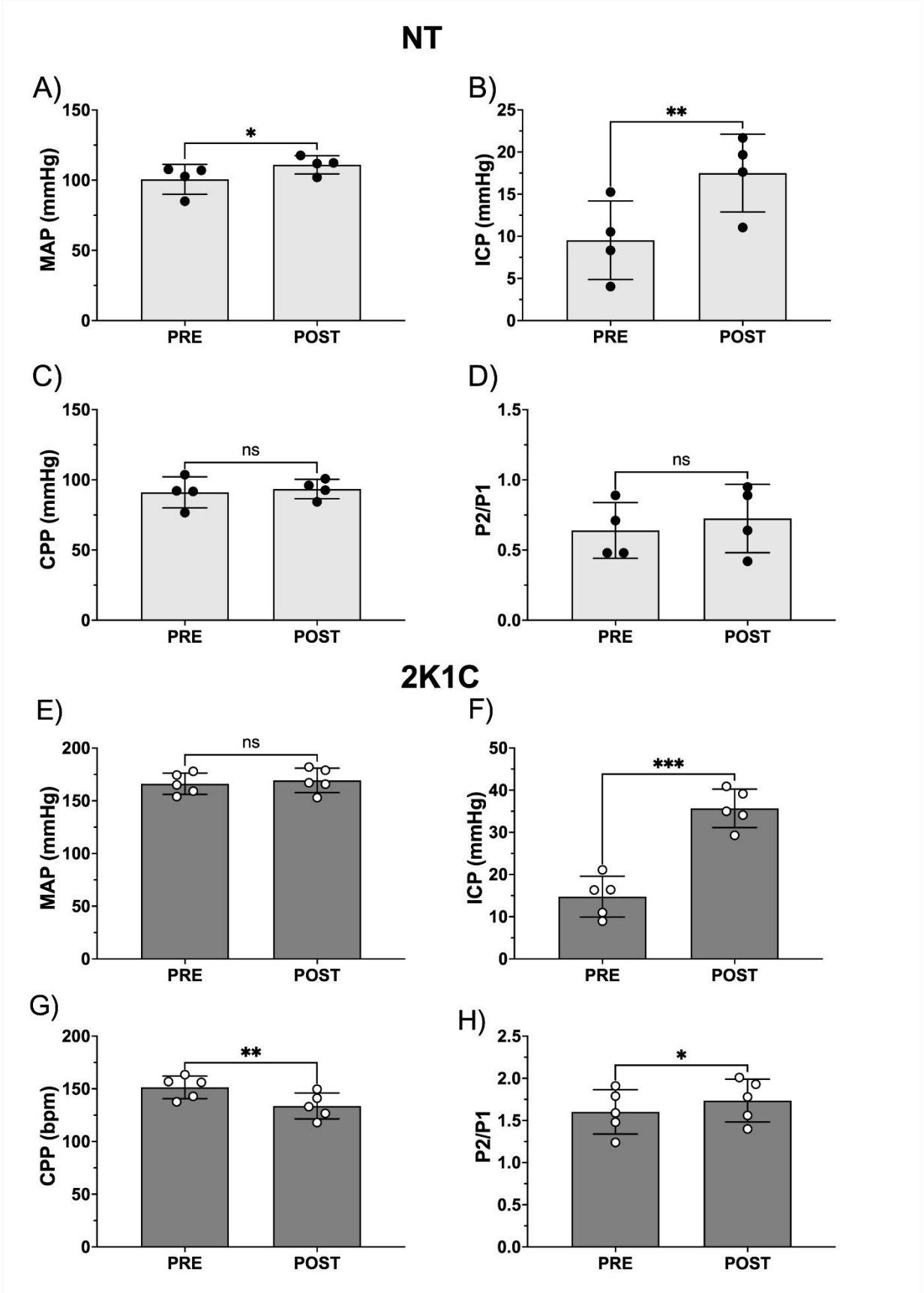
We have, however, to keep in mind that renovascular hypertension is a type of secondary hypertension, commonly caused by atherosclerosis or fibromuscular dysplasia (mostly in women) in one of the kidney arteries, leading to arterial stenosis and a consequent massive increase in the renin-angiotensin system, and as a consequence, severe hypertension[32,33]. The prevalence varies from 1-5% of all cases of hypertension; however, it may be higher, as it is not always diagnosed as such [32,33]. Therefore, caution is needed when extrapolating these findings to primary hypertension (90% of all cases of hypertension). To this end, studies on other models of hypertension, such as spontaneously hypertensive rats and Dahl-salt-sensitive rats, respectively, primary hypertension and salt-sensitive hypertension animal models, should also be conducted to determine whether the cerebral hemodynamic and cardiovascular changes observed in 2K1C rats are specific to this model or general across all forms of hypertension. Finally, considering that sex can be a biological variable for cardiovascular physiology [34], studies in females should also be addressed in the future.

Conclusions

The present results suggest that renovascular hypertension impairs the intracranial baroreflex: the compensatory pressor response to increased ICP is blunted, leading to reduced CPP and further deterioration of intracranial compliance. Therefore, from a translational perspective, the impaired intracranial compliance observed in 2K1C rats may reduce the

intracranial compensatory reserve rather than activate a physiological mechanism to preserve cerebral perfusion, thereby amplifying the pathological consequences of transient intracranial volume fluctuations.

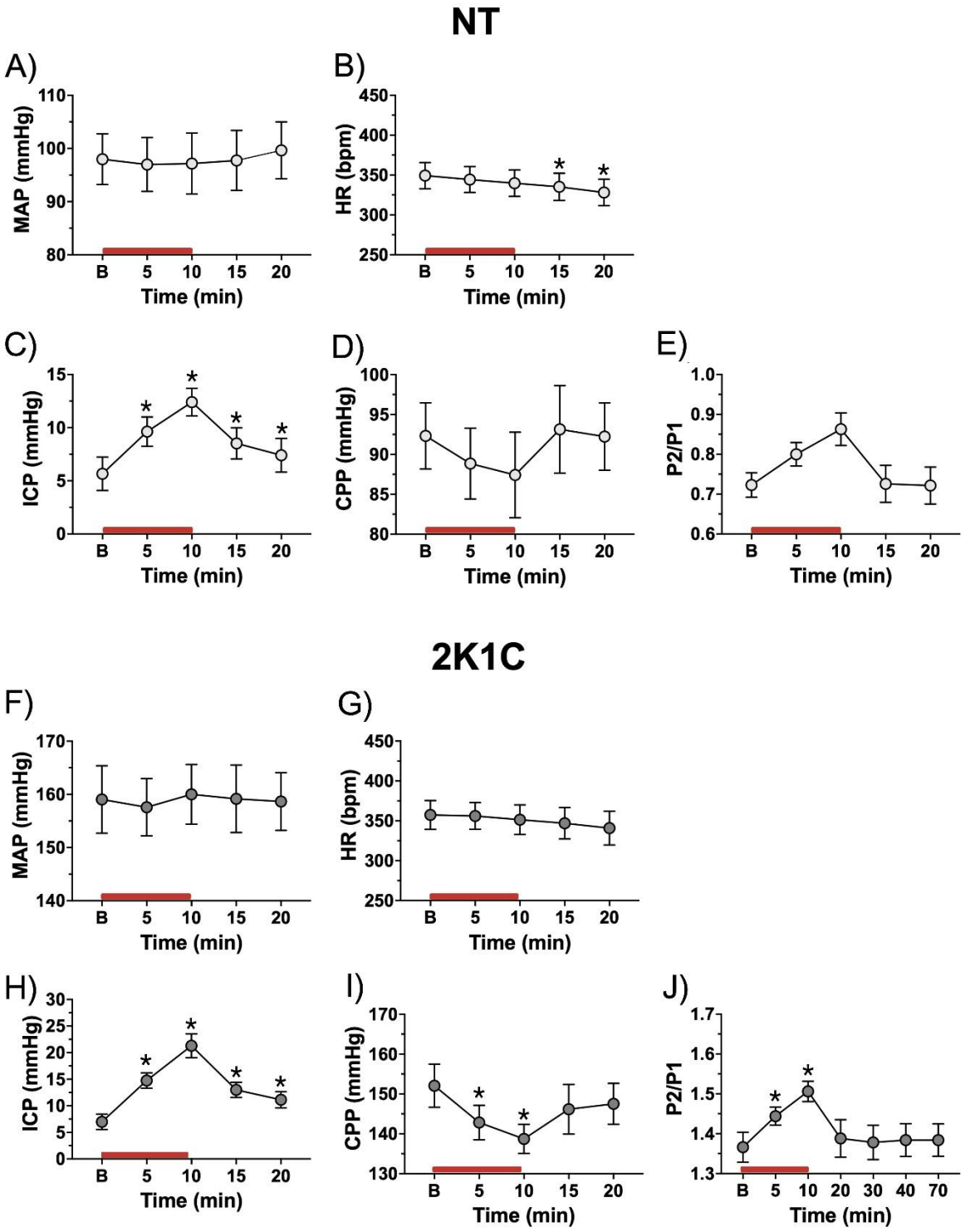
Figure


NT
A)
MAP (mmHg)
150
100
50
0
*
PRE
POST
B)
ICP (mmHg)
25
20
15
10
5
0
**
PRE
POST
C)
CPP (mmHg)
150
100
50
0
ns
PRE
POST
D)
P2/P1
1.5
1.0
0.5
0.0
ns
PRE
POST
2K1C
E)
MAP (mmHg)
200
150
100
50
0
ns
PRE
POST
F)
ICP (mmHg)
50
40
30
20
10
0
***
PRE
POST
G)
CPP (bpm)
200
150
100
50
0
**
PRE
POST
H)
P2/P1
2.5
2.0
1.5
1.0
0.5
0.0
*
PRE
POST

372

373

374 **Figure 1:** Cardiovascular and cerebral hemodynamic responses induced by the 30 µL infusion
375 (at 100 µL/min, intracerebroventricularly) of artificial cerebrospinal fluid in normotensive (NT, n
376 = 4) and 2-kidney,1-clip (2K1C, n = 5). Mean arterial pressure (MAP, A and E), intracranial
377 pressure (ICP, B and F), cerebral perfusion pressure (CPP, C and G), and P2/P1 ratio (D and H).
378 PRE means before the infusion, and POST means the peak response. Data are expressed as mean
379 ± SEM. Paired t-test; * $P<0.05$.


NT
A)
MAP (mmHg)
110
100
90
80
B
5
10
15
20
Time (min)
B)
HR (bpm)
450
400
350
300
250
C)
ICP (mmHg)
15
10
5
0
D)
CPP (mmHg)
100
95
90
85
80
E)
P2/P1
1.0
0.9
0.8
0.7
0.6
2K1C
F)
MAP (mmHg)
170
160
150
140
G)
HR (bpm)
H)
ICP (mmHg)
30
25
20
15
10
5
0
I)
CPP (mmHg)
170
160
150
140
130
J)
P2/P1
1.7
1.6
1.5
1.4
1.3
30
40
70

380

381

Figure 2: Cardiovascular and cerebral hemodynamic changes induced by the 100 µL infusion (10 µL/min) of artificial cerebrospinal fluid in normotensive (NT, n = 7) and 2-kidney,1-clip (2K1C, n = 5). Mean arterial pressure (MAP, A and F), heart rate (HR, B and G), intracranial pressure (ICP, C and H), cerebral perfusion pressure (CPP, D and I), and P2/P1 ratio (E and J). B means baseline (before the infusion), and the red bar indicates the infusion period. Data are expressed as mean ± SEM. Graphs A, C-J, repeated-measures one-way ANOVA followed by Dunnett's test (all points compared to baseline); Graph B, Friedman test followed by Dunn's test (all points compared to baseline); * P<0.05.

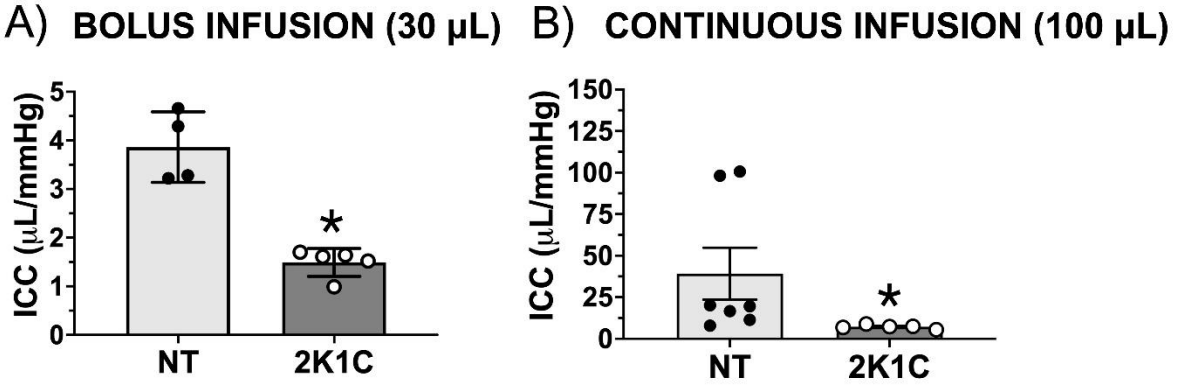


Figure 3: Intracranial compliance (ICC) taken from (A) Experiment 1 (bolus infusion – 30 µL) and (B) Experiment 2 (continuous infusion – 100 µL). Data are expressed as mean ± SEM; Mann-Whitney test for Experiments 1 and 2; * P< 0.05.

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