High Dietary Phosphate Intake Induces Hypertension and Augments Exercise Pressor Reflex Function in Rats

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ABSTRACT

An increasing number of studies have linked high dietary phosphate (Pi) intake to hypertension. It is well established that the rise in sympathetic nerve activity (SNA) and blood pressure (BP) during physical exertion is exaggerated in many forms of hypertension, which are primarily mediated by an overactive skeletal muscle exercise pressor reflex (EPR). However, it remains unknown whether high dietary Pi intake potentiates the EPR-mediated SNA and BP response to exercise. Accordingly, we measured renal SNA (RSNA) and mean BP (MBP) in normotensive Sprague-Dawley rats fed a normal Pi diet (0.6%, n=13) or high Pi diet (1.2%, n=13) for 3 months. As previously reported, we found that resting BP was significantly increased by 1.2% Pi diet in both conscious and anesthetized animals. Activation of the EPR by electrically-induced hindlimb contraction triggered greater increases in ΔRSNA and ΔMBP in the 1.2% as compared to 0.6% Pi group (126 ±25 vs. 42±9 %; 44±5 vs. 14±2 mmHg, respectively, P<0.01). Activation of the muscle mechanoreflex, a component of the EPR, by passively stretching hindlimb muscle also evoked greater increases in ΔRSNA and ΔMBP in the 1.2% as compared to 0.6% Pi group (109±27 vs. 24±7%, 38±7 vs. 8±2 mmHg, respectively, P<0.01). A similar response was produced by hindlimb intra-arterial capsaicin administration to stimulate the metaboreflex arm of the EPR. Thus, our data demonstrate a novel action of dietary Pi loading in augmenting EPR function through overactivation of both the muscle mechanoreflex and metaboreflex.

Keywords: phosphate, exercise pressor reflex, blood pressure, sympathetic nerve activity, hypertension, diet, Western
INTRODUCTION

Inorganic phosphates are widely used in the food industry as preservatives, flavor enhancers, and color stabilizers (1, 46). As a result, dietary phosphate (Pi) intake in the United States far exceeds the recommended daily allowance (1). High Pi intake is proposed to contribute to vascular calcification and cardiovascular (CV) mortality in patients with chronic kidney disease (CKD) (18). However, little attention has been paid to the potential role of Pi excess on the cardiovascular system in the general population with normal kidney function. A high Pi diet was recently shown to trigger blood pressure (BP) elevation in both normotensive rats (2) and spontaneously hypertensive rats (48), both with normal kidney function, in the resting condition. However, the influence of dietary Pi on BP regulation during physical exertion has not been determined.

Studies have demonstrated a correlation between dietary Pi intake and Pi concentration in the central nervous system, which may influence brain development (14, 15) and feeding behavior (5, 49). However, the influence of dietary Pi intake on the central nervous system control of the circulation has not been determined. This is a salient point as the sympathetic nervous system, an important autonomic component of the central nervous system, is known to play a major role in the pathogenesis of hypertension (8). Moreover, patients with primary hypertension not only display elevated levels of sympathetic nerve activity (SNA) at rest, but also augmented increases in SNA and blood pressure (BP) during exercise (6, 50). In primary hypertension, the heightened sympathetic and pressor responses are mediated, in part, by an overactive reflex originating from skeletal muscle, known as the exercise pressor reflex (EPR). The augmentation in EPR function is evoked both by thin fiber muscle afferents associated with metaboreceptors, which are activated slowly during ischemic muscle contraction, and mechanoreceptors, which respond quickly to muscle deformation (30, 32). Sensory information from these afferents is processed in central nervous system centers within the brainstem that regulate sympathetic outflow. Given the known correlation between dietary Pi intake and Pi concentration in the brain combined with the central nervous system’s role in regulating EPR-mediated sympathetic outflow, it is logical to suggest that dietary Pi loading could potentially induce sympathetic overactivity during stimulation of the EPR possibly contributing to the pathogenesis of Pi-induced hypertension. However, to date, the influence of dietary Pi on EPR function has not been elucidated.

Accordingly, we conducted studies to determine the cardiovascular and sympathetic responses to high dietary Pi loading in the normotensive Spraque Dawley (SD) rats with normal kidney function at rest and in response to muscle contraction (i.e. EPR activation) as well as during isolated mechanoreceptor and metaboreceptor stimulation.
METHODS

Animal models. All experiments were performed in male Sprague-Dawley rats. The animals were housed in standard rodent cages on 12 h light dark cycles and were randomly divided into either a group fed a control diet (0.6% total Pi, including 0.3% inorganic Pi, LabDiet/TestDiet 5002, St. Louis, MO, n=13) or a group fed a high phosphorus diet (1.2% total Pi, including 0.9% inorganic Pi, LabDiet/TestDiet modified 5002 #1812250, n=13) for 3 months (beginning at 11-12 weeks of age). Both diets contained 0.8% calcium (Ca), 0.3% sodium (Na), 0.2% magnesium (Mg), and 1% potassium (K). We chose total Pi of 0.6% to be the control diet because this proportion has been shown to be optimal for normal rodents (45). Thus, to mimic the excess Pi consumed daily by Americans, which is approximately twice the recommended daily allowance, we chose a 1.2% Pi diet for the experimental group in our study. The animals were allowed to eat ad libitum and were given free access to water. All studies were conducted in accordance with the US Department of Health and Human Services NIH Guide for the Care and Use of Laboratory Animals. The outlined procedures were approved by the Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center.

Plasma and urine biochemistry. Rats were acclimatized for 2 days in metabolic cages before 24-hour urine collection and measurement of daily food intake (difference in the weight of food provided and food recovered). Plasma and urinary Pi, Ca, -K, and Na were determined 12 weeks after consumption of either a high (1.2%) or normal (0.6%) Pi diet, using methods previously described (12, 34). Plasma creatinine concentrations were measured using a P/ACE MDQ Capillary Electrophoresis System and photodiode detector (Beckman-Coulter, Fullerton, CA) at 214 nm. (52)

Measurement of Blood Pressure in Conscious Animals. 2-3 days prior to surgical procedures below, systolic arterial pressure (SAP) was assessed in the conscious state by tail cuff in a subset of animals in each group (n = 10), using a CODA blood pressure system (Kent Scientific). Animals were acclimated to the measurement procedure and trained for 2 weeks by being placed in a restraining chamber and inflating the blood pressure cuff several times.

Experimental Protocols

General Surgical Procedures. after consumption of either a high (1.2%) or normal (0.6%) Pi diet for 12 weeks, rats were anesthetized with 1–4% isoflurane in oxygen and intubated for mechanical ventilation as described previously (29). Arterial blood pressure was continuously measured by a pressure transducer connected to a left carotid arterial catheter. To obtain electrocardiograph (ECG) recordings, needle electrodes were placed on the back of the animal. Heart rate (HR) was calculated from the time between
successive R waves. To measure RSNA, a branch of the renal nerve was exposed and attached to a pair of stainless steel wire electrodes. The nerve and electrodes were covered with silicone glue for insulation and fixation. The pre-amplified nerve signal was band-pass filtered at 150–1000 Hz then full-wave rectified and low-pass filtered with a cutoff frequency of 30 Hz. Animals were held in a stereotaxic head unit and then, for rendering the animals insentient, a pre-collicular decerebrate procedure was performed. Immediately after the decerebration, isoflurane anesthesia was discontinued.

**Procedures to activate the EPR.** A laminectomy exposing the lower lumber portions of the spinal cord (L₂–L₆) was performed as described previously (29, 40). The L₄ and L₅ ventral roots were carefully isolated and sectioned. The cut peripheral ends of the roots were placed on bipolar electrodes. The gastrocnemius, and soleus muscles of the right hindlimb were isolated. The calcaneal bone of the right hindlimb was cut and the Achilles’ tendon connected to a force transducer for the measurement of muscle tension. To activate the EPR, the gastrocnemius and soleus muscles were contracted by electrically stimulating the L₄ and L₅ ventral roots for 30s using constant current stimulation at 3 times motor threshold with a pulse duration of 0.1 ms at 40 Hz.

**Procedures to activate the mechanically-sensitive component of the EPR.** To evoke a mechanical stimulus similar to that elicited during muscle contraction, the gastrocnemius and soleus muscles of the right hindlimb were passively stretched for 30 sec using a rack-and-pinion system (30, 32). Care was taken to manually generate the same pattern as well as magnitude of muscle tension developed during static muscle contractions. This maneuver was used to selectively activate the mechanoreceptors associated with the mechanically-sensitive afferent fibers of the skeletal muscle mechanoreflex.

**Procedures to activate the chemically-sensitive component of the EPR.** Selective activation of chemically-sensitive metaboreceptors and associated skeletal muscle afferent fibers was achieved by injecting capsaicin into the arterial supply of the right hindlimb (0.3 μg/100 μL). Capsaicin was administered into the right common iliac artery while a reversible ligature placed around the right common iliac vein was occluded for 2 min. This maneuver was used to selectively activate the afferent fibers associated with the skeletal muscle metaboreflex (30, 32).

**End Experiment Procedures.** To validate that RSNA signals were recorded from postganglionic renal sympathetic fibers, an intravenous infusion of hexamethonium bromide (60 mg kg⁻¹) was given to abolish SNA at the end of experiments. RSNA background noise was determined over a 30 min period after the insentient decerebrated animal was humanely killed by intravenous injection of saturated potassium chloride (4 M, 2 ml/kg). The heart and lungs were excised and weighed. Further, the tibial length was measured.
Data Acquisition and Statistical Analyses

MAP, HR, RSNA and contractile tension data were acquired, recorded, and analyzed using data acquisition software (LabChart, ADInstruments) for the Powerlab analog-to-digital convertor (Powerlab8/30, ADInstruments) at a 1-kHz sampling rate. To analyze RSNA, full-wave rectified signals of RSNA as well as background noise signals were obtained. The noise signal component, which was defined as the signal recorded post mortem, was subtracted from rectified RSNA. To quantify RSNA responses to EPR stimulation, baseline values were calculated by averaging 30 s of data immediately prior to the onset of stimulation and were considered 100% of basal RSNA. Subsequently, changes in RSNA were expressed as a percent of baseline and the relative changes in RSNA (ΔRSNA, %) from baseline were evaluated. Data sets of 1 s averages for MAP, HR, RSNA and hindlimb tension were analyzed. Baseline values for all variables were determined by evaluating 30 s of recorded data before a muscle contraction. The peak response of each variable was defined as the greatest change from baseline elicited by contraction.

Statistical Analyses

Data were analyzed using unpaired t tests to identify differences between specific group means. The significance level was set at $P < 0.05$. Results are presented as means ± S.E.M.

RESULTS

Morphometric characteristics, biochemical changes, as well as baseline hemodynamics are presented in Table 1. The heart weight to body weight ratio tended to be higher in the 1.2% Pi than the 0.6% Pi diet group but the difference did not reach statistical significance (2.89±0.10 vs. 2.67±0.04 mg/g, respectively, $p = 0.051$). There were no significant differences in the heart weight to tibial length ratio or the lung weight to body weight ratio between the 2 groups. 24-hour urinary excretion of calcium (Ca), sodium (Na), and potassium (K) were not significantly different between the two groups. 24-hr urinary Pi excretion in the 1.2% Pi group was markedly higher compared to the 0.6% Pi group (77±5 vs. 12±1 mg/day, respectively, $p < 0.01$). There was no significant difference in serum creatinine or creatinine clearance between the 2 groups (0.35±0.01 vs. 0.37±0.01 mg/dL, respectively, $p = 0.3$ and 2.83 ± 0.17 vs. 2.64 ± 0.30 ml/min, respectively, $p = 0.6$). Additionally, there were no difference in urine volume, food intake, serum Pi, Ca, Na, and K between the 2 groups (all $p$ values > 0.1).

Intake of a high Pi diet for 3 months significantly increased tail cuff systolic BP compared to consumption of a normal Pi diet (109 ± 3 vs. 95 ± 2 mmHg, respectively, $p < 0.001$). Similarly, resting mean BP (120±5 vs. 93±4 mmHg, $p < 0.01$) as well as HR (355±5 vs. 333±9 beats per minute, $p < 0.05$) under 1% isoflurane anesthesia was significantly higher in the 1.2% Pi group when compared to the 0.6%
Pi group. After decerebration, however, there were no significant differences in baseline hemodynamics between groups. The baseline SNA to noise ratio was also not different between the two groups.

The peak BP, HR, and RSNA responses to activation of the EPR during static muscle contraction were significantly augmented in the high Pi group when compared to the control group (44±5 vs. 14±2 mmHg, P<0.01; 14±2 vs. 4±1 bpm, p < 0.01; 126±25 vs. 42±9%, P<0.01, respectively, Fig. 1 and Figure 2 B, E, H, and K). Importantly, muscle tension developed during ventral root stimulation was similar between the two groups (1.3±0.1 vs.1.4±0.1 kg, respectively, p > 0.1, Fig. 1-2). The integrated changes in MAP, HR, RSNA, and tension presented as area under the curve (AUC) over 30 seconds demonstrated similar results (Fig 2 C, F, I, and L).

Dietary Pi loading significantly exacerbated the rise in peak BP, HR and RSNA in response to stimulation of the muscle mechanoreflex during passive muscle stretch compared to rats fed a normal diet (38±7 vs. 8±2 mmHg, P<0.01; 11±2 vs. 3±1 bpm, p < 0.01; 109±27 vs. 24±7%, P<0.01, respectively, Fig. 3 and 4 B, E, H, and K). The integrated changes in MAP, HR, RSNA, and muscle tension showed identical results (Figure 4 C, F, I, and L). Dietary Pi loading also enhanced the BP, HR, and RSNA responses to stimulation of the muscle metaboreflex during capsaicin administration compared to the 0.6% Pi group (50±6 vs. 25±4 mmHg, P<0.01; 15±2 vs. 3±1 bpm, p < 0.01; 129±25 vs. 58±9 %, P<0.05, respectively, p < 0.05, Fig. 5-6). The integrated changes in MAP and HR was significantly higher in the 1.2% Pi compared to the 0.6% Pi group (Figure 6 C and F, p < 0.01). The AUC of RSNA during capsaicin administration tended to be higher in in the 1.2% Pi group but the difference did not reach statistical significance (p = 0.086, Fig 6. I).

**DISCUSSION**

The major findings from this investigation are three fold. First, consumption of a high Pi diet augments cardiovascular and sympathetic responses to EPR stimulation during muscle contraction. Second, high dietary Pi intake potentiates BP, HR and RSNA responses to both passive muscle stretch and intra-arterial capsaicin administration in the hindlimb, suggesting enhanced mechano- and metaboreflex function. Third, this detrimental effect of a high Pi diet occurs in the absence of renal failure, a disease condition known to be associated with hypertension and augmented EPR function (35, 36). Collectively, our present study provides the first direct evidence that chronic exposure to a high Pi diet in otherwise healthy animals induces sympathetic overactivation during EPR stimulation, resembling the phenotype observed in rodent models of non-Pi induced hypertension (28, 30).
The high Pi diet used in our study had the content that mimics the excess Pi consumed by the general American population as it contained twice the amount of total Pi compared to the control diet (1.2% vs. 0.6% total Pi) and was enriched with inorganic Pi (0.9% vs. 0.3% inorganic Pi). The extreme elevation in 24-hour urinary Pi excretion in the high Pi group is reflective of the exceedingly absorbable nature of inorganic Pi. Our study in rodents has revealed a novel action of Pi on the neural control of BP during physical exertion as the high Pi diet unequivocally potentiated the increase in SNA, BP, and heart rate to muscle contraction when compared to the resting condition. The sympathoexcitation induced by high Pi diet was mediated by both functional components of the exercise pressor reflex: the muscle mechanoreflex and metaboreflex. Although previous studies indicated that high salt intake enhanced EPR function in normotensive SD rats (28, 51), our current data indicated a similar property of dietary Pi which is independent of Na intake as evidenced by equivalent 24-h urinary Na excretion rates.

The mechanisms underlying Pi-induced enhancements in EPR function remain unknown. Ingestion of an excess amount of inorganic Pi has been shown to promote renal injury in rodents (10, 25). Furthermore, previous studies in patients with chronic kidney disease have demonstrated augmented EPR function, possibly via enhanced mechanoreflex function (35, 36). However, impaired renal function is not likely to explain our study results for two reasons. First, serum creatinine and creatinine clearance in the high Pi group was identical to the control group. Second, the decline in renal function associated with high dietary Pi was not typically observed in rodents with intact kidneys until total Pi content exceeded 2% (10, 33). A high Pi diet has also been shown to induce cardiomyopathy in mice with normal renal function (12). Previous studies in cardiomyopathic rats and patients with congestive heart failure have demonstrated enhanced EPR activity via selective mechanoreflex sensitization (27, 41, 43). In our study, rats subjected to chronic exposure of a high Pi diet tended to have increased heart weight to body weight ratios, suggesting development of left ventricular hypertrophy. However, the lung weight to body weight ratio in the high Pi group was not increased indicating that congestive heart failure had not developed. Thus, it is unlikely that cardiomyopathy induced by a high Pi diet is the primary cause of EPR dysfunction.

Aside from indirect effects of Pi on renal or cardiac function, another possibility includes direct stimulatory effects of Pi on the autonomic or pre-autonomic neurons in the central nervous system. Sodium-phosphate transporters (NaPi-2c) have been identified in many diencephalic regions, including the amygdala and third ventricle (11, 31). Expression of these transporters is altered by dietary Pi intake and concentration of Pi in the cerebrospinal fluid (CSF) (31). Another Pi transporter, PiT2, has also been identified in the choroid plexus of sharks and implicated in removal of Pi from the CSF (9). Dietary Pi
restriction has been shown to reduce Pi levels in the serum and CSF, which was accompanied by increased Pi appetite and Pi seeking behavior within 48 hours (5, 49). In our study, serum Pi was not altered by the high Pi diet though the 24-hr urinary Pi excretion was significantly increased. Whether consumption of the high Pi diet induced an elevated Pi milieu in the brain causing direct stimulation of brainstem centers involved in the generation of muscle reflex-induced central sympathetic outflow remains to be determined.

In addition to the potential direct effect of Pi on the sympathetic nervous system, consumption of a diet high in phosphate may alter baroreflex sensitivity constituting another mechanism by which EPR function could be augmented. It has been demonstrated that the baroreflex normally acts to restrain EPR-induced increases in BP and RSNA (42). In our study, the 1.2% Pi group displayed both elevated resting heart rate and blood pressure, suggesting impaired baroreflex control of heart rate at rest. Reductions in sensitivity could compromise the buffering capacity of the baroreflex contributing to the EPR overactivity observed. Future studies are needed to assess the effects of high dietary Pi on baroreflex control of blood pressure, heart rate and SNA during exercise. Exposure to a high Pi environment may induce alterations in the levels of many hormones involved in Pi homeostasis which could affect EPR function. Previous studies demonstrated that acute Pi loading by either enteral or intravenous routes induced release of phosphaturic hormones, including fibroblast growth factor 23 (FGF-23) and parathyroid hormone (PTH) (3, 7, 38, 39). FGF23 is a major hormone released from osteocytes in bone to augment renal phosphate excretion, thereby minimizing phosphate overload (19, 37). This action of FGF23 requires klotho, which functions as a co-receptor for transduction of FGF23 signaling (13). A high Pi diet has also been shown to reduce soluble klotho levels in the serum of mice (12). Soluble klotho is a multifunctional protein present in biological fluids including blood, urine and CSF. Whether a high Pi diet induces hypertension and sympathetic overactivation via increased expression of FGF23 and/or PTH or downregulation of klotho remains to be determined.

Pi is an essential component of many biologic molecules and is crucial for a large number of cellular functions (21). The recommended daily allowance (RDA) of phosphorus in adults is 700 mg/day according to the Institute of Medicine (44). Pi derived from vegetables or plants, which contain mainly organic phosphate, is poorly absorbed because it is present in the non-hydrolyzable phytate form (16, 17). Unfortunately, the Western diet is well known to contain enormous amounts of inorganic Pi, which is readily absorbed in the gastrointestinal tract (17). Inorganic Pi-containing food additives were found to be present in more than 40% of top selling grocery items, including frozen foods, dry food mixes, packaged meat, and soup (22). It is estimated that an average US adult consumes Pi of approximately 1,200 mg/day,
which is almost twice the recommended daily allowance (4). Emerging evidence suggests that excessive phosphate intake can potentially instigate a number of pathological sequelae, including atherosclerosis, myocardial infarction, vascular calcification, and stroke in patients with and without renal disease (4, 18, 26). Adding to this list, our study demonstrated that dietary Pi excess detrimentally affects the sympathetic regulation of BP during exercise by potentiating the function of both the muscle mechanoreflex and metaboreflex, the two major components of the EPR and, in doing so, may contribute to the pathogenesis of Pi-induced hypertension. Just as importantly, numerous epidemiological studies have demonstrated that exercise BP predicts subsequent development of stroke, myocardial infarction, and death (20, 23, 24, 47), independent of resting BP.

Our study is limited by several factors including a lack of molecular insight into mechanisms linking high dietary Pi to the pathogenesis of EPR dysfunction. Moreover, measurement of BP yielded lower levels of conscious BP than those obtained during isoflurane anesthesia, which was unexpected. However, the tail cuff measurement was limited to a single time point, which may not reflect fluctuations in BP over the longer time period analyzed under anesthesia. Despite the limitation of technique, both tail cuff BP and BP under anesthesia were higher in the 1.2% Pi group when compared to 0.6% Pi group. Thus, our study demonstrated a consistent BP-raising effect of dietary Pi loading in otherwise normal rodents. Our study may provide an explanation for the elevation in SNA and augmented EPR function in patients with chronic kidney diseases (35, 36) who are prone to develop Pi retention and hypertension. If our findings are confirmed in humans, our study results would call for a revision in the food labeling process to include inorganic phosphate. As with Na, such a revision would not only allow the American public to monitor their phosphate intake but also serve as a warning that their health could be compromised by excess consumption of Pi.

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**DISCLOSURES**
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REFERENCES


45. **SUBCOMMITTEE ON LABORATORY ANIMAL NUTRITION.** Nutrient Requirements of


FIGURE LEGENDS

**Figure 1.** Characteristic cardiovascular and sympathetic responses during static muscle contraction in representative Sprague Dawley (SD) rats fed with 0.6% Pi (left) and 1.2% Pi (right) for 12 weeks. The contraction-induced increases in arterial blood pressure (ABP) as well as raw and normalized renal sympathetic nerve activity (RSNA, %) were larger in the SD rat treated with 1.2% Pi compared with 0.6% Pi diet.

**Figure 2.** Summary data showing cardiovascular and sympathetic responses to activation of the EPR during static muscle contraction in the 0.6% Pi (n=13) and 1.2% Pi (n=13) rats. The time course of changes in MAP, HR, RSNA, and muscle tension are shown in Figure 2A, D, G, and J. The peak MAP, HR, RSNA, and muscle tension responses to muscle contraction are shown in Figure 2 B, E, H, and K. The integrated changes in MAP, HR, RSNA, and muscle tension presented as area under the curve (AUC) over 30 seconds are shown in Figure 2 C, F, I, and L. *P < 0.01 compared to 0.6% Pi.

**Figure 3.** Characteristic cardiovascular and sympathetic responses during passive muscle stretch in representative Sprague Dawley (SD) rats fed with 0.6% Pi (left) and 1.2% Pi (right) for 12 weeks. The stretch-induced increases in arterial blood pressure (ABP) as well as raw and normalized renal sympathetic nerve activity (RSNA, %) were larger in the SD rat treated with 1.2% Pi compared with 0.6% Pi diet.

**Figure 4.** Summary data showing cardiovascular and sympathetic responses to activation of the mechanically sensitive component of the EPR in the 0.6% Pi (n=13) and 1.2% Pi (n=13) rats. The time course of changes in MAP, HR, RSNA, and muscle tension are shown in Figure 4A, D, G, and J. The peak MAP, HR, RSNA, and muscle tension responses to muscle stretch are shown in Figure 4 B, E, H, and K. The integrated changes in MAP, HR, RSNA, and muscle tension presented as area under the curve (AUC) over 30 seconds are shown in Figure 4 C, F, I, and L. *P < 0.01 compared to 0.6% Pi.

**Figure 5.** Characteristic cardiovascular and sympathetic responses during selective activation of chemically-sensitive metaboreceptors by injecting capsaicin into the right iliac artery in representative Sprague Dawley (SD) rats fed with 0.6% Pi (left) and 1.2% Pi (right) for 12 weeks. The capsaicin-induced increases in arterial blood pressure (ABP) as well as raw and normalized renal sympathetic nerve activity (RSNA, %) were larger in the SD rat treated with 1.2% Pi compared with 0.6% Pi diet.
**Figure 6.** Summary data showing cardiovascular and sympathetic responses to activation of the metabolically sensitive component of the EPR in the 0.6% Pi (n=13) and 1.2% Pi (n=13) rats. The time course of changes in MAP, HR, and RSNA are shown in Figure 6A, D, and G. The peak MAP, HR, RSNA, and tension responses to intra-femoral capsaicin are shown in Figure 6 B, E, and H. The integrated changes in MAP, HR, and RSNA, presented as area under the curve (AUC) over 30 seconds are shown in Figure 6 C, F, and I. *P < 0.05 compared to 0.6% Pi.
Table 1. Morphometric characteristics, 24-hour urine and baseline hemodynamics.

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</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>93 ± 4</td>
<td>120 ± 5 *</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>333 ± 9</td>
<td>355 ± 5 †</td>
</tr>
<tr>
<td>Baseline RSNA to noise ratio</td>
<td>5.5 ± 1.1</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>After decerebration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>96 ± 6</td>
<td>100 ± 7</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>410 ± 21</td>
<td>400 ± 12</td>
</tr>
<tr>
<td>Baseline RSNA to noise ratio</td>
<td>5.2 ± 1.4</td>
<td>6.4 ± 1.3</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M. * P < 0.01, † p < 0.05 compared to 0.6% Pi
ABP (mmHg) | RSNA (μV) | RSNA (%) | Tension (kg)

0.6% Pi

1.2% Pi

10s