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ORIGINAL ARTICLE

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Improvement in perioperative care in pediatric cardiac surgery by shifting the primary focus of treatment from cardiac output to perfusion pressure: Are beta stimulants still needed?

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Abstract

Objective: An important aspect of perioperative care in pediatric cardiac surgery is maintenance of optimal hemodynamic status using vasoactive/inotropic agents. Conventionally, this has focused on maintenance of cardiac output rather than perfusion pressure. However, this approach has been abandoned in our center in favor of one focusing primarily on perfusion pressure, which is presented here and compared to the conventional approach.

Design: A retrospective study.

Setting: Regional center for congenital heart disease. University Hospital of Lausanne, Switzerland.

Patients: All patients with Aristotle risk score $\geq$8 that underwent surgery from 1996 to 2012 were included. Patients operated between 1996 and 2005 (Group 1: 206 patients) were treated according to the conventional approach. Patients operated between 2006 and 2012 (Group 2: 217 patients) were treated according to our new approach.

Interventions: All patients had undergone surgery for correction or palliation of congenital cardiac defects.

Outcome measurements: Mortality, duration of ventilation and inotropic treatment, use of ECMO, and complications of poor peripheral perfusion (need for hemofiltration, laparotomy for enterocolitis, amputation).

Results: The two groups were similar in age and complexity. Mortality was lower in group 2 (7.3% in group 1 vs 1.4% in group 2, $P < .005$). Ventilation times (hours) and number of days on inotropic/vasoactive treatment (all agents), expressed as median and interquartile range [Q1–Q3] were shorter in group 2: 69 [24–163] hours in group 1 vs 35 [22–120] hours in group 2 ($P < .01$) for ventilation, and 9 [3–5] days in group 1 vs 7 [2–5] days in group 2 ($P < .05$) for inotropic/vasoactive agents. There were no differences in ECMO usage or complications of peripheral perfusion.

Conclusions: Results in pediatric cardiac surgery may be improved by shifting the primary focus of perioperative care from cardiac output to perfusion pressure.

KEYWORDS

diastolic pressure, norepinephrine, intensive care, pediatric cardiac surgery, perfusion pressure, perioperative care

1 | INTRODUCTION

Perioperative care in pediatric cardiac surgery has many facets. One of the crucial facets is the maintenance of optimal hemodynamic status using various vasoactive and inotropic agents. Conventionally, this has focused primarily on maintenance of adequate cardiac output rather than perfusion pressure.[1–9] However, this approach has been abandoned in our center in favor of one focusing primarily on perfusion pressure. This new approach is presented here and compared to the conventional one.

2 | MATERIALS AND METHODS

This study was approved by our institutional review board (Ethics' committee of the University Hospital of Lausanne, Switzerland), which agreed that no informed consent from patients or their relatives was required. All authors had full access to all data included in this study, and take responsibility for its integrity.

2.1 | Our conventional approach

A conventional approach, focusing on maintenance of cardiac output, was used in our center for many years. Cardiac output was maintained by optimizing its three major contributing factors—preload, cardiac function, and afterload reduction. Cardiac function, in turn, was optimized by three measures: (1) stimulating/supporting systole (contractility) with beta stimulants and by maintaining adequate serum concentrations of ionized calcium, (2) prevention of arrhythmias by maintaining adequate levels of potassium and magnesium, and (3) facilitating diastole (relaxation) with lusitropic agents.

In terms of beta stimulation, dopamine ± dobutamine were used as first-choice agents at dosages of 5–10 μg/kg/min each. If this proved insufficient for maintenance of cardiovascular stability, epinephrine was added, usually starting at dosages of 0.1–0.2 μg/kg/min. Isoproterenol was also used on occasion, especially if acceleration of heart rate was desired. Dobutamine and isoproterenol are also potent vasodilators, thus also generating afterload reduction.

Serum concentrations of ionized calcium were maintained slightly high: 1.3–1.4 mmol/L. This was achieved with the administration of intravenous boluses of calcium chloride in the operating room after termination of cardiopulmonary bypass and as routine three-times-daily boluses on the ICU. On rare occasions, a continuous infusion was used instead, especially in small babies who particularly benefit from calcium. Likewise, magnesium chloride boluses were administered three times a day aiming to maintain serum concentrations no less than 0.7 mmol/L. This treatment with both calcium and magnesium was continued until patients started eating. Potassium levels were maintained no lower than 4.0 mmol/L.

In terms of lusitropy, on the other hand, all patients received milrinone (or amrinone early in our experience) at a dose of 0.75 μg/kg/min, with a starting loading dose of 50 μg/kg administered on cardiopulmonary bypass after removal of the aortic cross-clamp. These agents are also vasodilators. Therefore, they also fulfill the function of afterload reduction. Milrinone, in particular, has been found to significantly improve results in pediatric cardiac surgery.[10]

Conversely, norepinephrine was used much less frequently, since it is a strong vasoconstrictor and a weak beta stimulant. It was certainly never used as first-choice agent. This agent was used as a last resource in cases of refractory vasoplegia in patients that were already on high doses of other inotropic agents.

This treatment regime was adjusted in situations where cardiac dysfunction was thought to be mainly diastolic, and also in cases of valvar dysfunction. In diastolic dysfunction, the adjustment was in using less beta stimulants and relying more on a lusitropic agent. Using less beta stimulants results in less tachycardia as well, which is also beneficial in diastolic dysfunction. Tachycardia should also be avoided in cases of valvar stenosis. In valvar regurgitation, however, a degree of tachycardia may be allowed in conjunction with inotropic support and afterload reduction; all three actions may be generated with dobutamine or isoproterenol.

This treatment was monitored, and dosages adjusted, according to markers of adequate cardiac output—urine output, serum lactate levels, and mixed venous saturations.

2.2 | Our new approach

Our new approach shares most components of the conventional approach, including maintenance of adequate preload, cardiac function and afterload reduction, and monitoring the same indices of adequacy of cardiac output. However, it differs in two important respects: (1) in the form of optimizing cardiac function and (2) in the management of afterload reduction.

With respect to optimizing cardiac function, the new approach gives more weight to diastole than systole. To this effect, it minimizes beta stimulation while relying on lusitropic agents. In other words, it does what the conventional approach indicates for diastolic dysfunction, except that it does this in every case.

With respect to afterload reduction, this is usually achieved with the vasodilatory effect of lusitropic agents, and also low-dose

dopamine (too low for beta stimulation, but sufficient for DA1 receptor stimulation with possibly associated renal and gastrointestinal protection), although more potent vasodilators may be added if needed. However, independently of which vasodilator is used, the effect is closely monitored so that perfusion pressure (defined as mean arterial pressure minus central venous pressure) and specifically diastolic pressure are not compromised. These two pressures are maintained no lower than:

- 35 mm Hg in premature neonates
- 40 mm Hg in neonates born at term
- 50 mm Hg in infants and young children
- 60 mm Hg in older children and adolescents

Although these pressures are slightly higher than those seen in health, they are helpful postoperatively in order to secure tissue perfusion in the face of the inevitable generalized edema caused by cardiopulmonary bypass.

With the above differences and criteria in mind, the new mode of treatment may be presented as follows:

1. Dobutamine and isoproterenol have been abandoned completely.
2. The use of epinephrine has been reduced dramatically. It is used in only two circumstances: (1) as boluses during the management of cardiac arrest, (2) preoperatively in patients in severe cardiogenic shock, while preparations are being made for urgent surgery and/or to establish mechanical circulatory support.
3. Calcium, magnesium, and potassium levels are maintained in exactly the same way, and with the same target serum concentrations, as in the conventional approach described above.
4. All patients receive a low but fixed dose of dopamine at 3 μg/kg/min.
5. All patients also receive milrinone at 0.75 μg/kg/min after a loading dose of 50 μg/kg on cardiopulmonary bypass after removal of the aortic cross-clamp, as in the conventional approach.
6. A stronger vasodilator than milrinone and low-dose dopamine may be added to the treatment if afterload remains too high, that is, if blood pressure remains too high, especially if pulse pressure is low. In such cases, we use sodium nitroprusside, the dose of which is titrated to reduce blood pressure down to the above-mentioned target levels, but no lower. If pressures drop below these levels, this agent is stopped, but milrinone and dopamine are maintained at the above-mentioned infusion rates.
7. If perfusion pressure and/or diastolic pressure are lower than the target levels, norepinephrine is administered (again, without stopping milrinone and low-dose dopamine) provided this does not violate our bedside safety criterion for vasoconstriction (see below). The dose of norepinephrine is titrated to achieve the target pressures. The commonest doses used are 0.1–0.4 μg/kg/min, but much higher doses are also used occasionally. Conversely, in cases where pressures do not drop below the target levels, this agent would not be needed at all.

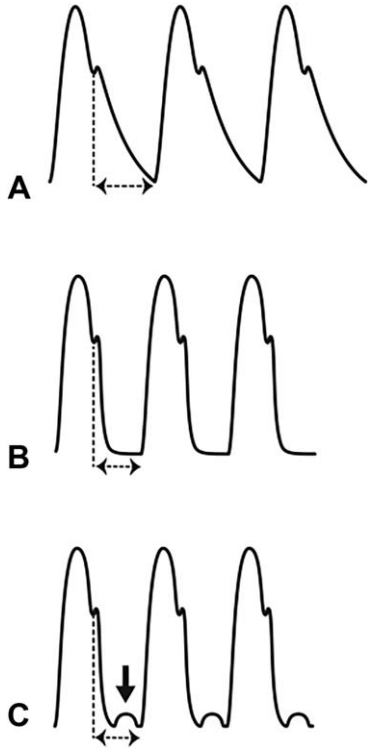

FIGURE 1 Arterial pressure curves illustrating how these may be used to verify the presence of forward flow during diastole. The dotted double-headed arrow indicates the diastolic phase. A. The diastolic phase has a slope (it is not flat). This indicates that there is diastolic forward flow, the amount of which is represented by the area under the diastolic curve (delineated by the horizontal dotted arrow and the vertical dotted line). In such circumstances, norepinephrine may be used safely, even at high doses. B. The diastolic phase is flat, indicating that there is little or no forward flow during diastole. This is typically seen in hypovolemia and is a warning sign that norepinephrine should not be used. C. If norepinephrine is used when the diastolic curve is flat, it may worsen the hemodynamic situation by causing some retrograde diastolic flow. This is seen as a small upstroke (shown by the solid black arrow) on the diastolic curve

8. Norepinephrine will have no effect in the very rare instances where patients have been taking phenoxybenzamine (as treatment of pulmonary hypertension). In such patients, norepinephrine is substituted with vasopressin.

2.3 | Our safety criterion for vasoconstriction

Vasoconstriction, regardless of whether this is with norepinephrine or vasopressin, would be unsafe in two circumstances: (1) when forward flow during diastole is compromised, (2) in the presence of aortopulmonary collateral arteries and/or surgical shunts.

Diastolic forward flow may be checked by arterial waveform analysis—specifically looking at the shape of the diastolic phase of the arterial pressure curve. Arterial waveform analysis should, however, be regarded as only a guide rather than a hard and fast rule, since it is subject to inaccuracies, for example, due to damping. Nevertheless, with

such limitations in mind, a diastolic pressure curve that has a slope (i.e., is not flat) indicates that forward flow is maintained during diastole, the amount of which is represented by the area under that part of the curve (Figure 1A). Therefore, norepinephrine may be used safely, even at high doses, in the absence of aortopulmonary collateral arteries or surgical shunts.

Conversely, a flat diastolic curve (Figure 1B) indicates that there is little forward flow during diastole and that norepinephrine should not be used. This is typically seen in hypovolemia requiring volume administration. Volume administration restores the slope of the diastolic pressure curve, and norepinephrine may then be used if needed. If norepinephrine is administered in the presence of a flat diastolic pressure curve, the hemodynamic situation is worsened such that there may be an element of retrograde blood flow during diastole. This will be manifested as a small upstroke on the diastolic pressure curve (Figure 1C). Norepinephrine, however, also provides venoconstriction and thus may potentiate preload until normovolemia is fully restored. Therefore, it may be useful in conjunction with volume replacement.

A flat diastolic pressure curve may also be seen when there is an important steal from the aorta, namely in severe aortic valvar regurgitation, and this would also contraindicate vasoconstriction. But this situation would be unusual after corrective surgery.

Other sources of aortic steal, namely aortopulmonary collateral arteries and surgical shunts, deserve a special mention. These conditions do not usually result in a flat diastolic curve, since the steal is not usually severe enough. In this respect, therefore, they allow vasoconstriction if needed. However, they also do require careful balancing of pulmonary and systemic circulations (Qp/Qs) within narrow limits. This balance may be disturbed by vasoconstriction, which may augment aortic steal and cause excessive pulmonary blood flow (i.e., augment Qp/Qs). Precisely for this reason, such cases particularly benefit from afterload reduction. Overall, any manipulation of vascular tone in these circumstances, both vasodilatation and vasoconstriction, must be titrated cautiously so that the pursuit of target pressures does not shift Qp/Qs outside acceptable limits of balance.

2.4 | Patient groups

Data from all patients operated in our center from 1996 to 2012 were examined. Throughout this period, the surgical team and principal anesthesiologist and intensive care specialist remained the same, as did the protocols of conduct of cardiopulmonary bypass and myocardial protection.

Although the full spectrum of operations for congenital heart disease are carried out in our center, only patients that had undergone operations with moderate or high risk were included in this study. Surgical risk was assessed according to the Aristotle score.[11] An Aristotle score of 8 was arbitrarily chosen as the cut-off point; only patients with a score of 8 or more were included in this study. These represent approximately one-third of our total workload.

Patients with an Aristotle score of 8 or more were divided into two groups. Group 1 consists of patients operated between 1996 and 2005 when our conventional perioperative approach was used. Group 2 consists of patients operated between 2006 and 2012 when the new approach was used. The two groups were compared with respect to:

- Hospital mortality.
- Ventilation times (via endotracheal tube, that is, not counting noninvasive ventilation).
- The duration of treatment with inotropic and/or vasoactive agents.
- Use of ECMO.
- Complications of low peripheral perfusion: Necessity of hemofiltration, laparotomy for enterocolitis, and amputation.

2.5 | Statistical analysis

Quantitative data are expressed as median and interquartile range [Q1–Q3]. Qualitative data are expressed as percentages. The one-sample Kolmogorov-Smirnov test showed that the distribution of data was not normal. Therefore, the statistical significance of differences between the two groups was assessed by the Mann-Whitney *U* test for quantitative data and Chi square test for qualitative data. These tests were carried out with PASW 18. Differences were considered significant at $P < .05$.

3 | RESULTS

Our findings are presented in Table 1. In summary, the two groups are comparable with respect to age and case complexity. However, our new approach (group 2) is associated with significantly lower mortality, ventilation times and duration of treatment with inotropic/vasoactive agents. On the other hand, there were no statistically significant differences with respect to the use of ECMO or the complications of poor peripheral perfusion (hemofiltration, laparotomy for enterocolitis, and amputation).

There was one case of lower limb amputation in group 1. This was a three-year-old boy with tetralogy of Fallot that was surgically corrected in 1997. He suffered from thrombosis of his femoral artery, possibly caused by a femoral arterial catheter.

4 | DISCUSSION

Pediatric cardiac surgery and its perioperative care have developed so much that good results are the norm. Nevertheless, results may be further improved by shifting the primary focus of perioperative care from cardiac output to perfusion pressure.

Conventionally, perioperative care in pediatric cardiac surgery has been based on the concept that what really matters is cardiac output rather than perfusion pressure. This is reflected in the publications on this subject, which describe strategies for optimizing stroke volume and cardiac output while blood pressure is hardly ever mentioned.[1–9] Accordingly, the conventional approach puts strong emphasis on enhancement of systole, since this is a potent way of increasing cardiac output. However, this clashes with

TABLE 1 Patient characteristics and perioperative and postoperative data

Variables examined	Group 1	Group 2	*P* value
Number of patients	206 (including 29 neonates)	217 (including 23 neonates)	
Age (years)	3 [0.6–7]	3.5 [0.9–6]	NS
Aristotle score	9 [8–10] Full range: 8 - 14.5	9 [8–10.3] Full range: 8 - 14.5	NS
Bypass times (minutes)	122 [99–157]	128 [103–160]	NS
Mortality	15 cases (7.3%)	3 cases (1.4%)	<.005
Ventilation times (hours)	69 [24–163]	35 [22–120]	<.01
Inotropic (all agents) times (days)	9 [3–5]	7 [2–5]	<.05
Use of ECMO	8 cases (3.9%)	5 cases (2.3%)	NS
Use of hemofiltration	4 cases (1.9%)	1 case (0.46%)	NS
Limb amputation	1 case (0.5%)	0	NS
Laparotomy for enterocolitis	1 case (0.5%)	0	NS

Results are expressed as percentages or medians and interquartile range [Q1–Q3]. Where a difference between the two groups is not statistically significant, this is reported as NS

developments in our understanding of cardiac physiology in the last two decades whereby we have realized the dominant role of diastole in cardiac function and dysfunction. This major paradigm shift is explained in several exhaustive review articles.[12–21] In broad terms, however, it may be summarized very briefly in terms of the energetics of the cardiac cycle.

The cardiac cycle is governed by the actin–myosin cross-bridge cycle, which depends on calcium fluxes into and out of the cytosol. Calcium entry into the cytosol (during the plateau phase of the action potential in systole) does not require energy. Its exit during diastole, however, consumes a great deal of energy (ATPase pump activity) and is a slower process. This makes relaxation a slow process, thus maintaining some tone throughout diastole that resists over-distension in response to filling, that is, some cross-bridging takes place at all times. These features make relaxation a very active process to the extent that diastole consumes much more energy, and is much more vulnerable, than systole. Diastole suffers more and earlier at times of low energy availability (hypoxia and/or ischemia). In addition, diastolic dysfunction eventually leads to systolic dysfunction. This is because, if the heart does not fill well, myocytes will not reach optimal length prior to systole, and will contract less well (Starling's law). Nevertheless, diastole is the limiting factor in cardiac function—one can have diastolic dysfunction without systolic dysfunction, but not vice versa. By the time systolic dysfunction begins to appear, diastolic dysfunction is already well established.

This crucial and pivotal role of diastole had remained hidden for a long time probably because, unlike systolic dysfunction, diastolic dysfunction is difficult to detect and quantify. Nevertheless, it does suggest strongly that cardiac care should focus primarily on diastole.

The conventional approach does provide diastolic care with lusitropic agents. But it also boosts systole substantially with beta stimulation and afterload reduction. This is the problem with focusing on cardiac output—it forces you to enhance systole. In doing so, the conventional approach acquires the following drawbacks:

1. It jeopardizes myocardial perfusion by reducing both diastolic pressure (consequence of afterload reduction) and diastolic time (due to tachycardia caused by beta stimulation, which also harms diastole).
2. It further discriminates against myocardial perfusion since the enhanced blood flow generated by this strategy is mainly systolic, being driven by beta stimulation. This contributes little to myocardial perfusion, which is mainly a diastolic phenomenon, even in the right ventricle if hypertrophied.
3. Beta stimulation increases the metabolic demand of the myocardium significantly.[5,6] Thus the heart would require much more coronary blood flow than usual, which it may not receive since this is already compromised.
4. Beta stimulation also increases the metabolic demand of the rest of the body. Therefore, the already-struggling heart has to work even harder to cater to this.

Overall, the conventional approach secures tissue perfusion (cardiac output) at the heart's expense. It forces the heart to serve the rest of the body when the heart itself is recovering from major surgery and needs care. This is a fundamental flaw. It led us to adopt an alternative approach that gives at least equal priority to the heart (specifically diastole). This was implemented with the following considerations:

1. Unlike for systolic dysfunction, there are not many ways of treating diastolic dysfunction, other than lusitropic agents, which should remain in place.
2. Apart from this, we can help the heart in only two ways: (1) By securing good myocardial perfusion, (2) By minimizing factors that would increase its metabolic demand and that of the rest of the body, that is, avoiding beta stimulation.

3. To secure myocardial perfusion, we must maintain adequate perfusion pressure (and specifically diastolic pressure) and diastolic time, that is, avoid excessive afterload reduction and tachycardia.
4. Adequate perfusion pressure also favors peripheral tissue perfusion, both directly and by improving systemic venous return (i.e., preload), which improves cardiac output.[22]
5. Afterload reduction may be achieved with the vasodilatory effect of lusitropic agents and low-dose dopamine, or more potent vasodilators may be added. However, the effect must not be such that diastolic and perfusion pressures drop below the levels required for adequate tissue (including coronary) perfusion. If this happens, the dose must be reduced, or the agent stopped altogether. If the vasodilator being used should continue because of its other benefits (lusitropic agents), norepinephrine should be added to rectify pressures. The overall management is a balance between vasodilatation and vasoconstriction, being guided by diastolic and perfusion pressures.

This is why we abandoned dobutamine and isoproterenol—both are potent vasodilators and beta stimulants, and cause tachycardia. This is also why calcium chloride is used for contractility; it does not increase the metabolic demand of the whole body and does not cause tachycardia.

Such focus on perfusion pressure, and its consequent liberal use of norepinephrine, although unusual in pediatric cardiac surgery, is not new to adult intensive care where it is greatly appreciated, including in cardiac surgery in some centers. In fact, norepinephrine is now often the first choice agent in the treatment of critically ill adults. This started with the treatment of septic shock,[23] but later extended to other areas including hepatorenal syndrome[24] and even cardiogenic shock.[25–29] Interestingly, these clinical scenarios are extreme forms of the same pathophysiology seen after cardiac surgery with cardiopulmonary bypass. The similarity with cardiogenic shock is obvious, but septic shock is just as close an analogy. Indeed, the pathophysiology inflicted by cardiopulmonary bypass is practically indistinguishable from that of septic shock, including myocardial dysfunction found in both scenarios in response to inflammatory mediators.[30,31]

Norepinephrine may raise two concerns: First, that it may jeopardize peripheral perfusion, and that some organs may be sensitive to this—limbs, brain, kidneys,[32] and the gastrointestinal system.[33,34] Second, that its advantage of assisting myocardial perfusion may be undermined and outweighed by increasing afterload thus harming cardiac function. With respect to the first concern, peripheral perfusion is not ignored by our new approach; on the contrary, it is supported with adequate perfusion pressure and moderated afterload reduction. This is reflected in our results with respect to peripheral perfusion, which are favorable. Furthermore, peripheral perfusion has not been an issue in any of the above-mentioned publications on the use of norepinephrine.[22–28] In addition, gastrointestinal mucosal perfusion seems unaffected by norepinephrine after cardiac surgery in adults.[35] Likewise, cerebral oxygen saturation seems unaffected by this agent during cardiopulmonary bypass in adults.[36] With respect to the second concern, vasoconstriction is enforced only to the extent of achieving minimum acceptable physiological perfusion pressures, that is, the infusion rate of norepinephrine is meticulously adjusted and calibrated, using syringe drivers that allow adjustments of 0.1 mL/h, to achieve precisely those pressures and no more. This does not generate anywhere near enough afterload to harm cardiac function.[18,37]

This study excluded patients operated prior to 1996 and after 2012 in order to eliminate several confounding factors, especially in making sure the principal care team members and protocols of cardiopulmonary bypass and myocardial protection remained the same throughout the study period (these changed at these two dates). In addition, prior to 1996, our unit was improved in several ways: (1) the introduction of nitric oxide and ECMO, (2) optimizing the nutritional protocol,[38] and (3) improving the sedation protocol, especially with respect to midazolam, which has potent negative cardiovascular effects.[39] Indeed, the dose of midazolam was significantly reduced to 0.04–0.12 mg/kg/h. If this proves insufficient, clonidine is added. After 2012, on the other hand, apart from the surgical team changing, milrinone was replaced with levosimendan in some high-risk cases.

This study has important limitations. It is retrospective, nonrandomized, and its control group is historical. Although we took all measures that we could to guard against the impact of era on results, we cannot eliminate this possibility. Another limitation is that its endpoints are crude (mortality, ventilation times, etc.). This is always a problem with retrospective studies where choice is limited—finer endpoints such as mixed venous saturations, lactate levels, and cerebral saturations were not available consistently. We are tempted to state that cerebral saturations do not drop as monitored by near-infrared spectroscopy, but this tool was not available early in our experience, nor is it clear that this is the best neuromonitoring method.[40]

5 | CONCLUSIONS

Despite the above-mentioned limitations, focus on perfusion pressure does appear to produce excellent results. This is reflected in a significantly reduced mortality without additional complications related to vasoconstriction, bearing in mind that vasoconstriction is carefully titrated and limited to physiological parameters. This has been our standard and exclusive approach since 2006.

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CONFLICT OF INTEREST

None.

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