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Phlebotomy Reverses the Hemodynamic Consequences of Thoracic Aortic Cross-clamping: Relationships Between Central Venous Pressure and Cerebrospinal Fluid Pressure

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In dogs (n = 11) anesthetized with sodium pentobarbital (to an isoelectric EEG), the authors investigated the influence of thoracic aortic cross-clamping (AXC) on systemic hemodynamics and cerebrospinal fluid pressure (CSFP) with concurrent measurement of total brain blood flow (tCBF) and regional (cervical, thoracic, and lumbar) spinal cord blood flow (SCBF). The effect of phlebotomy (to control the hemodynamic consequences of AXC) on tCBF and SCBF was assessed. Radioactive microspheres were injected at four time periods in each animal: 1) at baseline; 2) with application of the AXC; 3) after phlebotomy, to reduce the proximal mean arterial pressure (MAP_p) to baseline values; and 4) 2 min after removal of the AXC (mean AXC time 68 ± 6 min). With application of the AXC, the MAP_p, central venous pressure (CVP), and CSFP significantly increased (104 ± 6 to 156 ± 6 mmHg, 3.4 ± 0.4 to 5.2 ± 0.7 mmHg, and 3.3 ± 0.7 to 5.2 ± 0.8 mmHg, respectively), while distal mean aortic pressure (MAP_d) significantly decreased (98 ± 6 to 14 ± 1 mmHg). Phlebotomy (24 ± 3 $ml \cdot kg^{-1}$) significantly decreased MAP_p (to 106 ± 6 mmHg), CVP (to 1.6 ± 0.6 mmHg), and CSFP (to 1.2 ± 1.1 mmHg). The CSFP changed in parallel with the changes in CVP, a result suggesting that the alterations in CSFP depended on cardiac preload. The spinal cord perfusion pressure (SCPP; SCPP = MAP_d − CSFP) was unchanged after phlebotomy, since both MAP_d and CSFP decreased. The tCBF and cervical SCBF were unchanged when MAP_p increased by 50% with application of the AXC; this indicated that autoregulation was intact. The thoracic and lumbar SCBF significantly decreased after AXC application (17 and 6% of baseline flows, respectively). All regional SCBFs were unchanged with phlebotomy. With removal of the AXC, all regional blood flows increased above baseline values (tCBF by 33%, $P = 0.002$ *vs.* baseline; cervical SCBF by 39%, $P = 0.008$; thoracic SCBF by 83%, $P = 0.0001$; and lumbar SCBF by 59%, $P = 0.05$). The increase in regional blood flows in nonischemic regions (tCBF and cervical SCBF) was correlated with an increase in arterial CO_2 tension (Pa_{CO_2}) (39.5 ± 0.5 mmHg at baseline *vs.* 55.4 ± 0.4 mmHg at release of the AXC) and unrelated to the cerebral metabolic rate for oxygen (CMR_{O_2}) (unchanged from baseline values). The increase in Pa_{CO_2} presumably contributed to the increased flow in the ischemic regions (thoracic and lumbar spinal cord) as well. Phlebotomy reverses the hemodynamic consequences of thoracic AXC by treating the increase in cardiac preload that occurs with this intervention. The increase in CSFP (which occurred despite intact cerebral autoregulation) also was controlled by phlebotomy, indicating that this change also depended on the increase in right heart filling pressure. (Key words: Animal: dog. Blood pressure: aortic cross-clamping. Brain: blood flow. Measurement technique: radioactive microspheres. Spinal cord: blood flow.)

OPERATIVE REPAIR of the descending thoracic aorta necessitates cross-clamping of the aorta (AXC). This has four significant consequences for the patient: 1) proximal aortic hypertension (an increase in proximal mean aortic pressure [MAP_p]), which may cause acute left ventricular failure or ischemia, especially in the elderly and in those with coronary artery disease[1]; 2) increased cardiac preload due to increased venous return[2]; 3) decreased mean distal aortic pressure (MAP_d), which can cause renal and spinal cord ischemia[3]; and 4) increased cerebrospinal fluid pressure (CSFP), which can further compromise spinal cord blood flow (SCBF).[4] Treatment of proximal hypertension and increased preload is usually necessary for the patient to tolerate AXC during surgical reconstruction. However, this treatment may adversely affect spinal cord perfusion pressure (SCPP; SCPP = MAP_d − CSFP) by further decreasing MAP_d and increasing CSFP. These changes place the spinal cord at increased risk of ischemia and the patient at increased risk of paraplegia.

The incidence of paraplegia after surgical reconstruction of the thoracic aorta is as high as 20–40% in patients with diffuse aneurysmal dilatation or extensive dissection.[3,4] Recent experimentation has focused on the manipulation of SCPP to maximize SCBF during AXC.[5,6] Drainage of CSF has been advocated to decrease CSFP and thereby increase SCPP. This intervention counteracts the increase in CSFP seen with AXC. Although this treatment was first suggested 30 yr ago, concern about possible complications of CSF drainage has prevented this treatment from gaining wide clinical acceptance.[7]

Work by Stokland *et al.* indicates that many of the hemodynamic consequences of thoracic AXC are a result of increased preload secondary to autotransfusion from vascular beds below the clamp (especially the splanchnic vascular bed).[8] This increased preload may increase cerebral blood volume (CBV) and CSFP and thus decrease SCPP. We hypothesized that phlebotomy would reverse both the hemodynamic consequences and the increase in CSFP associated with thoracic AXC.

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Materials and Methods

This study was approved by the Committee for Animal Experimentation at the University of Manitoba. Eleven mongrel dogs (17.4 ± 2.3 kg; mean ± SEM) were anesthetized with sodium pentobarbital (25 $mg \cdot kg^{-1}$). The trachea was intubated and the animal's lungs ventilated with 100% O_2 to maintain the arterial carbon dioxide tension (Pa_{CO_2}) at 35–40 mmHg. The dog was positioned in a stereotactic head-frame in a modified sphinx position. Bipolar EEG electrodes were placed over the parietal hemispheres bilaterally. The EEG was continuously recorded by an Interspec Medical Neurotrac® EEG monitor. Additional pentobarbital was administered until the EEG became isoelectric. A continuous infusion of sodium thiopental was initiated at 10 $mg \cdot kg^{-1} \cdot h^{-1}$ and titrated to maintain the EEG isoelectric for the duration of the experiment. Body temperature was maintained at 37 ± 1° C by a servo-controlled temperature probe integrated with a heating lamp and pad.

The right femoral artery and vein and right brachial artery were cannulated for hemodynamic measurements and for blood withdrawal. The femoral venous catheter was advanced into the thorax for central venous pressure (CVP) monitoring. The femoral arterial catheter was advanced into the distal aorta to monitor MAP_d. A double-lumen catheter (7.5-Fr) inserted into the brachial artery permitted continuous monitoring of proximal aortic pressure (MAP_p) as well as intermittent blood withdrawal. The superior sagittal sinus (SSS) was exposed by trephine and the posterior one third cannulated nonocclusively by insertion of a 22-G intravenous catheter. Continuous CSFP measurements were recorded by inserting a 22-G spinal needle, by micromanipulator, into the cisterna magna. A left thoracotomy was performed, and the left atrium (LA) exposed and catheterized for radioactive microsphere injection.

All blood pressures and the CSFP were recorded by calibrated Gould P23® transducers referenced at the level of the cisterna magna, except for that of the CVP, which was referenced at the level of the right atrium. Data were recorded on paper by an oscillograph (recorder model 2600S®, Gould) and on hard disk by an IBM PC-AT® computer-based digital acquisition system (Dataq Instruments®). Arterial and SSS blood gases and hemoglobin were measured before and after each microsphere injection by an ABL 300 Acid–Base Laboratory (Radiometer®).

Each animal's vital signs were allowed to stabilize for a minimum of 30 min after invasive procedures were completed. At completion of surgery, heparin 100 $U \cdot kg^{-1}$ was administered intravenously. After the first microsphere injection, the descending aorta was occluded with a vascular clamp, 2.5 cm distal to the left subclavian artery. A second microsphere injection was completed at stable Pa_{CO_2} and anesthetic depth. By controlled phlebotomy, blood was withdrawn from the brachial artery catheter until MAP_p returned to the baseline values seen with the first microsphere injection. Once MAP_p had stabilized, a third microsphere injection was performed. Prior to the fourth microsphere injection, the blood withdrawn was reinfused and the vascular clamp removed from the aorta (mean AXC time 68 ± 6 min). The fourth microsphere injection was performed 2 min after removal of the AXC. No attempt was made to control the anticipated increase in Pa_{CO_2} during this injection.

Approximately 2×10^6 microspheres (15 μm in diameter) were injected into the LA for each flow determination.[9] The randomly selected microspheres were labeled with ^{46}Sc, ^{85}Sr, or ^{141}Ce (3M Company) or ^{95}Nb or ^{113}Sn (New England Nuclear). A Harvard pump withdrew blood (20 ml) from the brachial artery for 240 s, starting 15 s before each microsphere injection.

After a lethal injection of sodium thiopental, a necropsy was completed to ensure proper placement of catheters. Tissue sections from the left and right kidneys were obtained. The entire brain was excised. After removal of the pia mater, the entire brain was sectioned into specific regions (left and right frontal, parietal, occipital cortex, basal ganglia, cerebellum, and brain stem). The entire spinal cord was removed and processed similarly to the brain, and then sectioned into cervical (foramen magnum to first thoracic vertebra), thoracic, and lumbar (first lumbar vertebra to cauda equina) regions. The organ and blood samples were placed in the gamma counter (LKB Compugamma®) after being weighed. Counts per minute were converted to regional blood flow (milliliters per gram per minute) by computer program with the use of standard equations.

Total brain blood flow (tCBF) in milliliters per gram per minute was determined by summing weighted flows to all brain regions and dividing by total brain weight. Cerebral perfusion pressure (CPP) was calculated as MAP_p − mean CSFP; SCPP as MAP_d − mean CSFP; and cerebral metabolic rate for O_2 (CMR_{O_2}) as cerebral hemispheric blood flow × (arterial − SSS O_2 content) in milliliters O_2 per gram per minute.

Time-related changes were evaluated by analysis of variance (ANOVA) for repeated measures. When ANOVA was significant, comparisons were made with the least-squares means test. Bonferroni's correction was applied ($P < 0.05/n$; where n = number of comparisons) when multiple comparisons were made. The corrected P value was considered statistically significant. Data are presented as means ± SEM.

Results

Temperature and arterial blood gas data are shown in table 1. A significant decrease in temperature (0.6° C)

TABLE 1. Temperature and Arterial Blood Gas Data

Variable	Baseline	AXC on	Phlebotomy	AXC off
Temperature (°C)	37.4 ± 0.2	37.2 ± 0.2	37.0 ± 0.3*	36.8 ± 0.2*
Hemoglobin (g/dl)	13.8 ± 0.7	13.7 ± 0.7	14.2 ± 0.8	14.4 ± 0.9
Pa_{CO_2} (mmHg)	39.5 ± 0.5	38.4 ± 0.4	38.8 ± 0.6	55.4 ± 0.4*†
*p*H	7.33 ± 0.01	7.33 ± 0.01	7.26 ± 0.01*†	7.13 ± 0.03*†
Arterial O_2 content (vol %)	20.5 ± 1.1	20.4 ± 1.1	20.9 ± 1.2	21.1 ± 1.3
SSS O_2 content (vol %)	14.7 ± 1.0	15.5 ± 1.0	13.9 ± 1.0	15.9 ± 1.4

n = 11; mean ± SEM.
* $P < 0.05$ *versus* baseline; † $P < 0.05$ *versus* AXC on.
SSS = superior saggital sinus.

occurred from baseline to the third and fourth injection periods. The hemoglobin concentration was stable throughout the experiments. The Pa_{CO_2} was constant for the first three measurement periods but increased significantly for the final measurement with removal of AXC. The arterial *p*H decreased over time for the third and fourth injection periods. The arterial and SSS O_2 contents were stable throughout the experiment. The mean volume of blood withdrawn to restore MAP_p to baseline values after application of the AXC was 24 ± 3 $ml \cdot kg^{-1}$.

The hemodynamic consequences of application of the AXC, phlebotomy, and removal of AXC are shown in table 2. At baseline, MAP_p and MAP_d were similar. With application of the AXC, MAP_p increased and MAP_d decreased. With phlebotomy, MAP_p returned to baseline values. The MAP_d decreased but not significantly. With removal of the AXC, both pressures again equalized, but at a significantly lower pressure than at baseline. With application of the AXC, SCPP decreased significantly. No further decrease in SCPP was seen with phlebotomy, since both MAP_d and CSFP decreased.

The close relationship between CSFP and CVP during the course of the experiment is shown in figure 1. With application of the AXC, both CSFP and CVP increased significantly from baseline. With phlebotomy and the return of MAP_p to baseline values, both CSFP and CVP decreased, by similar magnitudes. With transfusion and removal of the AXC, both pressures increased significantly above those in the preceding time period. Figure 2 shows the relationship of tCBF and CMR_{O_2} over time. With application of the AXC, tCBF was unchanged when MAP_p increased by 50%.

The regional SCBF changes over time are shown in figure 3. The cervical SCBF was unchanged for the first three flow periods. A significant increase in cervical SCBF was seen with removal of the AXC. With application of the AXC, thoracic and lumbar SCBF decreased markedly. No significant decrease in regional flow was seen with phlebotomy; this was consistent with a stable SCPP postphlebotomy. Both MAP_d and CSFP decreased with phlebotomy, and therefore SCPP remained unchanged. With declamping, both thoracic and lumbar SCBFs increased markedly.

Phlebotomy did not cause a further decrease in renal blood flow after AXC. Baseline renal flow was 3.88 ± 0.40 $ml \cdot g^{-1} \cdot min^{-1}$. With application of AXC, renal flow decreased significantly, to 0.92 ± 0.14 $ml \cdot g^{-1} \cdot min^{-1}$. With phlebotomy, renal flow was statistically unchanged from that seen with application of AXC, at 0.48 ± 0.06 $ml \cdot g^{-1} \cdot min^{-1}$. With declamping, flow increased to 3.44 ± 0.38 $ml \cdot g^{-1} \cdot min^{-1}$, a value not significantly different from baseline.

Discussion

For more than 30 yr, investigators have consistently demonstrated an increase in CSFP with thoracic AXC.[5-7] There is agreement that the increase in CSFP places the spinal cord at increased risk for ischemia. To date, the explanations for the increase in CSFP include loss of ce-

TABLE 2. Hemodynamic Data with Aortic Cross-clamping

Variable	Baseline	AXC on	Phlebotomy	AXC off
MAP_p (mmHg)	104 ± 6	156 ± 6*	106 ± 6†	68 ± 8*†
CSFP (mmHg)	3.3 ± 0.7	5.2 ± 0.8*	1.2 ± 1.1†	5.2 ± 0.9*†
CPP (mmHg)	98 ± 7	150 ± 6*	105 ± 5†	68 ± 8*†
MAP_d (mmHg)	98 ± 6	14 ± 1*	7 ± 1*	61 ± 7*†
SCPP (mmHg)	95 ± 6	9 ± 1*	6 ± 1*	56 ± 7*†

n = 11; mean ± SEM.
* $P < 0.05$ *versus* baseline; † $P < 0.05$ *versus* AXC on.
MAP_p = proximal mean arterial pressure; CSFP = cerebrospinal fluid pressure; CPP = cerebral perfusion pressure; MAP_d = distal mean arterial pressure; SCPP = spinal cord perfusion pressure.

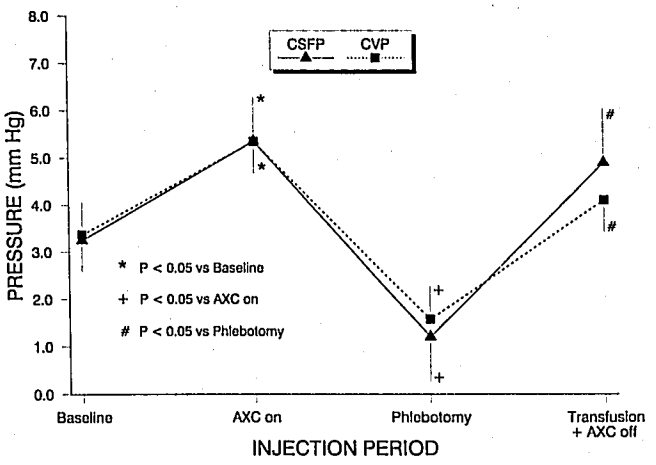

FIG. 1. Relationship between cerebrospinal fluid pressure (CSFP) and central venous pressure (CVP) at baseline, with application of AXC (AXC on), after phlebotomy to reduce proximal MAP to baseline values, and after transfusion and then removal of the AXC (AXC off). Mean ± SEM; n = 11.

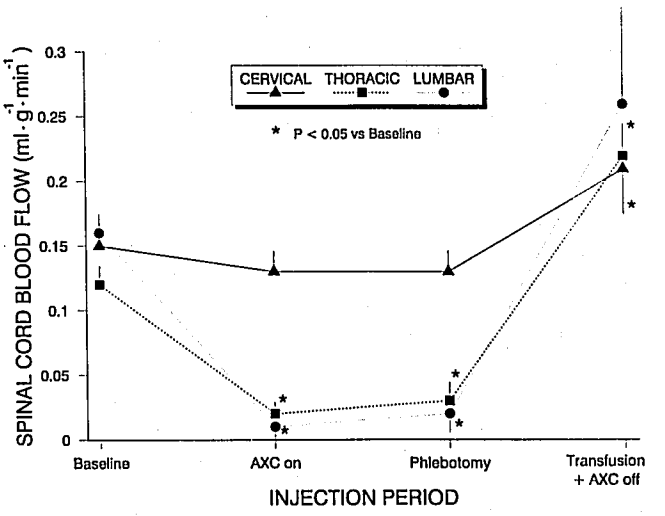

FIG. 3. The relationship between the regional spinal cord blood flows and injection periods described in figure 1.

rebral autoregulation with increased CPP, brain stem reflex, and spinal cord edema with decreased compliance of the neuraxis.[4,5] The relationship between CSFP and cerebral blood flow and SCBF has not been investigated under conditions in which cerebral autoregulation should be intact (*e.g.*, deep barbiturate anesthesia). Moreover, previous investigators have not recognized that CSFP may increase as a result of the increase in cardiac preload, in what is a well-described consequence of thoracic AXC.

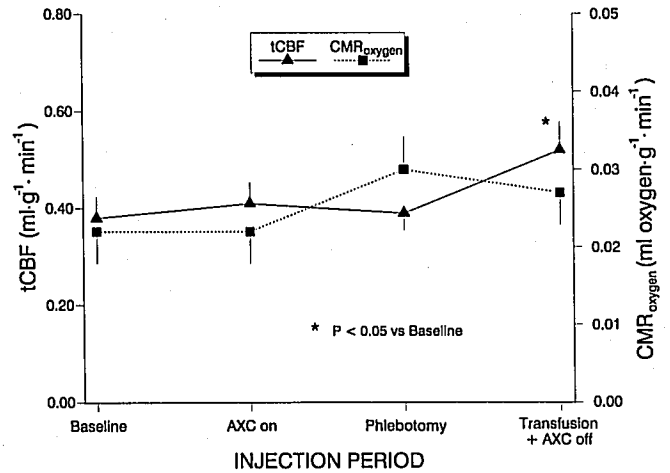

FIG. 2. Relationship between total cerebral blood flow (tCBF) and cerebral metabolic rate for oxygen (CMR_{oxygen}) for the injection periods described in figure 1. The lack of change in tCBF with application of AXC (AXC on) indicates that during deep barbiturate anesthesia, the cerebrovasculature autoregulated when CPP increased with thoracic aortic cross-clamping. A constant CMR_{oxygen} throughout indicates that anesthetic depth (to an isoelectric EEG) was stable. The increase in tCBF with release of the AXC in the presence of unchanged CMR_{oxygen} indicates vasodilation of the cerebral vasculature; presumably a consequence of increased Pa_{CO_2} with release of the cross clamp.

The explanation for the increase in CVP secondary to AXC has been delineated elegantly by Stokland *et al.*[8] They showed that with AXC, preload increased secondary to translocation of blood from the lower body. If the inferior vena cava (IVC) and aorta were clamped simultaneously, no increase in preload or MAP_p was observed. Blood transfused during simultaneous clamping of the aorta and IVC mimicked the effect of AXC alone. The volume of blood required to cause this effect was identical to the volume of blood withdrawn in this study (25 $ml \cdot kg^{-1}$). Thus, in the current study, in dogs with healthy hearts, the increase in afterload secondary to AXC was not the major cause of increased preload.

Further evidence for the importance of increased preload to explain the hemodynamic consequences of thoracic AXC has been provided by the work of Caldini *et al.*[2] If the peripheral circulation is modelled as two compartments with different time constants, AXC removes the compartment with the long time constant (presumably the splanchnic vascular bed) from the peripheral circulation. Blood from this compartment is translocated to the compartment with the short time constant, and thus a paradoxical increase in venous return, increasing right heart filling pressure, is promoted. In addition, an afterload-dependent increase in preload may occur in the clinical situation when AXC causes acute cardiac decompensation in patients with preexisting heart disease.

The parallel relationship between CSFP and CVP seen in the current study indicates a dependent relationship. This relationship has been delineated by Wagner and Traystman.[10] They showed that for venous outflow pressures of greater than −1.0 ± 1.0 mmHg, CSFP increased simultaneously with venous pressure. A rapid increase of CSFP occurs coincident with the increase in CVP after application of the AXC. We suggest that this increase in

CSFP is a consequence of an increase in CBV caused by increased back pressure (elevated CVP) secondary to increased filling of the distensible cerebral venous bed.

Our results indicate that control of proximal aortic hypertension by phlebotomy is not associated with a further decreased in SCPP, since both MAP_d and CSFP decrease by similar amounts. Phlebotomy did not cause a statistically significant decrease in thoracic and lumbar SCBF. Our data (fig. 3) indicate that in the presence of deep barbiturate anesthesia, SCBF below the clamp site was very low (approximately 0.02 $ml \cdot g^{-1} \cdot min^{-1}$ before phlebotomy and thus not likely to change to any significant degree with this intervention).

Management of the hemodynamic consequences of thoracic AXC is fundamentally important for anesthetists managing patients undergoing aortic reconstruction. Standard therapy for management of the proximal aortic hypertension is sodium nitroprusside (SNP) infusion.[1] However, experiments in dogs suggest that because of its cerebral vasodilatory effects, SNP infused to control proximal hypertension after AXC may worsen neurologic outcome. In dogs, when SNP was infused to control proximal hypertension after AXC, regional CBF increased 2.5-fold.[11] Marini *et al.* demonstrated that control of proximal hypertension with SNP increased CSFP 100%.[12] These results suggest that SNP markedly decreases inflow resistance to the brain but has only limited impact on outflow resistance, and thereby increases CBV and CSFP. Both of these studies demonstrated significant decreases in MAP_d with SNP infusion. Thus, with AXC, SNP decreases MAP_d and simultaneously elevates CSFP, and thereby decreases SCPP. This combination of effects on SCPP may place the spinal cord at increased risk of ischemia.

Recent experiments have focused on manipulating SCPP to maximize SCBF during AXC.[5,6] Drainage of CSF has been advocated to decrease CSFP and thereby increase SCPP. This intervention counteracts the increase in CSFP seen with AXC. After CSF drainage (usually to a negative CSFP), the SCPP is usually still calculated as MAP_d − CSFP. This apparent increase in SCPP may, in part, be factitious, because under such circumstances CVP must be the real outflow pressure. Studies in dogs demonstrate only a 10% incidence of paraplegia with AXC of 40 min when CSF drainage was undertaken prior to AXC, as compared to a 100% incidence without drainage. When the AXC was applied for 60 min, the corresponding results were 30% *versus* 100%.[6]

In a clinical trial of 24 patients, CSF drainage caused no complications, and no patient developed paraplegia.[6] However, lumbar CSF drainage is not without risks. The major risk is iatrogenic local hemorrhage with lumbar puncture. After systemic heparinization, further bleeding may occur and result in intrathecal or epidural hematoma, and thereby increase the risk of paraplegia or adhesive arachnoiditis. Concern about the possible complications of CSF drainage has prevented this treatment from gaining wide acceptance.

In conclusion, this study indicates that proximal aortic hypertension, increased CVP, and increased CSFP after thoracic AXC all were controlled by phlebotomy. The increase in CSFP with thoracic AXC is correlated closely to the increase in CVP. Thus, phlebotomy to manage the preload increase seen with thoracic AXC may provide an alternate means to control the hemodynamic consequences of thoracic AXC without compromise of SCPP.

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