Pressor effect of electroacupuncture on hemorrhagic hypotension

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SYUU, Yi, Hiromi Matsubara, Shingo Hosogi, and Hiroyuki Suga. Pressor effect of electroacupuncture on hemorrhagic hypotension. Am J Physiol Regul Integr Comp Physiol 285: R1446–R1452, 2003.—Neiguan (PC-6) is a traditional acupoint in each forearm and overlies the trunk of the median nerve. Previous studies show that electroacupuncture (EA) at the Neiguan acupoint could improve not only myocardial ischemic dysfunction by inducing a depressor response but also recover hemorrhagic hypotension by inducing a pressor response. However, their physiological mechanisms are not yet elucidated. We investigated the pressor effect of Neiguan EA and its mechanism by focusing on left ventricular (LV) performance in a canine hemorrhagic hypotension model. We hemorrhaged 36 anesthetized and thoracotomized mongrel dogs and decreased LV end-systolic pressure (ESP) to 70 mmHg (35% decrease). We obtained LV pressure-volume (P-V) data with a micromanometer catheter and a conductance catheter. One-hour Neiguan EA significantly recovered the decreased ESP, end-diastolic volume, and stroke volume by 32 ± 13%, 27 ± 13%, and 39 ± 17%, respectively (P < 0.05), without changing heart rate and the slope of the end-systolic P-V relation. Neiguan EA inhibited a hemorrhage-induced increase in plasma catecholamines. However, vecuronium (neuromuscular blocking agent) administration abolished the antihypotension effect of Neiguan EA. Furthermore, Neiguan EA was much more effective than a nonacupoint thigh EA. We conclude that Neiguan EA achieved the antihypotension effect by improving LV filling of the hemorrhage-depressed LV performance despite the inhibition of the hemorrhage-increased plasma catecholamines. This pressor effect seemed to accompany an increased venous return by Neiguan EA-increased vasomotor tone and muscle pump. This study demonstrated a scientific basis for the therapeutic efficacy of acupuncture in the treatment of hemorrhagic hypotension and shock.

Neiguan acupoints; left ventricular performance; vasomotor tone; cardiovascular response; muscle pump

IN TRADITIONAL CHINESE MEDICINE, acupuncture therapy has been performed for thousands of years to treat a variety of diseases and disorders by inserting fine needles at specific loci of the human body called acupoints (20). Three hundred sixty-five acupoints had already been described in the earliest classic text of traditional Chinese medicine, Huangdi’s Internal Classic, written about 2,000 years ago (33). It described rules and advice for the use of the acupuncture therapy. However, the effectiveness of acupuncture therapy and its mechanisms remain to be established scientifically.

Although some previous studies tried to prove the beneficial effects of acupuncture therapy on certain diseases (2, 4, 31), their conclusions are not persuasive enough because they lack scientific evidence of the underlying mechanisms. Consequently, acupuncture therapy is still hidden under a veil of mystery and yet unaccepted internationally. However, acupuncture therapy has been developed from enormous trials and errors and performed clinically in China for several thousand years. This situation may resemble the past situation of the digitalis therapy for congestive heart failure. Namely, digitalis had been used empirically but effectively for about 200 years without definite scientific evidence until its validity was recently proved scientifically (6a, 10). Thus it seems meaningful to evaluate the efficacy of acupuncture therapy by using scientifically sound methods and concepts.

Among many acupoints, we were interested in the Neiguan (PC-6) acupoint, because it has been considered to affect the cardiovascular system (6, 18, 19, 25, 31, 32). Our previous study shows that electroacupuncture (EA) at Neiguan acupoints (Neiguan EA) improved hemodynamics and increased cardiac contractility in anesthetized open-chest dogs under normotensive conditions (30). A previous clinical study in China showed that acupuncture could raise blood pressure and had a therapeutic effect on shock (16). Thus acupuncture could be used to elevate low blood pressure in hypotensive patients. Song et al. (27) reported that Neiguan EA could improve hemorrhagic hypotension in rabbits. However, the mechanism of the pressor effect of Neiguan EA on hemorrhagic hypotension still remained unclear.

In the present study, we scrutinized this phenomenon by analyzing the effect of Neiguan EA on left

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ventricular (LV) performance in a canine hemorrhagic hypotension model. We successfully observed that Neiguan EA has a pressor effect on the hemorrhagic hypotension and partly obtained physiological evidence for its mechanism.

METHODS

Surgical Preparation

Thirty-six adult mongrel dogs (body weight 7–12 kg) were anesthetized with pentobarbital sodium (10–15 mg/kg iv) after premedication with ketamine hydrochloride (7 mg/kg im) and intubated in each experiment. Anesthesia was maintained with pentobarbital sodium (1–2 mg·kg\(^{-1}\)·h\(^{-1}\) iv) and fentanyl (200 µg/h iv). All experimental studies were performed according to the animal use guidelines set by the National Institutes of Health and the American Physiological Society.

We inserted a fluid-filled catheter in the right femoral artery for blood withdrawal and arterial pressure measurement. We also cannulated the right atrium via the right femoral vein for blood withdrawal and arterial pressure measurement as well as the right femoral vein for administration of drugs and fluids. Arterial blood gases and pH were maintained within their physiological ranges by adjusting ventilation and oxygen supply. The chest of the dog in a supine position was opened by median sternotomy under artificial ventilation, and the pericardium was cut open.

We introduced a precalibrated 2.5-Fr. micromanometer-tipped catheter (SPR-524, Millar Instruments, Houston, TX) and an 8-Fr. conductance catheter (custom made by Inter Medical, Osaka, Japan) into the LV chamber through the apex to measure LV pressure and volume.

LV Volume Measurements

The conductance catheter had eight platinum ring electrodes, of which the six inner electrodes (6.5 mm apart) sensed five segmental conductance (Gi, i = 1–5) signals. The conductance catheter method of measuring LV volume (LVV) was described in detail in our previous study (30) and elsewhere (1, 12). By injecting a hypertonic saline (0.2 g NaCl/ml, 2 ml) into the right atrial cannula, we measured the constant offset volume (Vc) only twice before and at the end of each experiment as usual and confirmed that Vc remained stable (1, 12, 30). Inasmuch as we obtained a stable Vc by injecting 2 ml hypertonic saline in our preliminary experiments, we used the same 2 ml hypertonic saline in all dogs. In our preliminary experiments, we compared stroke volume (y) calculated from conductance volume vs. that (x) calculated from aortic flow obtained by electromagnetic flowmeter during caval occlusion every 30 min for 2 h in four dogs in our previous study (30). Our data showed a high correlation between them as indicated by \( y = 0.98x - 0.20 \) with a correlation coefficient ranging between 0.97 and 0.99 among the four dogs. The coefficient of variation of stroke volume differences between x and y was <5%. We excised the LV and measured its weight to normalize LVV for 100 g of LV mass.

Data Analysis

ECG, LV pressure, and segmental conductance volume signals (Gi) were digitized with an analog-to-digital converter (Lab Nb, National Instruments, Austin, TX) at a sampling frequency of 500 Hz and stored in a computer. To exclude the respiratory changes in hemodynamics, we stopped artificial ventilation during data recording.

We analyzed the pressure-volume (P-V) data obtained during a transient aortic occlusion with our original software designed with LabView 3.1 (National Instruments). LV end-systolic elastance (Ees) was obtained by fitting the left upper corners of several P-V loops obtained during the aortic occlusion by linear regression. Ees has been demonstrated to be the most load-insensitive index of LV contractility (29) and considered appropriate for studying the inotropic response during hypovolemic shock (13, 34). A brief decrease in preload by a vena caval occlusion or a transient increase in afterload by a descending aortic occlusion is an accepted method to obtain Ees (13, 34). Several previous studies suggest that the aortic occlusion method is better to obtain Ees during hemorrhagic hypotension than the caval occlusion, because a critical reduction of coronary perfusion pressure induced by caval occlusion may distort Ees inadvertently (21, 24, 34).

Experimental Protocols

All the dogs were bled by 20 ml/kg (~20–25% of the total blood volume) via the femoral artery (5). This caused a hemorrhagic hypotension with an ~35% decrease in ESP (~70 mmHg). As described in RESULTS, we found this hemorrhagic hypotension level remained stable in the control group of dogs without Neiguan EA. No fluid and blood were transfused during hemorrhagic hypotension, except for a little saline (0.4 ml/min) to give the intravenous anesthetics.

We began experiments and recorded the hemodynamic parameters at baseline and during hypotension (15, 30, 50, 70, and 90 min after hemorrhage) in the control and experimental dog groups (see below). During the initial 30 min after hemorrhage as a control period of hemorrhagic hypotension, neither treatment nor stimulation was given to dogs in either control or Neiguan EA groups. At 30 min of hemorrhage, we began either the main protocol of EA or vecuronium administration for the next 60 min. These procedures are described below.

Protocol 1: effect of Neiguan EA and thigh EA on LV performance during hemorrhagic hypotension. Twenty-four of thirty-six dogs were divided into a control group (n = 8), a Neiguan EA group (n = 8), and a thigh EA group (n = 8) (see Table 1). In the Neiguan EA group, we inserted two stainless steel acupuncture needles (Suzhou Acupuncture Medical Appliance, Suzhou, China) at Neiguan acupoints in bilateral forearms (3 cm above the joint of paw, between the tendons of the long palmar muscle and the radial flexor muscle of the wrist) perpendicularly to a depth of 18–19 mm. Then we electrically stimulated the Neiguan acupoints at 5 V and 40 Hz, with visible local muscle tetanic contractions using an EA stimulator (WQ-6F, Dong Hua Electronic Instrument Factory, Beijing, China) for 60 min. In our previous study, we found 5 V and 40 Hz to be the most effective electric stimulation (30). The correct positioning at Neiguan acupoint was confirmed by observing slight repetitive paw flexion during stimulation (6). In four dogs of Neiguan EA group, we also observed the effect of post-Neiguan EA on left ventricular performance for an additional 120 min to investigate whether the effects of Neiguan EA are temporary.

In the thigh EA group, we performed EA at nonacupoint thigh muscle sites (mid point, lateral side) following the same procedure as in the Neiguan EA group.

Protocol 2: effect of vecuronium administration on Neiguan EA during hemorrhagic hypotension. Inasmuch as Neiguan EA caused slightly visible rhythmic local muscle contractions, we investigated Neiguan EA in the presence of muscle paralysis induced by vecuronium to examine the degree of...
contribution of the muscle pump function to the mechanisms of EA. The remaining 12 dogs were divided into “vecuronium without Neiguan EA” group (control group, n = 6) and “vecuronium with Neiguan EA” group (experiment group, n = 6) (Table 1). We began intravenous administration of vecuronium (nondepolarizing neuromuscular blocking agent) at a rate of 0.02 mg kg⁻¹ min⁻¹ at 30 min after hemorrhage and continued it for 60 min. EA technique was exactly the same as that described in protocol 1.

Statistics

All values are presented as means ± SD. P < 0.05 was used for significance in all statistical tests. One-way ANOVA was used to compare body weight, LV weight, removed blood volume, and percent reduction of ESP among the five groups in protocols 1 and 2 (Table 1). Two-way repeated-measures ANOVA was used for comparison of the data from the experiments shown in Table 2. When there was a statistically significant difference at P < 0.05, the values at all times during hemorrhagic hypotension were compared with baseline value, and the 50-, 70-, and 90-min posthemorrhage values were compared with the 30-min posthemorrhage value, using Bonferroni-Dunn post hoc test.

RESULTS

Changes in Systemic Physiological Variables

Figure 1 shows the representative series of P-V loops of the in situ canine LV at baseline, 30, and 90 min after hemorrhage without (control, top) and with Neiguan EA (bottom). Hemorrhage decreased end-systolic pressure (ESP), end-diastolic volume (EDV), and SV, but increased Ees in both groups. In the control group, at 90 min of hemorrhage, despite no change in ESP, further decreases in EDV and SV were observed (Fig. 1C, top). On the other hand, Neiguan EA markedly increased the once decreased ESP, EDV, and SV (Fig. 1C, bottom).

Changes in systemic physiological variables in all experiments are summarized in Table 2. In control group, ESP remained at ≈70 mmHg during hemorrhagic hypotension, whereas Neiguan EA significantly increased ESP, EDV, and SV by 32 ± 13%, 27 ± 13%, and 39 ± 17%, respectively (P < 0.05, 30 vs. 90 min after hemorrhage), without significantly changing HR and Ees. In addition, Neiguan EA significantly increased CVP by 48 ± 15% (P < 0.05, 30 vs. 90 min after hemorrhage), suggesting that EDV was improved by the increased venous return. Thigh nonacupoint EA caused less stiffening of the thigh muscle than the paw flexion by Neiguan EA and elicited less cardiovascular effect than Neiguan EA. Thus Neiguan EA increased CVP, ESP, EDV, and SV much more effectively than Neiguan EA.

Vecuronium decreased EDV and CVP despite 1-h Neiguan EA. As a result, ESP and SV decreased by −20% in a pattern similar to “vecuronium without Neiguan EA” group. There was also no significant difference in Ees and HR between the vecuronium groups without and with Neiguan EA (Table 2).

We observed that Neiguan EA significantly improved the LV performance suppressed by hemorrhage and maintained it during Neiguan EA (Table 2). However, the antihypotension effect of Neiguan EA disappeared 120 min after Neiguan EA was stopped (data not shown). Namely, the beneficial effect gradually disappeared once the EA was stopped.

Neurohormonal Systems

The concentration of plasma catecholamines progressively increased and doubled in the control group. One-hour Neiguan EA significantly decreased the further increase in plasma catecholamines and maintained them at certain levels (Table 2). Figure 2 shows that plasma vasopressin has a significant increase by −13 times (P < 0.05) after hemorrhage, and 1-h Neiguan EA inhibited the increase close to the prehemorrhagic level. However, when Neiguan EA was stopped, the plasma vasopressin increased again progressively compared with the baseline (P < 0.05).

DISCUSSION

This is the first study to show that Neiguan (PC-6) EA improved hemorrhage-induced suppression of LV performance in anesthetized dogs under hemorrhagic hypotension. The pressor effect seemed to accompany an increased venous return by Neiguan EA-increased venous return. Thigh nonacupoint EA caused less stiffening of the thigh muscle than the paw flexion by Neiguan EA and elicited less cardiovascular effect than Neiguan EA. Thus Neiguan EA increased CVP, ESP, EDV, and SV much more effectively than thigh EA.

Vecuronium decreased EDV and CVP despite 1-h Neiguan EA. As a result, ESP and SV decreased by −20% in a pattern similar to “vecuronium without Neiguan EA” group. There was also no significant difference in Ees and HR between the vecuronium groups without and with Neiguan EA (Table 2).

We observed that Neiguan EA significantly improved the LV performance suppressed by hemorrhage and maintained it during Neiguan EA (Table 2). However, the antihypotension effect of Neiguan EA disappeared 120 min after Neiguan EA was stopped (data not shown). Namely, the beneficial effect gradually disappeared once the EA was stopped.

Table 1. Body weight, left ventricular weight, removed blood volume, and percentage of reduction in ESP in each group

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Group</th>
<th>Body Wt, kg</th>
<th>Left Ventricular Wt, g</th>
<th>Removed Blood Volume, ml</th>
<th>% Reduction in ESP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control (n = 8)</td>
<td>10.8 ± 1.5</td>
<td>45.0 ± 9.6</td>
<td>200.0 ± 35.1</td>
<td>35 ± 13</td>
</tr>
<tr>
<td>Neiguan EA (n = 8)</td>
<td>9.0 ± 2.2</td>
<td>45.8 ± 13.1</td>
<td>201.4 ± 34.6</td>
<td>34 ± 6</td>
<td></td>
</tr>
<tr>
<td>Thigh EA (n = 8)</td>
<td>9.4 ± 1.5</td>
<td>46.9 ± 7.5</td>
<td>204.3 ± 34.6</td>
<td>36 ± 9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Vecuronium without Neiguan EA (n = 6)</td>
<td>10.6 ± 2.6</td>
<td>50.7 ± 14.8</td>
<td>215.6 ± 26.9</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>Vecuronium with Neiguan EA (n = 6)</td>
<td>P &gt; 0.05</td>
<td>47.1 ± 7.1</td>
<td>195.1 ± 31.6</td>
<td>33 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

Results are means ± SD. Blood was removed from each group of animals to cause −35% decrease in end-systolic pressure (ESP). The percentage of reduction in ESP was from baseline to the 30 min after hemorrhage. No significant difference in each variable was observed among the 5 groups (ANOVA, P > 0.05) in protocols 1 and 2. EA, electroacupuncture.
Hemorrhagic hypotension is known to activate cardiopulmonary and baroreceptor reflexes, consequently mobilizing the sympathoadrenal defense system. Three main compensatory reflex responses are usually observed during hemorrhage: 1) augmented cardiac sympathetic tone (increase in heart rate and cardiac contractility), 2) augmented vasomotor tone (constriction of both resistance and capacitance vessels), 3) release of adrenal medullary catecholamines. These reflex responses will tend to restore both cardiac output and arterial pressure, but they will not be maintained equally.

The new findings from this study are 1) Neiguan EA significantly recovered the decreased ESP, EDV, and SV without changing heart rate and the cardiac contractility (Ees); 2) vecuronium administration abolished the pressor effect of Neiguan EA; 3) Neiguan EA was much more effective than a nonacupoint thigh EA; 4) Neiguan EA inhibited the hemorrhage-induced catecholamines and vasopressin release.

We would speculate that the mechanism of the pressor effect of Neiguan EA on hemorrhagic hypotension might be a somatosympathetic cardiovascular response under the electrical stimulation of the median nerve. This stimulation may have further activated compensatory mechanisms to increase cardiac output and raise blood pressure. Three possibilities will be addressed separately below.

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Cardiac Sympathetic Contribution

Neiguan EA has been shown to raise the reduced blood pressure as well as increase the diminished stroke volume, heart rate, and cardiac contractility in rabbits during hemorrhagic hypotension (27). However, the previous study did not give a satisfactory explanation for the antihypotension mechanism of Neiguan EA. Furthermore, they assessed the cardiac contractility by dP/dt max, which is highly susceptible to changes in ventricular preload. We then suspected that they merely observed the increase in dP/dt max caused by an increase in EDV.

We also found that Neiguan EA significantly improved hemorrhage-induced hypotension and hypovolemia (Table 2). However, unlike the previous study (27), we observed increases in heart rate and cardiac contractility (Ees) after inducing hemorrhagic hypotension, but no significant differences existed in either of these two indexes between control and Neiguan EA groups (Table 2). We therefore speculate that the pressor effect of Neiguan EA was not due to the cardiac sympathetic contribution. Because we added neither fluid nor blood, the increased EDV could reasonably be caused by increased venous return. The possible explanations of the increased venous return induced by Neiguan EA were described as follows.

Sympathetic Vascular Response

In our preliminary study using two hemorrhaged dogs similar to the present study, we observed that the plasma vasopressin increased significantly after inducing hemorrhage-induced hypotension (Fig. 2).

Fig. 2. Effects of Neiguan EA and post-Neiguan EA on plasma vasopressin during hemorrhagic hypotension. *P < 0.05: each time point vs. baseline. b30: 30 min after hemorrhage. EA60: 1-h Neiguan EA. P30, P60, and P120: 30, 60, and 120 min after stoppage of Neiguan EA.
direct median nerve stimulation yielded similar beneficial results to the present ones (unpublished). Comparison of the present and preliminary results suggests the possibility that the somatosympathetic vascular response partly contributes to the increased LV filling. Previous studies have shown that Neiguan acupoint has projections to the cardiac and vasomotor centers in the medulla as well as to the spinal segment (C6-T1); it thereby could cause a sympathetic vascular response (17). In circulatory shock, the increased vasoconstriction will notably increase the circulating plasma volume by decreasing the circulatory capacity so that the remaining blood volume will create a greater venous filling pressure and by lowering the general capillary hydrostatic pressure to promote fluid transfer from tissues to the plasma. Venoconstriction can significantly decrease venous capacitance and shift blood toward the heart, assisting venous return (28).

Although the vasoconstriction could also be caused by compensatory mechanisms during hemorrhagic hypotension, our control group did not show any improvement of hemorrhage-induced falls in blood pressure and stroke volume, indicating inactivation of the compensatory mechanisms. As Neiguan EA significantly improved the hypovolemic hypotension, we speculated that Neiguan EA produced general vasoconstriction, which is particularly marked in the skin, skeletal muscle, and splanchnic and renal vascular beds by activating sympathetic vascular responses.

The sympathetic vascular responses could be induced by the neurohumoral activation of catecholamines and vasopressin or activation of the somatosympathetic reflex pathway (9, 28). Interestingly, we found in the control group that the plasma catecholamine and vasopressin concentrations markedly increased after hemorrhage and progressively increased accompanying decreases in blood pressure and cardiac output. However, Neiguan EA reversed the hemorrhagic hypotension as well as inhibited the further increase in plasma catecholamines and vasopressin and maintained them at certain levels. Thus the demonstration of a constraining influence of EA on hemorrhagic hypotension may warrant new studies of the underlying pathways or mechanisms for the benefits of EA in hemorrhagic shock.

**Muscle Pump Contribution**

Several previous studies have suggested that electrical stimulation-induced rhythmic muscle contractions can activate the skeletal muscle pump (14, 15). In our present study, we also observed that Neiguan EA caused visible rhythmic local muscle contractions. Therefore, we speculated that Neiguan EA probably increased the venous return by activating the muscle pump. To examine our speculation, we investigated the effect of the muscle paralysis induced by vecuronium on Neiguan EA. We observed that vecuronium administration abolished the beneficial effect of Neiguan EA on hemorrhagic shock, supporting our speculation.

Faghrí et al. (8) reported that continuous electrical stimulation-induced leg muscle contractions improved lower leg venous circulation and increased SV and cardiac output, presumably by activating skeletal muscle pump, during surgery (8). We therefore examined whether EA at a nonacupoint thigh muscle site could elicit similar effects to Neiguan EA. Because the Neiguan EA caused slight visible repetitive paw flexion and vecuronium abolished its pressor effect, we suspected a significant contribution of skeletal muscle contraction on the effect. Although the thigh nonacupoint EA increased ESP and SV to some extent, the pressor effect of thigh EA was much less than that of Neiguan EA despite the larger mass of skeletal muscles in the thigh. This seems to negate the possibility of the local stimulation of skeletal muscles by EA as the predominant cause of the pressor effect of Neiguan EA.

Although we could not provide qualitative data to compare the vasomotor tone and muscle pump between Neiguan EA and thigh EA in the present study, we observed the specific pressor effect of Neiguan EA on hemorrhagic hypotension. However, considering that the site of the Neiguan acupoint overlies the trunk of the median nerve, we believe that the activation of afferent input from certain somatic nerves may effectively cause the vasoconstriction in some particular organs and activate muscle pump by somatosympathetic cardiovascular response (26) rather than by direct electrical muscle stimulation.

Since we first observed the beneficial effects of Neiguan EA, we adopted it to maintain mean arterial blood pressure of the metabolic support dog in our routine cross-circulation heart experiment (22). The support dog is unthoracotomized, although anesthetized with pentobarbital sodium and fentanyl. Until we adopted Neiguan EA, mean arterial pressure gradually decreased and we had to maintain it by transfusing blood reserved from the donor heart dog or by infusing saline. However, since we adopted Neiguan EA, mean arterial pressure usually remained stable above 90 mmHg over several hours with little need of blood transfusion (22).

In dogs, the spleen is an organ capable of storing a large volume of red blood cells from the general circulation. This reservoir function of the spleen has been implicated as important for hemodynamic compensation during hemorrhagic shock (7). A previous study shows that in dogs, the spleen maintains LV performance during hemorrhage (11). Further studies are warranted to clarify if the splenic contraction is involved in the mechanism of the Neiguan EA-induced pressor response in hemorrhagic hypotension.

In summary, Neiguan EA improves suppressed LV performance by an improved venous filling and recovers the reduced blood pressure during hemorrhagic hypotension. The mechanism of this antihypotension effect of Neiguan EA seems to be due to an increased venous return by augmented vasomotor and venomotor tone under a certain level of skeletal muscle contraction. These results provide scientific evidence for the effectiveness of the acupuncture therapy that has been
adopted for several thousand years based on long clinical experience in China.

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DISCLOSURES

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