Low-Salt Diet Enhances Vascular Reactivity and Ca\(^{2+}\) Entry in Pregnant Rats With Normal and Reduced Uterine Perfusion Pressure

Jena B. Giardina, Kathy L. Cockrell, Joey P. Granger, Raouf A. Khalil

Abstract—Salt moderation is often recommended to prevent excessive increases in blood pressure during pregnancy, particularly in women who are prone to pregnancy-induced hypertension; however, the vascular effects of low dietary salt intake during pregnancy are unclear. We investigated whether a low-salt diet during pregnancy alters the mechanisms of vascular smooth muscle contraction. Active stress and \(^{45}\)Ca\(^{2+}\) influx were measured in endothelium-denuded aortic strips of virgin and normal pregnant Sprague-Dawley rats and a hypertensive pregnant rat model produced by reduction in uterine perfusion pressure (RUPP), fed either a normal-sodium (NS, 1% NaCl) or low-sodium diet (LS, 0.2% NaCl) for 7 days. The mean arterial pressure was as follows: virgin/NS 108 ± 8, virgin/LS 117 ± 7, pregnant/NS 102 ± 3, pregnant/LS 117 ± 4, RUPP/NS 119 ± 3, and RUPP/LS 133 ± 6 mm Hg. Phenylephrine (Phe) caused concentration-dependent increases in active stress and \(^{45}\)Ca\(^{2+}\) influx that were greater in RUPP rats than in normal pregnant or virgin rats and were enhanced in pregnant/LS and RUPP/LS compared with pregnant/NS and RUPP/NS, respectively. High KCl (16 to 96 mmol/L), which stimulates Ca\(^{2+}\) entry from the extracellular space, also caused increases in active stress that were greater in RUPP than in normal pregnant, in pregnant/LS than in pregnant/NS, and in RUPP/LS than in RUPP/NS rats. The Phe-induced \(^{45}\)Ca\(^{2+}\) influx–active stress relation was greater in RUPP/NS than in pregnant/NS and was enhanced in pregnant/LS and RUPP/LS compared with pregnant/NS and RUPP/NS, respectively. In Ca\(^{2+}\)-free (2 mmol/L ethylene glycol bis(\(\beta\)-aminoethyl ether)-N,N,N',N''-tetra-acetic acid) Krebs, stimulation of intracellular Ca\(^{2+}\) release by Phe (10\(^{-5}\) mol/L) or caffeine (25 mmol/L) caused a transient contraction that was not significantly different in all groups of rats. Thus, a low-salt diet in pregnant and RUPP rats is associated with increases in vascular reactivity that involves Ca\(^{2+}\) entry from the extracellular space but not Ca\(^{2+}\) release from the intracellular stores. The enhancement of the Phe-induced Ca\(^{2+}\) influx–active stress relation in pregnant and RUPP rats on a low-salt diet suggests activation of other vascular contraction mechanisms in addition to Ca\(^{2+}\) entry. Although it is difficult to extrapolate the experimental data in rats to clinical data in women, the increased vascular reactivity and Ca\(^{2+}\) entry and the possible enhancement of additional vascular contraction mechanisms with a low-salt diet suggest that reduction of dietary salt intake should be carefully monitored during pregnancy and pregnancy-induced hypertension. (Hypertension. 2002;39[part 2]:368-374.)

Key Words: arterial pressure ■ muscle, smooth, vascular ■ calcium

Normal pregnancy is associated with reductions in systemic vascular resistance, arterial pressure, and the vascular reactivity to circulating vasoconstrictors.\(^1\)\(^-\)\(^4\) In 5 to 7% of pregnancies, women develop a condition called pre-eclampsia, which is characterized by edema, increased intravascular coagulation, proteinuria, increased systemic vascular resistance, and pregnancy-induced hypertension.\(^5\)\(^-\)\(^6\) Although pregnancy-induced hypertension is a major cause of maternal and fetal mortality, the exact mechanism of this disorder has not yet been clearly identified. Studies in pregnant animal models have led to the hypothesis that reduction in the uteroplacental perfusion pressure and the ensuing placental ischemia during late pregnancy trigger a sequence of cellular and molecular events that eventually lead to increased systemic vascular resistance and pregnancy-induced hypertension.\(^7\)\(^-\)\(^9\) In support of this hypothesis, we recently used a pregnant rat model with reduced uterine perfusion pressure (RUPP), produced by clipping the lower abdominal aorta and the uterine branches of the ovarian arteries, and found that the arterial pressure and vascular reactivity are significantly enhanced in RUPP rats compared with normal pregnant rats.\(^10\)\(^-\)\(^11\)

Because a high-salt diet is often linked to the pathogenesis of hypertension, particularly in salt-sensitive individuals,\(^12\)\(^-\)\(^13\)
it has been thought that salt moderation during pregnancy may protect against excessive increases in arterial pressure and pregnancy-induced hypertension in women. In effect, earlier clinical studies have shown favorable effects of severe sodium-restricted diet in lowering the incidence of eclampsia in women with pregnancy-induced hypertension. Also, experimental studies have shown that a high-salt diet is associated with significant elevations of arterial pressure in pregnant rats and rabbits, and particularly in pregnant rats and sheep with RUPP. However, recent clinical studies have shown minimal benefits of sodium restriction during pregnancy and raised questions regarding the practice of prescribing a low-salt diet to hypertensive pregnant women.

The purpose of the present study was to test the hypothesis that a low-sodium diet in normal pregnant and RUPP rats is associated with alterations in the mechanisms of vascular smooth muscle contraction. Experiments were designed to investigate (1) whether the vascular reactivity to the α-adrenergic agonist phenylephrine is altered during a low-sodium diet in normal pregnant and RUPP rats and (2) whether a low-sodium diet in normal pregnant and RUPP rats is associated with changes in the Ca$^{2+}$ mobilization mechanisms of vascular smooth muscle contraction, namely Ca$^{2+}$ release from the intracellular stores and Ca$^{2+}$ entry from the extracellular space.

**Methods**

**Animals**

Virgin and time-pregnant (day 12) Sprague-Dawley rats (12 weeks) were housed individually and maintained on ad libitum standard rat diet and tap water in a 12-hour light/dark cycle. The rats were divided into six groups, 12 rats each: virgin on normal salt (NS) diet, virgin on low-salt (LS) diet, pregnant/NS, pregnant/LS, RUPP/NS, and RUPP/LS. The NS rats were fed a diet that contained 1% sodium chloride. The LS groups were fed a diet that contained 0.2% sodium chloride. The rats were kept on their respective diets for 7 days. All procedures followed the guidelines of the Animal Care and Use Committee at the University of Mississippi Medical Center.

**Protocol for RUPP**

On day 14 of pregnancy, pregnant rats destined to be in the RUPP group were anesthetized with isoflurane, and the abdominal cavity was opened by a midline incision, the lower abdominal aorta was exposed, and a silver clip (0.23 mm ID) was placed around the aorta above the iliac bifurcation. This procedure reduces uterine perfusion pressure in the gravid rat by ~40%. Because compensation of blood flow to the placenta occurs through an adaptive increase in ovarian blood flow, a silver clip (0.1 mm ID) was also placed on the main uterine branches of both the right and left ovarian arteries. With the use of this protocol, the RUPP rats showed features similar to those observed in preeclampsia in women, including proteinuria, impaired renal function as indicated by reduction in glomerular filtration rate and renal plasma flow, and intrauterine growth retardation as indicated by decreased litter size and pup weight. RUPP rats in which the clipping procedure resulted in maternal death or total resorption of the fetuses were excluded from the study. Control pregnant and virgin rats were sham operated.

**Measurement of Mean Arterial Pressure**

Rats were anesthetized with isoflurane and underwent a surgical procedure to implant a PE-50 arterial catheter in the carotid artery. The catheter was filled with heparin and exteriorized at the back of the neck. Rats were housed individually in metabolic cages and allowed to recover for 48 hours. On the day of the experiment (typically day 19 of gestation or the equivalent in virgin rats), each rat was placed in a Plexiglas restrainer. The carotid arterial catheter was connected to a Statham pressure transducer, and the arterial pressure in conscious rats was recorded on a Grass polygraph (Model 7D, Astro-Med).

**Tissue Preparation**

Rats were anesthetized by inhalation of isoflurane. The thoracic aorta was excised, placed in oxygenated Krebs solution, and cleaned of connective tissue. The aorta was cut transversely into 3-mm-wide strips. For avoiding the contribution of the endothelium to the observed vascular responses, the endothelium was removed by gently rubbing the vessel interior with wet filter paper. Removal of the endothelium was routinely verified by the absence of acetylcholine (10−6 mol/L)-induced vasorelaxation in vascular strips precontracted with Phe (3×10−7 mol/L).

**Isometric Contraction**

One end of the vascular strip was attached to a glass hook using a thread loop, and the other end was connected to a Grass force transducer (FT03). Vascular strips were stretched to Lmax (1.5× the unloaded initial length, L). The strips were allowed to equilibrate for 1 hour in tissue bath filled with 50 mL of Krebs solution continuously bubbled with 95% O2/5% CO2 at 37°C. The changes in isometric contraction were recorded on a Grass polygraph (Model 7D).

Three different agonists were used. The α-adrenergic agonist Phe was used to stimulate both Ca$^{2+}$ release from the intracellular Ca$^{2+}$ stores and Ca$^{2+}$ entry from the extracellular space. Caffeine was used to activate the Ca$^{2+}$-induced Ca$^{2+}$ release mechanism from the intracellular stores. High-KCl solution was used to activate the Ca$^{2+}$ entry mechanism from the extracellular space.

Two control high-KCl (96 mmol/L) contractions followed by rinsing with Krebs solution 3×10−6 minutes were first performed. Increasing concentrations of Phe or KCl were applied, and concentration-contraction curves were constructed. In other experiments, the vascular strips were incubated in nominally 0 Ca$^{2+}$ Krebs for 10 minutes and stimulated with Phe (10−3 mol/L), then increasing concentrations of extracellular Ca$^{2+}$ (0.1, 0.3, 0.6, 1.0, and 2.5 mmol/L) were added to the bathing solution and the changes in Phe contraction were measured. In another set of experiments, the vascular strips were incubated in Ca$^{2+}$-free (2 mmol/L ethylene glycol bis(β-aminoethyl ether)-N,N,N',N'-tetra-acetic acid [EGTA]) Krebs for 5 minutes, then stimulated with Phe (10−3 mol/L or caffeine (25 mmol/L) to stimulate Ca$^{2+}$ release from the intracellular stores, and the resulting transient contraction was measured.

**45Ca$^{2+}$ Influx**

Vascular strips were incubated in Krebs solution containing specific [Ca$^{2+}$], then stimulated with Phe (10−3 mol/L) for 10 minutes. The tissues were transferred to the respective radioactive 45Ca$^{2+}$-labeled solution (specific activity 2 μCi/mL; ICN) for 90 s. Preliminary experiments have shown that the relation between Ca$^{2+}$ uptake and time is linear during 15-, 30-, 60-, and 90-s exposures to the 45Ca$^{2+}$ label. The tissues were transferred to ice-cold Ca$^{2+}$-free (2 mmol/L EGTA) Krebs for 45 minutes to quench extracellular 45Ca$^{2+}$ label. The vascular strips were weighed and placed in 2 mL of hypotonic (5 mmol/L) ethylenediamine-tetraacetic acid for 24 hours at 4°C to disrupt the cell membranes and release the intracellular content of 45Ca$^{2+}$. The next day, 4 mL of Ecolite scintillation cocktail was added, and the samples were counted in a scintillation counter (Beckman LS 6500).

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Solutions and Chemicals
Normal Krebs contained (in mmol/L) 120 NaCl, 5.9 KCl, 25 NaHCO3, 1.2 NaH2PO4, 11.5 Dextrose, 1.2 MgCl2, and 2.5 CaCl2 at pH to 7.4. For nominally 0 Ca2+, Krebs, CaCl2 was omitted. For Ca2+-free Krebs, CaCl2 was omitted and replaced with 2 mmol/L EGTA. The high-KCl depolarizing solution was prepared as Krebs but with equimolar substitution of NaCl with KCl. L-Phenylephrine, acetylcholine, and caffeine were prepared in distilled water. All other chemicals were of reagent grade or better.

Statistical Analysis
The developed force was corrected for the cross-sectional area of each individual strip and expressed as active stress (N/m2) using the equation stress=force/cross-sectional area, where cross-sectional area=width (tissue density×length of the strip), and tissue density=1.055 g/cm3. Data were expressed as the mean±SEM and compared using analysis of variance followed by Bonferroni posttest to compare each group. Differences were considered statistically significant if P<0.05.

Results
On the day of the experiment, the mean arterial pressure in virgin/NS rats (108±8 mm Hg) was not significantly different from virgin/LS (117±7 mm Hg). The arterial pressure was significantly greater in pregnant/LS (117±4 mm Hg) compared with pregnant/NS (102±3 mm Hg) and in RUPP/LS (133±6 mm Hg) compared with RUPP/NS (119±3 mm Hg). The arterial pressure in RUPP rats on NS or LS diet was significantly greater than that in pregnant rats on NS or LS diet, respectively.

In vascular strips of virgin, pregnant, and RUPP rats, Phe caused concentration-dependent increases in active stress (Figure 1). The Phe concentration-active stress curve was slightly greater in virgin/LS than in virgin/NS (Figure 1A) but significantly greater in pregnant/LS than in pregnant/NS (Figure 1B) and in RUPP/LS than in RUPP/NS (Figure 1C). When the Phe response was presented as a percentage of the maximum, Phe was slightly more potent in virgin/LS (median effective concentration [EC50] 1.4x10-8 M) than in virgin/NS (EC50 2.7x10-8 M) but markedly more potent in pregnant/LS (EC50 0.5x10-8 M) than in pregnant/NS (EC50 4.1x10-9 M) and in RUPP/LS (EC50 0.2x10-8 M) than in RUPP/NS (EC50 3.4x10-8 M) (Figures 1D through 1F).

To investigate whether the differences in active stress reflect changes in Ca2+ release from the intracellular stores, we measured Phe- and caffeine-induced contraction in Ca2+-free (2 mmol/L EGTA) Krebs. In Ca2+-free Krebs, Phe (10-5 mol/L) and caffeine (25 mmol/L) caused a transient increase in active stress in vascular strips of virgin rats, which was not significantly different from that in pregnant and RUPP rats on NS or LS diets (Figures 2A and 2B).

Membrane depolarization by high KCl is known to stimulate Ca2+ entry from the extracellular space. Increasing concentrations of KCl caused concentration-dependent increases in active stress (Figure 3). The KCl concentration-active stress curve was slightly greater in virgin/LS than in virgin/NS (Figure 3A) but significantly enhanced in pregnant/LS compared with pregnant/NS (Figure 3B) and in RUPP/LS compared with RUPP/NS (Figure 3C).

To investigate further the role of Ca2+ entry, we measured the Phe (10-5 mol/L)-induced contraction and 45Ca2+ influx at increasing concentrations of extracellular Ca2+. In all groups of rats, increasing concentrations of extracellular Ca2+ were associated with concentration-dependent increases in Phe-induced active stress and 45Ca2+ influx (Figure 4). The Phe-induced [Ca2+]i, active-stress relation was slightly greater in virgin/LS than in virgin/NS (Figure 4A) but significantly enhanced in pregnant/LS compared with pregnant/NS (Figure 4B) and in RUPP/LS compared with RUPP/NS (Figure 4C). The Phe-induced 45Ca2+ influx was slightly but not significantly enhanced in virgin/LS compared with virgin/NS (Figure 4D) but was significantly greater in pregnant/LS than in pregnant/NS (Figure 4E) and in RUPP/LS than in RUPP/NS (Figure 4F).

The data from Figures 4A and 4B were used to construct the Ca2+-influx–active stress relation in virgin, pregnant, and RUPP rats on NS and LS diets (Figure 5). If the increases in active stress associated with LS diet involve changes only in the Ca2+ entry mechanisms, then the Ca2+-influx–stress relation in LS rats would not be different from that in NS rats.
As shown in Figure 5A, the Phe-induced Ca\textsuperscript{2+} influx–stress relation was not significantly different between virgin/LS and virgin/NS rats. In contrast, the Ca\textsuperscript{2+} influx–stress relation was significantly enhanced in pregnant/LS compared with pregnant/NS (Figure 5B) and in RUPP/LS compared with RUPP/NS (Figure 5C).

Discussion

The main findings of the present study are as follows: (1) the arterial pressure is significantly greater in pregnant and RUPP rats on LS diet than in those on NS diet, (2) the vascular reactivity is greater in pregnant and RUPP rats on LS diet compared with those on NS diet, (3) the increased vascular reactivity during LS diet in pregnant and RUPP rats is associated with increases in Ca\textsuperscript{2+} entry from the extracellular space but not Ca\textsuperscript{2+} release from the intracellular stores, and (4) the Phe Ca\textsuperscript{2+} influx–stress relation is enhanced in pregnant and RUPP rats on LS diet compared with those on NS diet.

We found that LS diet in Sprague-Dawley virgin rats caused slight but insignificant increases in the arterial pressure. This is consistent with reports that LS diet is associated with modest changes in the blood pressure in Dahl salt-resistant rats\textsuperscript{26} and lean female rabbits.\textsuperscript{27} The arterial pressure was significantly increased in pregnant/LS diet in pregnant and RUPP rats, we found that the vascular reactivity to Phe was enhanced in pregnant/LS compared with pregnant/NS and in RUPP/LS compared with RUPP/NS. The increased vascular reactivity to Phe with LS diet can be explained, in part, by an increase in the sensitivity to Phe at the \(\alpha\)-adrenergic receptor level. This is supported by the present observation that Phe was more potent and that the Phe EC\textsubscript{50} was markedly smaller in rats fed LS diet compared with rats on NS diet. However, the enhanced vascular reactivity could also be due to stimulation of signaling mechanisms downstream from \(\alpha\)-adrenergic receptor activation.

It is generally accepted that activation of \(\alpha\)-adrenergic receptors by agonists such as Phe causes activation of rats compared with normal pregnant rats is consistent with our previous findings and suggests possible enhancement of the mechanisms of vascular smooth muscle contraction in RUPP rats.\textsuperscript{10}

The arterial pressure was significantly increased in pregnant/LS compared with pregnant/NS and in RUPP/LS compared with RUPP/NS rats. In the search for the possible vascular mechanisms involved in the observed elevated arterial pressure during LS diet in pregnant and RUPP rats, we found that the vascular reactivity to Phe was enhanced in pregnant/LS compared with pregnant/NS and in RUPP/LS compared with RUPP/NS. The increased vascular reactivity to Phe with LS diet can be explained, in part, by an increase in the sensitivity to Phe at the \(\alpha\)-adrenergic receptor level. This is supported by the present observation that Phe was more potent and that the Phe EC\textsubscript{50} was markedly smaller in rats fed LS diet compared with rats on NS diet. However, the enhanced vascular reactivity could also be due to stimulation of signaling mechanisms downstream from \(\alpha\)-adrenergic receptor activation.

It is generally accepted that activation of \(\alpha\)-adrenergic receptors by agonists such as Phe causes activation of
phospholipase C and increases the hydrolysis of phosphatidylinositol 4,5-bisphosphate into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol.29 IP3 stimulates Ca2+ release from intracellular stores, and diacylglycerol stimulates protein kinase C.29,30 In addition, α-adrenergic agonists enhance Ca2+ entry through the plasma membrane Ca2+ channels.23 We found that the transient Phe- and caffeine-induced contractions in Ca2+-free solution, which are often used as a measure of IP3-induced Ca2+ release and Ca2+-induced Ca2+ release from the intracellular Ca2+ stores, respectively, were not significantly different in the virgin, pregnant, and RUPP rats on NS and LS diet, suggesting that the enhanced vascular reactivity during LS diet is not due to changes in Ca2+ release from the intracellular stores. However, the enhanced Phe-induced Ca2+ influx in pregnant and RUPP rats on LS diet suggests enhancement of Ca2+ entry from the extracellular space. To determine the possible Ca2+ entry pathway involved, we investigated whether LS diet is associated with changes in the vascular reactivity to high KCl. High KCl is known to cause membrane depolarization and to stimulate Ca2+ entry through voltage-gated Ca2+ channels.23 The observation that the KCl-induced stress was enhanced in pregnant and RUPP rats on LS diet compared with those on NS diet provides additional evidence that Ca2+ entry from the extracellular space is enhanced under these conditions. The cause of the increased Ca2+ entry into vascular smooth muscle during LS diet is not clear but may be related to possible activation of the renin-angiotensin system. This is supported by reports that LS diet is associated with increases in renin release and the levels of circulating angiotensin II.31,32 This is also supported by reports that angiotensin II increases the permeability of Ca2+ channels in vascular smooth muscle.33 However, activation of the reverse mode of the Na+/Ca2+ exchanger34,35 during LS diet and thereby stimulation of Ca2+ entry into vascular smooth muscle cells cannot be excluded under these conditions.

To investigate whether other mechanisms in addition to Ca2+ entry contribute to the increased vascular reactivity during LS diet, we compared the relation between Phe-induced Ca2+ entry and active stress in rats fed LS and NS diets. If the increase in vascular reactivity during LS diet is merely due to increases in Ca2+ entry through plasma membrane Ca2+ channels, then one would expect the Phe-induced Ca2+ entry–active stress relation to be similar in LS and NS.
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The Ca\(^{2+}\) entry–stress relation did not appear to be different between virgin/LS and virgin/NS rats. Conversely, the Phe-induced Ca\(^{2+}\) entry–stress relation was significantly enhanced in pregnant/LS compared with pregnant/NS and further enhanced in RUPP/LS compared with RUPP/NS. These data suggest that other Phe-stimulated contraction mechanisms in addition to Ca\(^{2+}\) entry through plasma membrane Ca\(^{2+}\) channels are enhanced during LS diet in pregnant and RUPP rats. These additional mechanisms may include the following: (1) Phe may inhibit Ca\(^{2+}\) extrusion mechanisms such as the plasmalemmal Ca\(^{2+}\) pump and the Na\(^+\)/Ca\(^{2+}\) exchanger (forward mode), (2) Phe may disrupt superficially located Ca\(^{2+}\) buffering systems and thus allow more Ca\(^{2+}\) to be available for the myofilaments to cause contraction, and (3) Phe may increase the myofilament force sensitivity to Ca\(^{2+}\) or perhaps stimulate a completely Ca\(^{2+}\)-independent pathway. For example, Phe may activate protein kinase C through increased formation of diacylglycerol.

The causes of the greater enhancement of the mechanisms of vascular contraction with LS diet in pregnant and RUPP rats compared with virgin rats are not clear but could still be related to the activity of the renin-angiotensin system. It has been shown that the renin-angiotensin system is activated during normal pregnancy to maintain blood pressure. Although the plasma levels of renin and angiotensin II do not seem to be elevated in hypertensive pregnant women,37 but the renin-angiotensin system is activated during pregnancy.1069. Although the plasma levels of renin and angiotensin II do not seem to be elevated in hypertensive pregnant women,38–40 or in pregnant dogs or rats with RUPP,41,42 the vasopressor responses to angiotensin II have been shown to be increased in preeclamptic women43,44 and in rat models of “hypertension during pregnancy” produced by inhibition of nitric oxide synthesis.45,46 Also, strong synergistic interactions between angiotensin II and \(\alpha\)-adrenergic agonists such as Phe on the mechanisms of vascular smooth muscle contraction have been reported.47–49 However, whether salt depletion in pregnant and RUPP rats increases the number of angiotensin receptors and/or the sensitivity of the angiotensin receptors to intravenous administration of angiotensin II is unclear and should be investigated in the future. Also, other factors in addition to the renin-angiotensin system could be involved in the enhanced mechanisms of vascular contraction with LS diet in pregnant and RUPP rats and should represent important areas for future investigation.

In conclusion, LS diet in pregnant and RUPP rats is associated with increases in vascular reactivity to \(\alpha\)-adrenergic vasoconstrictor agonists. The increased vascular reactivity during LS diet in pregnant and RUPP rats is due mainly to increased Ca\(^{2+}\) entry from the extracellular space but not Ca\(^{2+}\) release from the intracellular stores. The enhancement of the Phe-stimulated Ca\(^{2+}\) influx–active stress relation during LS diet in pregnant and RUPP rats suggests activation of other vascular contraction mechanisms in addition to Ca\(^{2+}\) entry. Although it is difficult to extrapolate the experimental data in rats to clinical data in women, the increased vascular reactivity and Ca\(^{2+}\) entry and the possible enhancement of additional vascular contraction mechanisms with LS diet suggest that reduction of dietary salt intake should be carefully monitored during pregnancy and pregnancy-induced hypertension.

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