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ORIGINAL RESEARCH

The Impact of Hyponatremia in Aortic Valve Surgery Using Histidine–Tryptophan–Ketoglutarate Cardioplegia

Claudiu Ghiragosian[1,2], Dragos-Florin Baba[3*], Marius Harpa[1,2], Alexandra Puscas[1], Radu Balau[1,2], Hussam Al Hussein[2,4], Simina Elena Ghiragosian-Rusu[5], Calin Avram[6], Radu Mircea Neagoe[7], Horatiu Suciu[1,2]

[1] Department of Surgery IV, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania
[2] Cardiovascular Surgery Department, Emergency Institute for Cardiovascular Disease and Transplantation, Tîrgu Mureș, Romania
[3] Department of Cell and Molecular Biology, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania
[4] Department of Anatomy-Embriology M1, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania
[5] Department of Pediatrics III, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania
[6] Department of Medical Informatics and Biostatistics, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania
[7] Department of Surgery II, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology, Tîrgu Mureș, Romania

ABSTRACT

Background: Histidine–tryptophan–ketoglutarate (HTK) cardioplegia is one of the most widely used methods of cardioplegia. This solution is hyponatremic compared to blood, and the rapid infusion of a substantial volume of hyponatremic solution will result in a notable reduction in serum natrium (Na) levels. The aim of this study was to analyze changes in serum Na concentration following HTK cardioplegia infusion in aortic valve surgery, and to investigate the association between hyponatremia and postoperative outcomes in patients who underwent aortic valve replacement surgery. **Materials and Methods:** This retrospective study involved 302 patients who underwent aortic valve replacement surgery between June 2023 and June 2024 at the Emergency Institute for Cardiovascular Diseases and Transplantation, Tîrgu Mureș, Romania. Based on their preoperative serum Na levels, the patients were divided into a low Na group (Na < 136 mEq/l) and a normal/high Na group (Na ≥136 mEq/l). Outcomes measured were operative short-term mortality, as well as in-hospital postoperative complications such as neurological impairment, surgical reintervention, new onset atrial fibrillation (AFib), and sustained ventricular fibrillation (VF) or ventricular tachycardia (VT). **Results:** Before surgery, the mean Na concentration was 134.0 ± 1.3 mmol/l in the low Na group and 140.5 ± 3.2 mmol/l in the normal/high Na group. After surgery, the mean Na concentration decreased to 134.5 ± 3.4 mmol/l in the low Na group and to 135.5 ± 8.1 mmol/l in the normal/high Na group. Logistic regression analysis of the outcomes showed a significant association between low preoperative Na concentrations and surgical reintervention for hemorrhagic cause, being a risk factor (OR = 3.65; 95%CI 1.18–11.34; p = 0.025). The 7-day mortality was 7.6% in the low Na group vs. 1.1% in the normal/high Na

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group, and 30-day mortality was 10.9% in the low Na group vs. 1.6% in the normal/high Na group. We found a significant association between low preoperative Na levels and 7-day mortality (OR = 7.40; 95% CI 1.57–34.90; p = 0.011), as well as low preoperative Na levels and 30-day mortality (OR =7.36; 95% CI 2.05–26.42; p = 0.002). **Conclusions:** Our findings suggest that the occurrence of complications is primarily associated with preoperative rather than postoperative hyponatremia, even when there are minor deviations from the normal range.

Keywords: perioperative hyponatremia, histidine–tryptophan–ketoglutarate cardioplegia, aortic valve surgery

CORRESPONDENCE

Dragos-Florin Baba
Str. Gheorghe Marinescu nr. 38
540139 Târgu Mureș, Romania
Tel: +40 265 215 551
Email: dragos-florin.baba@umfst.ro

INTRODUCTION

Histidine–tryptophan–ketoglutarate (HTK) or Bretschneider cardioplegia is one of the most widely used methods of cardioplegia owing to its capacity to provide prolonged cardioprotection with a single administration. This solution is hyponatremic compared to blood (15 mmol/l vs. 135–145 mmol/l), and the recommended administration dose is 20 ml/kg within 6–8 min. Consequently, the rapid infusion of a substantial volume of hyponatremic solution will result in a notable reduction in serum natrium (Na) levels. The management of cardiac surgical cases presents a significant challenge in the context of electrolyte imbalances. Serum Na is one of the main electrolytes of concern because of the significant adverse effects associated with its imbalance. It is crucial to consider the timing of hyponatremia and the rapidity of its onset. In severe cases, rapidly induced hyponatremia will precipitate cellular swelling, with significant ramifications, especially for the central nervous system (e.g., cerebral edema, demyelination syndrome) and an increased risk of postoperative mortality.[1,2] Hyponatremia that has developed insidiously is often better tolerated, and it can also be an indicator of heart failure. Hyponatremia after cardiac surgery is typically the result of hemodilution caused by cardioplegia and priming of the cardiopulmonary bypass circuit. Conversely, hypernatremia is less prevalent. In the preoperative period, it is often indicative of renal or hepatic pathology, whereas in the postoperative period, it may result from the administration of hypertonic solutions and renal-free water loss due to diuretic use.

The cardiac biochemical processes involved in cardioplegia have been intensively studied over time, yet the systemic effects of these agents have been largely overlooked.[3] There is currently no consensus on the management of hyponatremia secondary to cardiac surgery. In particular, the tolerance limits of serum Na concentration remain unknown, as well as what the potential risk-to-benefit ratio is for correcting hyponatremia in its mild-to-moderate forms.

The aim of this retrospective study was to analyze changes in serum Na concentration following Bretschneider cardioplegia infusion in aortic valve surgery, and to investigate the association between hyponatremia and postoperative outcomes in a group of patients who underwent aortic valve replacement (AVR) between June 2023 and June 2024 at the Emergency Institute for Cardiovascular Diseases and Transplantation of Tîrgu Mureș, Romania. Additionally, we seek to determine whether perioperative hyponatremia necessitates urgent corrective action.

MATERIALS AND METHODS

The study included adult patients who had undergone elective surgery for AVR (regardless of prosthesis type), with valvular stenosis or insufficiency, whether congenital or acquired. The exclusion criteria were as follows: concomitant procedures, age under 18 years, retrograde or combined cardioplegia, and emergency surgery. Demographic data included age, sex, and comorbidities. The patients were divided into two groups according to their preoperative serum Na levels: the first group comprised patients with low Na levels (<136 mEq/l), and the second consisted of subjects with normal or elevated Na levels (≥136 mEq/l).

Data collection involved the sampling of blood from all patients at two key time points: before anesthetic induction (T1) and at the time of admission to the intensive care unit (ICU) (T2). Left ventricular ejection fraction (LVEF) and transvalvular gradient were calculated and recorded using transthoracic echocardiography 1 day before and on day 7 after surgery. The echocardiographic data included in the study were documented by a single cardiologist.

Outcomes measured were operative short-term mortality, as well as in-hospital postoperative complications such as neurological impairment, surgical reintervention, new onset atrial fibrillation (AFib), and sustained ventricular fibrillation (VF) or ventricular tachycardia (VT). Postoperative evolution markers, such as duration of mechanical ventilation and need for inotropic support, echocardiographic measurements (LVEF, transvalvular gradient) and blood tests (pH, lactate) were compared between the two groups.

The cardioplegia solution, developed by Bretschneider, was employed as a crystalloid substitute with antegrade administration at a temperature of 4 °C, as previously described by Bretschneider *et al.*, with re-administration at 90 min during aortic cross-clamping. The cardioplegia solution was infused in accordance with the manufacturer's recommendations.

DEFINITIONS

Operative death was defined as any death occurring within 30 days of the surgical intervention or up to the time of discharge. Neurological dysfunction was defined as a symptomatic transient psychotic syndrome, stroke, or coma that is non-pharmacologically induced. All cases of new-onset postoperative AFib, VT, and VF were included in the study. The study focused on arrhythmias that had developed subsequent to the patient's admission to the ICU. Additionally, the cases of re-exploration for hemostasis were recorded, which refers to repeated intervention for cardiac tamponade or bleeding from the time of ICU admission until discharge. Furthermore, hemorrhagic events secondary to subsequent medical procedures, such as the suppression of chest tubes or temporary pacemaker wires, were excluded from the study.

ETHICS APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Emergency Institute for Cardiovascular Disease and Transplantation of Tîrgu Mureș (protocol code 3240/15.04.2024) and by the Ethics Committee of the "George Emil Palade" University of Medicine, Pharmacy, Science and Technology of Tîrgu Mureș (approval no. 3103/29.04.2024).

STATISTICAL ANALYSIS

Data analysis was performed with MedCalc v.19 (MedCalc Software). We determined mean values, s.d., medians, and 95% confidence intervals (CIs). The normal distribution of the data was assessed using the Shapiro–Wilk test. Parametric values were compared using Student's t-test and nonparametric data with the Mann–Whitney U-test. Categorical variables were compared using the chi-squared test. We established the optimal cut-off levels for preoperative Na blood concentration for 7-day and 30-day mortality, using receiver operating characteristic (ROC) curves and maximum Youden's index. We also calculated the odds ratios (OR) between the preoperative Na cut-off and mortality. Associations between preoperative Na levels and complications, such as surgical reintervention caused by postoperative hemorrhage, new AFib, intraoperative VT/VF, and postoperative neurological impairment, were determined using logistic regression. The significance threshold was set at 0.05.

RESULTS

From our total cohort of 302 patients, 36.3% (110 out of 302) were female, the majority of them being in the age group of 61–70 years (46.0%; 139 out of 302 patients). Regarding comorbidities, 119 patients (39.3%) were diagnosed with dyslipidemia, 60 patients (19.8%) with obesity, 69 (22.8%) with diabetes mellitus, and 218 (71.9%) with arterial hypertension. The mean preoperative LVEF was 52.1 ± 8.0%, the mean diameter of the left ventricle (LV) was 53.8 ± 8.5 mm, the maximum aortic gradient was 82.0 ± 25.9 mmHg, and the medium gradient was 50.1 ± 17.3 mmHg.

The mean Na concentration was 138.0 ± 4.1 mmol/l before the surgery and 135.1 ± 6.6 mmol/l after surgery. Before surgery, the mean Na concentration was 134.0 ± 1.3 mmol/l in the low Na group and 140.5 ± 3.2 mmol/l in the normal/high Na group. After surgery, the mean Na concentration decreased to 134.5 ± 3.4 mmol/l in the low Na group and to 135.5 ± 8.1 mmol/l in the normal/high Na group. More patients were from the normal/high Na group (29.5% vs. 26.1%; p = 0.002) had a lower preoperative pH (p = 0.022) and lactate concentration (p = 0.015) (Table 1).

The mean duration of the AVR procedure was significantly shorter in the low Na group (337.5 min vs. 402.1 min; p < 0.001), with a longer mean duration of bypass (122.5 min vs. 93.8 min; p < 0.001), aortic clamp (81.3 min vs. 66.7 min; p < 0.001), orotracheal intubation (13.7 h vs. 9.9 h; p < 0.001), and inotropic/vasopressor support administration (1.8 days vs. 1.6 days; p = 0.018). Mean ultrafiltrate during cardiopulmonary bypass was 1,862 ml. No significant differences were seen in terms of the other patient characteristics (Table 1).

Logistic regression analysis of the outcomes showed a significant association between low preoperative Na concentrations and surgical reintervention for hemorrhagic cause, being a risk factor (OR = 3.65; 95%CI 1.18–11.34; p = 0.025). No statistically significant association was found between Na levels and new onset of AFib, sustained VT/VF, and postoperative neurological impairment (Table 2).

TABLE 1. Baseline characteristics of patients according to preoperative Na levels

Variables	Na ≤ 136 mmol/l (*n* = 119)	Na > 136 mmol/l (*n* = 183)	p value
Age (n, %)			
<60 years	31 (26.1)	54 (29.5)	0.002†*
61–70 years	48 (40.3)	91 (49.7)	0.056†
>70 years	40 (33.6)	38 (20.8)	0.545†
Female (n, %)	38 (31.9)	72 (39.3)	0.924†
Comorbidities (n, %)			
Dyslipidemia	43 (36.1)	76 (41.5)	0.258†
Obesity	21 (17.6)	39 (21.3)	0.830†
Diabetes mellitus	23 (19.3)	46 (25.1)	0.430†
Arterial hypertension	78 (65.5)	140 (76.5)	0.968†
Preoperative echocardiography			
LVEF, % (median, 95% CI)	55.0 (50.0–55.0)	55.0 (50.0–55.0)	0.841#
Ao max gradient, mmHg (median, 95% CI)	80.0 (75.0–84.0)	80.0 (77.0–85.0)	0.389#
Ao medium gradient, mmHg (median, 95% CI)	48.0 (45.3–52.7)	49.0 (46.0–53.0)	0.564#
LV diastolic diameter, mm (median, 95% CI)	53.0 (52.0–55.0)	52.0 (50.0–54.0)	0.099#
Preoperative blood levels			
pH (median, 95% CI)	7.45 (7.42–7.47)	7.42 (7.41–7.43)	0.022#*
Lactate, mmol/l (median, 95% CI)	1.4 (1.4–1.5)	1.3 (1.2–1.4)	0.015#*
Surgery duration, min (mean ± s.d.)	337.5 ± 81.4	402.1 ± 264.1	<0.001#*
Bypass duration, min (mean ± s.d.)	122.5 ± 53.1	93.8 ± 34.1	<0.001#*
Aortic clamp duration, min (mean ± s.d.)	81.3 ± 34.4	66.7 ± 23.8	<0.001#*
Postoperative orotracheal intubation, h (mean ± s.d.)	13.7 ± 15.9	9.9 ± 10.0	<0.001#*
Postoperative inotropic/vasopressor support, days (mean ± s.d.)	1.8 ± 1.9	1.6 ± 2.0	0.018#*
Postoperative echocardiography			
LVEF, % (median, 95% CI)	50.0 (45.0–55.0)	50.0 (45.0–55.0)	0.253#
Ao max gradient, mmHg (median, 95% CI)	22.0 (20.0–24.0)	21.0 (18.0–23.0)	0.804#
Ao medium gradient, mmHg (mean ± s.d.)	8.0 (7.0–8.0)	7.0 (6.8–8.0)	0.225#
Postoperative blood levels			
Na, mmol/l (median, 95% CI)	134.8 (133.6–135.5)	134.9 (134.7–135.6)	0.253#
pH (median, 95% CI)	7.42 (7.39–7.45)	7.45 (7.42–7.47)	0.197#
Lactate, mmol/l (median, 95% CI)	1.4 (1.3–1.7)	1.5 (1.4–1.7)	0.847#

Mann–Whitney U test; † chi-squared test; * statistically significant

TABLE 2. Postoperative outcomes

Variables	Na ≤ 136 mmol/l (*n* = 119)	Na > 136 mmol/l (*n* = 183)	OR (95% CI)	p value
Surgical reintervention (n, %)	10 (8.4)	5 (2.7)	3.65 (1.18–11.34)	0.025#*
New onset of AFib (n, %)	8 (6.7)	19 (10.4)	0.73 (0.30–1.77)	0.485#
Sustained VT/VF (n, %)	2 (1.7)	3 (1.6)	0.39 (0.07–2.01)	0.259#
Neurological impairment (n, %)	1 (0.8)	3 (1.6)	0.35 (0.03–3.77)	0.384#
7-day mortality (n, %)	9 (7.6)	2 (1.1)	7.40 ((1.57 -34.90)	0.011*
30-day mortality (n, %)	13 (10.9)	3 (1.6)	7.36 (2.05–26.42)	0.002*

Data obtained through logistic regression analysis. * Statistically significant.

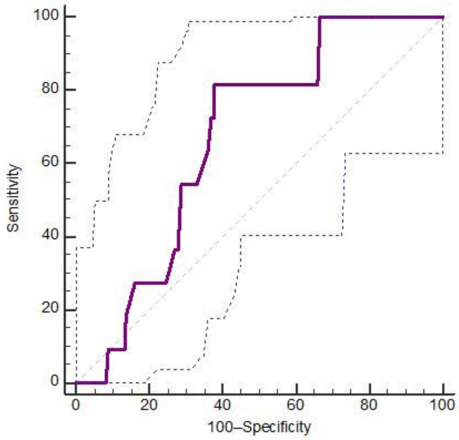

FIGURE 1. ROC curve analysis of preoperative Na levels in predicting 7-day postoperative mortality

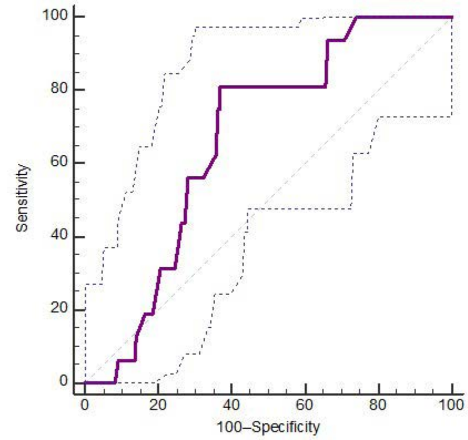

FIGURE 1. ROC curve analysis of preoperative Na levels in predicting 30-day postoperative mortality

The 7-day mortality was 7.6% (9 out of 119 patients) in the low Na group compared with 1.1% (2 out of 183 patients) in the normal/high Na group, and 30-day mortality was 10.9% (13 out of 119 patients) in the low Na group vs. 1.6% (3 out of 183 patients) in the normal/high Na group. We found a significant association between low preoperative Na levels and 7-day mortality (OR = 7.40; 95% CI 1.57–34.90; p = 0.011), as well as low preoperative Na levels and 30-day mortality (OR =7.36; 95% CI 2.05–26.42; p = 0.002) (Table 2).

The results of the ROC analysis and maximum Youden's index suggest that the optimal cut-off value for preoperative Na levels was ≤136 mmol/l for the prediction of 7-day postoperative mortality. This threshold had an area under the curve (AUC) of 0.672 (95% CI 0.615–0.724; p = 0.005), with 81.8% sensitivity and 62.2% specificity (Figure 1).

The same cut-off level (Na ≤ 136 mmol/l) was suggested by the Youden's index in the prediction of 30-day postoperative mortality, with an AUC of 0.668 (95% CI 0.612–0.721; p = 0.001), with 81.2% sensitivity and 62.9% specificity (Figure 2).

DISCUSSION

The findings of our study indicate that preoperative hyponatremia has a significant impact on short-term mortality rate. Many patients with aortic valve disease have congestive heart failure with low LVEF, renal failure, and other comorbidities, sometimes requiring complex valve surgery. A common factor in all of these conditions is most often hyponatremia, which is present in 15–30% of patients presenting to hospital, irrespective of the underlying pathology.[4] The prevalence of hyponatremia in patients with heart disease is estimated to be between 1% and 24%.[5] Patients with low serum Na levels exhibit increased catecholamine and vasopressin levels, as well as heightened reactivity of the renin–angiotensin–aldosterone system. It is proven that these biochemical alterations result in impaired renal and hepatic microcirculation. Although myocardial injury is a potential consequence, it has not been conclusively demonstrated in human studies. However, an increased susceptibility to the adverse effects of the ischemia–reperfusion phenomenon in conditions of hyponatremia has been demonstrated in isolated rat hearts.[6,7] These laboratory results are consistent with the results of our study. Furthermore, the patients with preoperative hyponatremia in our study experienced prolonged aortic cross-clamp and cardiopulmonary bypass times in comparison to those with normal serum Na levels. This suggests that hyponatremia is predominantly identified in patients with advanced cardiac lesions requiring extensive surgical correction. Despite these observations, it remains unclear whether hyponatremia per se has a negative effect on the myocardium and, implicitly, on postoperative outcome, or it is a marker of organ dysfunction and comorbidities. In clinical practice, hydroelectrolytic and acid–base dysfunctions are corrected preoperatively, if the patient's condition allows. Furthermore, there are numerous cases in which these corrections cannot be performed without addressing the underlying cardiac lesion.[8] Accordingly, in the course of our investigation, 39.4% of patients were subjected to surgical intervention while exhibiting a preoperative hyponatremic status. Other studies have found results that are consistent with our findings. It has been stipulated that even a small decrease in preoperative natrium levels is correlated with an increase in mortality, a correlation that increases proportional to the severity of hyponatremia. Research has demonstrated that even values within the normal range (135–138 mEq/l) are linked to an increased risk of mortality following cardiac surgery.[9,10]

Furthermore, we demonstrate that there is no statistical correlation between decreased postoperative Na concentration and either mortality or adverse events. Although there was an average decrease of 2.9 mmol/l compared to preoperative values, this difference had no effect on the postoperative outcome. Other studies that have reported an increased incidence of postoperative adverse events due to hyponatremia have reported much higher mean postoperative Na decreases of 4–15 mmol/l.[11,12] These discrepancies may be attributed to the use of ultrafiltration in the configuration of each cardiopulmonary bypass circuit at our institution, which inhibits dilution and consequently prevents hyponatremia and maintains blood osmolarity.[13] Other studies with increased postoperative hyponatremia do not specify the use of ultrafiltration, or its use has been confined to a relatively limited number of patients.[11] The calculated excess fluid, predominantly derived from cardioplegia (1,600–2,000 ml) and circuit priming (1,100–1,300 ml), is effectively eliminated. The mean volume filtered in our cohort was 1,862 ml, and no further corrective measures were necessary to address hyponatremia, as a slight reduction in Na levels was noted postoperatively. A review of the literature revealed a universal consensus among studies that assessed postoperative osmolarity. Specifically, the findings indicated that osmolarity remains within normal limits when HTK cardioplegia and ultrafiltration are used. As a representative study, in a cohort of 60 patients undergoing cardiac surgery with cardiopulmonary bypass, Yu-Ning Hu *et al.* showed that there were no postoperative seizures or symptoms of demyelination, as evidenced by quantitative electroencephalography and Mini-Mental State Examination scores.[14]

The osmolarity of Bretschneider cardioplegia is slightly higher than that of blood (310 mOsm/kg vs. 275–300 mOsm/kg).[12,15] It should be noted that our study did not record osmolarity values, because the determination of osmolarity is not a standard procedure in our center. It has been demonstrated that the correction of hyponatremia in an isotonic state can have significant adverse effects, as a hyperosmolar state can readily develop with deleterious effects.[16] Furthermore, demyelination syndrome can occur in case of rapid correction of Na.[17]

STUDY LIMITATIONS

It is possible that the omission of certain data from this retrospective study may have influenced perioperative Na values and, consequently, the study results. The administration of parenteral fluids, vasopressin, and diuretics, as well as laboratory tests, such as blood glucose and osmolarity, are all absent from our analysis. In the case of preoperative hyponatremia, it is important to consider for how long the dysnatremia has been developing, as the rate of decline in Na levels can have a significant effect on the patient's condition.

Although the number of patients with perioperative hypernatremia is small, given that hypernatremia is also linked to elevated adjusted mortality rates, the inclusion of patients with hypernatremia in the control group may have diminished the effect of hyponatremia on outcomes.

CONCLUSIONS

In conclusion, the findings of our study indicate that the occurrence of complications is primarily associated with preoperative rather than postoperative hyponatremia, even when there are minor deviations from the normal range.

It is possible to implement safe and effective methods to prevent intraoperative hemodilution secondary to Bretschneider cardioplegia. These methods are preferred over the correction of iso-osmolar hyponatremia. It is not advised to correct mild forms of hyponatremia, as the treatment itself, rather than the hyponatremia, is associated with an increased mortality rate and a higher incidence of adverse events.

The existing literature contains a paucity of studies that have evaluated the relationship between HTK, hyponatremia, and the incidence of adverse events in adult cardiac surgery. Consequently, the optimal strategy for the management of HTK-related hyponatremia remains a topic of debate. It is imperative that future prospective studies use standardized intraoperative electrolyte monitoring.

FUNDING

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INFORMED CONSENT

Written informed consent was obtained from all subjects involved in the study.

DATA AVAILABILITY

Further data are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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