

Relationship between Transesophageal Echocardiography-Derived Pulmonary Artery Systolic Pressure Measurements and Early Morbidity in Patients Undergoing Coronary Artery Bypass Grafting

Abstract

Context: We studied the relationship between intraoperative transesophageal echocardiography-derived (TEE-derived) pulmonary artery systolic pressure (PASP) measurements with early morbidity in on-pump coronary artery bypass grafting (CABG) surgery. **Aims:** The objective of the study was to assess whether TEE-derived elevated PASP is independently predictive of significant morbidity. **Settings and Design:** Prospective observational study in a university hospital. **Materials and Methods:** Around 54 patients who underwent CABG under cardiopulmonary bypass (CPB) were divided into two groups; with PASP ≥ 35 mmHg and PASP < 35 mmHg, assessed by intraoperative TEE. Outcomes studied were poor coronary revascularization, postoperative arrhythmias, myocardial infarction, respiratory failure, intra-aortic balloon pump use, pacemaker dependence, significant inotrope use, prolonged intensive care unit stay, and the total length of stay in the hospital. Mortality analysis was not a part of this study since expected sample sizes were low. **Results:** Patients with PASP ≥ 35 mmHg had a higher risk of respiratory failure, increased inotrope use and prolonged hospital stay, although multivariate analysis failed to demonstrate an independent association of PASP with these outcomes. Diabetes mellitus (DM), peripheral vascular disease, low cardiac output and elevated mitral annular E/e' ratio were significantly associated with higher pulmonary arterial pressures. Multivariate analysis showed that PASP was independently associated with higher mitral annular E/e' ratio. **Conclusions:** Our study, therefore, suggests that higher PASP may predict higher left ventricular filling pressures, and although elevated PASP ≥ 35 mmHg may be associated with DM; peripheral vascular disease, lower intraoperative cardiac output, postoperative respiratory failure, higher inotrope use, and delayed hospital discharge, it is not an independent predictor of any of these variables.

Keywords: *Cardiopulmonary bypass, coronary artery bypass graft, pulmonary, systolic pressure, transesophageal echocardiography*

Introduction

The incidence of coronary artery disease (CAD) has been on the rise since 1990. Although the death rate due to cardiovascular diseases has declined by 24.7%,^[1] the burden of the disease remains high, accounting for nearly one-third of all deaths in patients above 35 years of age.^[2] Coronary artery bypass grafting (CABG) remains a mainstay in the treatment of patients with advanced coronary artery disease.

In this context, one must note that the presence of high pulmonary arterial pressures has been linked to outcomes in the immediate postoperative period.^[3-5] However, only 4 out of 19 preoperative

risk stratification models used pulmonary hypertension as a risk factor. Significantly, the EuroSCORE and EuroSCORE 2 models, which have the highest discriminating power include pulmonary hypertension as a risk factor. Most of the studies relating pulmonary arterial pressures with outcomes have used catheter-based measurements. However, recent years have seen a decline in the use of Swan-Ganz catheters, in the context of routine cardiac surgery.

With the advent of continuous-wave Doppler studies, it is possible to estimate pulmonary artery pressures noninvasively.^[6,7] While Doppler-derived pulmonary artery pressures from transthoracic echocardiography-driven studies have been known to affect perioperative outcomes, in terms of adverse

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morbidity and mortality, there are few studies in this regard relating pulmonary pressures derived from intraoperative transesophageal Doppler echocardiographic examination to postoperative outcomes. This is especially important because the values of PASP recorded intraoperatively under anesthesia, are likely to be different owing to different loading conditions than those obtained preoperatively from a transthoracic echocardiogram. Hence, whether values measured intraoperatively can predict outcomes is not clear.

The primary objective of the study was to assess if the elevation of PASP as estimated by intraoperative TEE, in patients undergoing elective CABG surgery, was independently predictive of early perioperative morbidity in these patients. We also wanted to identify the risk factors associated with such elevation of PASP. Mortality analysis was not part of this study since the expected sample size was low, given that it was a time-bound project. Further, mortality rates in CABGs in recent years have generally been extremely low, ranging from between 2–3% so as to make any meaningful comparison difficult in a study with expected low sample size. However, the complication rates from these procedures, are still significant, ranging anywhere between 20–30%. Hence, the morbidity rates might still be of relevance, even with smaller samples.

Materials and Methods

Study population

The study participants were patients who were candidates for isolated CABG on CPB enrolled between February 2017 and August 2018. Patients with significant right ventricular outflow tract obstruction, those undergoing redo CABGs, those with a previous history of cardiac surgical procedures and patients with contraindications for the performance of TEE were excluded from the study. A total of 78 patients were enrolled in the study, of whom 54 (69%) had analyzable tricuspid regurgitation (TR) jets and were therefore allocated into the two study groups.

The study was approved by the Institutional Ethics Committee for Human Studies (No. JIP/IEC/2015/22/787; Dated 15.02.2016) and informed consent was taken from the patients undergoing CABG on CPB. The study was conducted over a 1.5 year period. The patients were informed about the requirement for TEE. They were also informed that there would be no direct benefits of participating in the study. Demographic characteristics such as age, sex, body mass index (BMI), history of risk factors of CAD such as the family history of CAD, cigarette smoking, diabetes mellitus (DM), hyperlipidemia, hypertension, peripheral vascular disease, and cerebrovascular disease were recorded for each patient preoperatively. The cardiac status, including the NYHA class, ejection fraction, and the number of coronary vessels involved were also noted.

Anesthetic management

All patients were premedicated with intramuscular morphine sulfate (0.1 mg/kg) 1 hour before surgery. They were monitored by electrocardiogram (ECG), invasive blood pressure, central venous pressure line, and arterial pressure-based cardiac output monitoring and peripheral oxygen saturation. After administration of 0.05–0.07 mg/kg midazolam, general anesthesia was induced with fentanyl, propofol, and vecuronium in adequate doses to intubate the patients. Thus, a standard general anesthetic regimen was followed in all patients. Controlled ventilation with oxygen and air with sevoflurane adjusted to 0.6–0.7 minimal alveolar concentration (MAC) along with an infusion of propofol and fentanyl, with boluses of morphine and vecuronium, were used for maintenance of anesthesia. No regional and/or fast track protocols of anesthesia were employed in these patients. All the relevant measurements were done 30 min after induction of anesthesia. During the time of obtaining measurements, hemodynamics was maintained at close to baseline levels ($\pm 20\%$) by the use of vasoactive drugs as appropriate. The anesthetic and other aspects of management were carried out by an independent anesthesiologist not involved in the study.

Data acquisition

Flotrac™ (Edwards Lifesciences, Irvine, CA, USA) transducers were used to obtain cardiac output from an arterial cannula using a Vigileo™ (Edwards Lifesciences, Irvine, CA, USA) monitor. All TEE assessments were performed by a single attending anesthesiologist with a fellowship in echocardiography and about 10 years' experience in transesophageal imaging, using standardized instruments (MyLab™ 50 X-Vision Gold, ESAOTE Biomedica, Genoa, Italy with TEE132 Multiplane probe) and protocols. All parameters were measured in triplicate and averaged. In addition to the standard M-mode, 2-dimensional and color Doppler imaging, continuous-wave Doppler examination of tricuspid flow, pulsed-wave Doppler examination of mitral inflow, and Doppler tissue imaging of the medial and lateral mitral annulus were performed in each subject.^[8] The individual parameters were measured using a prespecified methodology.

TR was evaluated at the mid-esophageal level using Doppler echocardiography. The maximum TR jet was identified using continuous-wave Doppler across the tricuspid valve in the modified bicaval and mid-esophageal 4-chamber views. A Doppler signal was defined as adequate if there was a $\leq 20^\circ$ alignment and a full envelope. The systolic right ventricular to right atrial pressure gradient (trans-tricuspid gradient) was obtained using the modified Bernoulli equation ($4 \times \text{peak tricuspid regurgitant velocity}^2$). Right atrial pressure was obtained from the central venous catheter and was then added to the calculated gradient to yield PASP. Echocardiographic estimates of PASP obtained in this fashion have been

shown to correlate well with invasive measurements over a wide range of values (correlation coefficients ranging between 0.89 and 0.97).^[6,8-10]

Estimation of mitral annular E/e' ratio was done in mid-esophageal 4-chamber view with pulse wave Doppler. First transmitral flow velocity was obtained by pulse wave Doppler across the mitral valve outlet. Then, using tissue Doppler, the medial and lateral mitral annular tissue velocities were obtained using pulse wave Doppler. The ratio of early transmitral flow velocity (E) to early mitral annular tissue velocity (e') was obtained for both the medial and lateral annulus and the average of this used as an echo-derived estimate of left ventricular diastolic pressure.^[11] This index (E/e') has been shown to reliably detect elevated left ventricular diastolic pressure in patients with elevated echo-derived PASP, who are undergoing right heart catheterization.^[12] However, average e' velocity may not accurately represent a global diastolic function in the presence of basal, lateral, and septal wall motion abnormalities, and hence the E/e' ratios may not be accurate under these circumstances.

Evaluation

Based on TEE findings, the patients were divided into two groups as per the PASP: control group (PASP <35 mmHg) and study group (PASP ≥35 mmHg). This cutoff was based upon the values suggested by the American Academy of Family Physicians (AAFP), who propose that an estimated systolic pulmonary arterial pressure of 35 to 40 mmHg or greater on echocardiography is suggestive of pulmonary hypertension.^[13] Thus, we hoped to include mainly patients with well-documented pulmonary hypertension in the study group and not merely mild elevations in PASP. Patients with no analyzable TR jet were excluded from the study. The STROBE diagram of the study is shown in Figure 1.

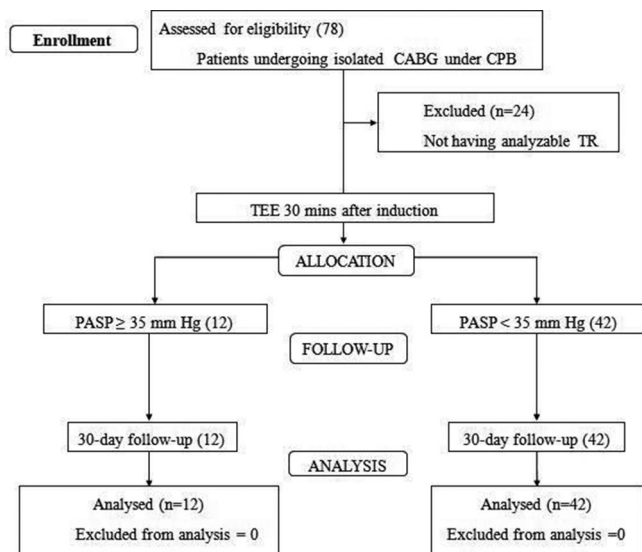


Figure 1: Strobe diagram of the study

The assessment of early post-CABG morbidity depended on the postoperative complications of 1. poor coronary revascularization, 2. postoperative arrhythmias, 3. postoperative myocardial infarction (MI), 4. postoperative respiratory failure, 5. intra-aortic balloon pump use, 6. pacemaker dependence 7. significant inotrope use, 8. prolonged ICU stay (>24 h), and 9. prolonged total length of stay in hospital (>7 days). Poor coronary revascularization was defined as any patient who would require anticoagulant therapy in the form of heparin infusion after the operation due to the inadequacy of performed graft or endarterectomy. This requirement for postoperative heparin infusion was based on the surgeon's perception of the quality of his targets and/or endarterectomy. The usage of heparin infusion as a bridge to eventual antiplatelet therapy, typically introduced on the first postoperative morning was employed as a marker of the same. Significant inotrope use was defined as the requirement of inotropes even after 24 h of completion of surgery. Postoperative respiratory failure was defined as the duration of mechanical ventilation more than 48 h or reintubation following cardiac surgery. Postoperative arrhythmias were recorded if they were sustained beyond 5 min in the postoperative period or required pharmacological or electrical therapy. The diagnosis of postoperative myocardial infarction was defined as the appearance in the ECG of a significant new Q wave (≥30 ms and ≥0.1 mV in two or more contiguous leads) and an echocardiographic image of disturbances in the segmental contractility in an area consistent with the ECG disturbances. In view of the small sample size, mortality analysis was not planned.

Statistical analysis

The study was undertaken over 18 months and on-pump CABG surgeries fulfilling the preset inclusion and exclusion criteria were enrolled. Although the total number of such patients was 78, only 54 patients had recordable TR jets and were hence analyzed. Our center is a low-volume center that does around 250 CABGs annually. However, following application of inclusion (off-pump CABGs and combined valve CABGs were not part of the study) and exclusion criteria, as also ensuring that sharing of patients for multiple trials is not done, left us with an enrolment of 78 patients.

Descriptive and inferential statistical analyses were carried out in the present study. Results of continuous measurements have been presented as mean ± SD (min-max) and results of categorical measurements as the number (%). Significance has been assessed at 5% level. The following assumptions on data have been made: 1. dependent variables were normally distributed, 2. samples drawn from the population were random, and cases of the samples were independent.

Student's *t*-test (two-tailed, independent) has been used to find the significance of study parameters on

a continuous scale between two groups (intergroup analysis) on metric parameters. Chi-square/Fisher exact test has been used to find the significance of study parameters on a categorical scale between two or more groups, the nonparametric setting for qualitative data analysis. Fisher's exact test has been used when cell samples were very small.

Logistic regression analysis was employed to find the correlation of positivity with clinical variables (Adj OR = 1, no relationship, Adj OR > 1, positive association and Adj OR < 1: negative association).

The statistical software SPSS 18.0 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.), and R environment ver. 3.2.2 (2015, Vienna, Austria) were used for the analysis of the data and Microsoft Word and Excel to generate graphs, tables, and so on.

Results

Based on our study's definitions, 54 patients were divided into two groups depending on whether the PASP was <35 mmHg or not, upon TEE assessment, following induction of anesthesia and stabilization of hemodynamics at values $\pm 20\%$ of baseline. Normality of all continuous variables was determined by using the Kolmogorov-Smirnov test. Among the various continuous data, age, BMI, ejection fraction, cardiac output, and E/e' were found to follow a normal distribution. PASP was found to be distributed non-normally.

The demographic data of all the studied patients ($n = 54$), i.e., all the patients who had analyzable TR jets are given in Table 1. The table also contains baseline physiological parameters and the functional class of the patients. From this table it can be seen that in patients analyzed, there was a significant difference in the occurrence of DM and peripheral vascular disease, as well as measurements of cardiac output and E/e' among the two groups. This suggests an association between these variables and the presence of elevated pulmonary artery pressures.

Table 2 compares the incidence of postoperative morbidity variables in patients with PASP < and ≥ 35 mmHg. From the results shown in Table 2, it is found that patients with higher PASP have a higher incidence of respiratory failure (33.3% vs 7.1%) with a P value of 0.036, increased inotrope use (91.7% vs 52.4%) with P value of 0.018 and prolonged hospital stay (83.3% vs 28.6%) with a P value of 0.001. The incidences indicated might not be representative of morbidity rates in general, given that the sample size of the index study was fairly small. However, despite the small sample size and the fact that the data is from a single-center, we believe the differences in morbidity between patients with and without elevated PASP are relevant and needs further exposition in a larger study directed at identical outcomes.

Table 1: Baseline characteristics and clinical data of studied patients based on PASP

Characteristic	PASP <35 (n=42)	PASP ≥ 35 (n=12)	P
Age	55.74 \pm 7.25	55.83 \pm 10.21	0.971
Sex			
Male	35 (83.3%)	9 (75%)	0.674
Female	7 (16.7%)	3 (25%)	
BMI	24.64 \pm 3.83	26.55 \pm 6.05	0.190
Family history of CAD	6 (14.3%)	2 (16.7%)	1.000
Smoking	16 (38.1%)	7 (58.3%)	0.211
Diabetes mellitus	19 (45.2%)	10 (83.3%)	0.024
Opioid addiction	0 (0%)	0 (0%)	-
Hyperlipidemia	4 (9.5%)	2 (16.7%)	0.605
Hypertension	18 (42.9%)	6 (50%)	0.748
Peripheral vascular disease	0 (0%)	2 (16.7%)	0.046
Cerebrovascular disease	3 (7.1%)	1 (8.3%)	1.000
Recent MI	20 (47.6%)	9 (75%)	0.093
Ejection Fraction	53.67 \pm 12.16	49.58 \pm 9.40	0.289
Functional Class			
1	0 (0%)	0 (0%)	0.379
2	26 (61.9%)	5 (41.7%)	
3	15 (35.7%)	7 (58.3%)	
4	1 (2.4%)	0 (0%)	
Number of Coronary involvement			
1	0 (0%)	0 (0%)	0.306
2	3 (7.1%)	2 (16.7%)	
3	39 (92.9%)	10 (83.3%)	
Cardiac Output	4.80 \pm 1.69	3.54 \pm 1.10	0.019
E/e'	8.94 \pm 3.49	12.43 \pm 2.45	0.002

Table 2: Postoperative complications based on PASP

Complication	PASP <35	PASP ≥ 35	P
Poor coronary revascularization	12 (28.6%)	3 (25%)	1.000
Postoperative arrhythmia	10 (23.8%)	2 (16.7%)	0.714
Perioperative MI	6 (14.3%)	2 (16.7%)	1.000
Respiratory failure	3 (7.1%)	4 (33.3%)	0.036
Intraaortic balloon pump	5 (11.9%)	4 (33.3%)	0.098
Pacemaker dependence	0 (0%)	0 (0%)	-
Increased inotrope use	22 (52.4%)	11 (91.7%)	0.018
Prolonged ICU stay	15 (35.7%)	8 (66.7%)	0.056
Prolonged hospital stay	12 (28.6%)	10 (83.3%)	0.001

In Table 3, the multivariate analysis of demographic and baseline parameters as predictors of elevated PASP is shown. The peripheral vascular disease could not be analyzed in the multivariate analysis since there were inadequate positive values. Multivariate testing demonstrated significant odds only for elevated E/e' to be associated with a high PASP.

The univariate and multivariate analysis of outcome variables as a function of elevated PASP (≥ 35 mmHg) is shown in Table 4. None of the parameters studied, demonstrated significant odds of association with an elevated PASP.

Discussion

These are the first intraoperative TEE-based data showing that higher PASPs have an association with DM, peripheral vascular disease, lower cardiac outputs, and impaired relaxation in patients undergoing isolated CABG surgery. Higher PASP was also associated with deleterious postoperative outcomes such as an increased incidence of respiratory failure, greater inotrope use, and longer hospital stay. Notably, higher PASP was not found to have an independent association with DM, peripheral vascular disease, lower cardiac output, respiratory failure, greater inotrope usage, or for prolongation of hospital stay. Presumably, increased E/e' may serve as a predictor of elevation of pressures in the pulmonary circulation and thus may potentially, be a novel therapeutic target. Although the E/e' ratios in our study were not >14, which is the cutoff suggested for diagnosing diastolic dysfunction in the recent joint recommendations put up by the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI), it is within the 10–14 range suggested for defining impaired relaxation in the same guidelines.^[14]

Pulmonary artery pressures generally decline after induction of anesthesia, consequent to the altered loading conditions on the heart due to vasodilation and changes in preload and afterload. Therefore, TEE-based Doppler indices need to be interpreted with caution. However, in our study, we attempted to ensure normalization of preload and afterload to preinduction levels, by volume infusion and boluses of phenylephrine, so as to ensure that the filling pressures and invasive arterial blood pressure came up to within 20% of preinduction values, prior to initiating the Doppler measurements.

Left ventricle dysfunction disrupts the right ventricle function by increasing pulmonary arterial pressure which causes biventricular dysfunction. Optimum treatment of the underlying left heart disease is recommended for

patients who have pulmonary hypertension due to left heart disease.^[15] Currently, one of the most effective and common methods in the treatment of ischemic heart disease is coronary artery surgery. As has been reported earlier in patients with serious cardiac illnesses,^[16-20] the Doppler velocity profiles have a close association with values obtained with invasive pulmonary artery occlusion pressure (PAOP) monitoring in the presence of significant LV systolic dysfunction. This implies that clinicians can diagnose definitive cardiogenic pulmonary edema when the Doppler indices are suggesting an increased PAOP since patients with cardiac failure characteristically have elevated LV filling pressures. Thus E/e' was found to be an important multivariate predictor of higher PASP and therefore, could be a potential marker of both early diastolic dysfunction as well as diminished vascular compliance.

Whether these elevations in PASP need intraoperative management in these patients or not, is still not clear, but given the primacy that diastolic dysfunction currently receives, as an indicator of poor outcomes in patients with cardiovascular disease, it is likely that such therapy would require targeting of both the left heart as well as the pulmonary vasculature.

In patients undergoing CABG surgery on CPB, among the CAD risk factors, diabetes mellitus and peripheral vascular disease were more frequent in the patients with PASP ≥ 35 mmHg than in the patients with PASP <35 mmHg, while cardiac outputs were higher and E/e' ratios were lower, in the latter group of patients. The frequencies of some adverse post-operative outcomes assessed, such as respiratory failure, prolonged use of inotropes and duration of hospital stay, were higher in patients in the higher PASP group, while, the duration of ICU stay, although lower in the group with lower PASP, did not however attain statistical significance (35.7% vs 66.7%; *P* value 0.056).

Among other clinical variables studied, it was seen that recent perioperative myocardial infarction (MI) was associated with longer discharge time from the hospital in the univariate analysis but not in the adjusted model. Among post-CABG complications, however, PASP was not found to be an independent predictor of any of the complications tested such as respiratory failure, inotrope use or hospital discharge durations in the multivariate logistic regression analysis. However, the association of higher PASP with these outcomes may imply a prognostic value of preoperative reporting of PASP for determining

Table 3: Multivariate analysis for independent variables associated with elevated pulmonary artery systolic pressure

Variable	Adjusted OR	95% CI		P
		Lower	Upper	
Diabetes mellitus	7.24	0.94	55.44	0.057
Cardiac Output	0.51	0.26	1.01	0.054
E/e'	1.43	1.10	1.85	0.007

Table 4: Unadjusted and adjusted model for significant outcome variables based on Pulmonary artery systolic pressure

	Unadjusted				Adjusted			
	OR	95% CI		P	OR	95% CI		P
		Lower	Upper			Lower	Upper	
Respiratory failure	6.5	1.21	34.85	0.036	9.24	0.81	106.02	0.074
Significant Inotrope	10.0	1.18	84.56	0.018	11.11	0.34	151.29	0.071
Prolonged hospital stay	12.5	2.37	65.69	0.001	2.04	0.34	12.06	0.433

the severity of pulmonary hypertension and postoperative morbidities. Morbidity following cardiac surgery in the form of postoperative cardiac events, prolonged ventilation, renal insufficiency, and infectious and neurologic complications were studied by Tuman *et al.*^[21] They concluded that pulmonary hypertension defined by mean pressure >25 mmHg was associated with morbidity following isolated CABG surgeries with an odds ratio of 1.77 and a *P* value of 0.0018. However, in the multivariate analysis, it was not proved to be individually predictive of morbidity after cardiac surgeries.

Strengths and limitations

Strengths of this study include the prospective, intraoperative TEE-based approach, echocardiographic characterization of left ventricular impaired relaxation, uniform assessment of PASP by standard TEE views with accurate measurements of right atrial pressures, as opposed to presumed right atrial pressures used for such calculation in the echocardiography laboratory, and morbidity assessment in a sample of the patients undergoing CABG surgery. The study examines the association of PAsPs in the subjects enrolled, with a number of other risk factors of potential physiological significance. There are several examples of statistically modest, yet clinically important associations, between preoperative risk factors and their significant consequences on the heart, one such being the correlation between severity and/or duration of systemic hypertension with the degree of left ventricular hypertrophy.^[22] In our study, the overall number of events permitted adjustment for multiple covariates to give clinically significant results, for all of the variables studied, except for peripheral vascular disease, as a risk factor, in which the numbers were too low for analysis.

The limitations of our study include the absence of mortality indices from it, in view of the small sample size of this study. Another limitation of this study could be the fact that we did not record the medication history for each of the patients, and its possible that some of these may have had an impact on the postoperative complications.

Conclusions

Our study, therefore, shows that elevated pulmonary arterial pressures may be predictive of elevated left ventricular end-diastolic pressures that would need to be factored perioperatively. Our results seem to raise the possibility of impaired left ventricular relaxation associated with pulmonary hypertension, similar to its association with systemic hypertension. Although elevated PASP ≥ 35 mmHg may be associated with DM, peripheral vascular disease, lower intraoperative cardiac output, postoperative respiratory failure, higher inotrope usage, and delayed hospital discharge, it is not an independent predictor of any of these variables.

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Conflicts of interest

There are no conflicts of interest.

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