Can alveolar–arterial oxygen gradient predict severity of pulmonary embolism?

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Background The perceived risk for pulmonary embolism (PE) can be assessed by oxygenation and calculation of the alveolar–arterial (A-a) oxygen (O_2) gradient. We attempt to evaluate the efficacy of A-a O_2 gradient for the diagnosis of PE and if it can predict the degree of severity of PE.

Patient and methods This study is a prospective study conducted on 70 patients presented by signs or symptoms of suspected acute PE. Arterial-blood gases including arterial partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and arterial oxygen saturation (SaO_2) and computed tomography pulmonary angiography were done on admission.

Results Fifty patients proved to have PE by computed tomography pulmonary angiography. The patients were divided into (a) nonhigh-risk and (b) high-risk groups. There was a significant difference between the two groups regarding pulmonary artery obstructive index. Although A-a gradients were high in all studied patients with positive PE in comparison to negative PE patients, there was no significant difference between high-risk and nonhigh-risk groups regarding PaO_2 (mmHg), arterial oxygen saturation, %, A-a O_2, $PaCO_2$. In addition, no significant relationship was detected between arterial-blood gas parameters regarding PaO_2 and SaO_2 with pulmonary artery obstructive index; also $PaCO_2$ and A-a O_2 gradients were nonsignificant.

Conclusion The A-a O_2 gradient values are clinically important in the diagnosis of patients with PE because it is easy to perform and is a bedside test. However, it may be incapable of detection of severity of PE.

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Introduction

Pulmonary embolism (PE) that is associated with hemodynamic instability is an important cause of morbidity and mortality in the emergency and cardiovascular setting [1].

PE is considered very important in the differential diagnosis of many clinical presentations in the emergency room as the presenting symptoms and signs of PE such as chest pain, hemoptysis, and dyspnea are nonspecific and only 35% of patients actually have PE from all suspected of having PE [2].

We need a diagnostic testing to diagnose suspected cases of PE in the emergency room aiming at avoidance of risk of anticoagulation or a dangerous recurrence of thromboembolism if left untreated. For the evaluation of possible PE in the emergency room we require the integration of clinical suspicion with the diagnostic imaging [3]. The alveolar–arterial (A-a) is a simple test used to help in the diagnosis of PE [4].

In acute PE, patient abnormalities in oxygenation occurring may be related to the emboli size, pulmonary artery obstructive index (PAOI), diagnosis of cardiopulmonary disease, and the time lag after embolization [5].

Computed tomography pulmonary angiography (CTPA) has become the golden method of imaging in acute PE diagnosis [6]. It allows adequate detection of the pulmonary thromboemboli to the levels of pulmonary segments; also expect adverse outcomes in clinical state [7].

In this study, we attempt to evaluate the efficacy of A-a oxygen (O_2) gradient for the diagnosis of PE and if it can predict the degree of severity of PE.

Patients and methods

This study was conducted on 100 patients in ELMINIA University Hospital and included patients presented to the emergency department, respiratory, coronary, or general ICU presented by

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signs or symptoms of suspected acute PE. Ethics committee approval was obtained and a written consent form taken from all patients who were enrolled in the study. Thirty patients were excluded due to high renal functions. The remaining 70 patients underwent CTPA and 50 patients had proven pulmonary emboli.

Clinical assessment

(1) Complete history taking.
(2) Complete general and local examination.
(3) Probability scores: Wells score [8] and revised Geneva score [9] for PE were calculated for each patient.

Arterial-blood gas (ABG) included arterial partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and arterial oxygen saturation (SaO_2) which were measured on admission to the emergency department on room air. Also, A-a ratio was calculated by the following equations:

$$\begin{aligned} A-a\ \text{gradient} &= PAO_2PaO_2 \\ &= \text{Alveolar component} \\ &\quad - \text{arterial component.} \end{aligned}$$

$$1-\text{Alveolar component(alveolar air equation)} = \left\{150-\left(\frac{PaCO_2}{0.8}\right)\right\}$$

$$.PAO_2 = PiO_2 - PACO_2/R = .FIO_2(Patm - pH_2O). - .(PaCO_2/R).$$

where

(1) PaO_2=partial pressure of alveolar oxygen.
(2) PiO_2=partial pressure of inspired oxygen.
(3) $PaCO_2$=partial pressure of arterial carbon dioxide.
(4) FiO_2=fraction of inspired oxygen.
(5) Patm=atmospheric pressure (at sea level=760 mmHg).
(6) PH_2O=water partial pressure in alveolus, 100% saturated (at sea level=47 mmHg)
(7) R=respiratory quotient (normally 0.8).

$$PAO_2 = 0.21\times(760-47)-(PaCO2/0.8).$$

$$PAO_2 = 150-(PaCO_2/0.8).$$

Arterial component=PaO_2

A-a O_2 gradient less than 20 mmHg was considered normal, while A-a gradient of more than 20 mmHg was considered abnormally wide [4].

Computed tomography pulmonary angiography procedure

This study used a 16-slice multidetector CT scanner; PA was done using LightSpeed General Electric Medical Systems, Milwaukee, Wisconsin, USA. CT scans were performed using the following parameters: 120 kV, 100 mA, with 0.75 mm collimation and pitch of 1.22. Image reconstruction was done using a slice thickness of 1 mm, with interval reconstruction 0.7 mm, and was scanned from the cranial to the caudal direction in the area that begins from the supra-aortic trunk ends in the base of the lungs.

The patients were ordered to lie in supine position with an injection of 80–100 ml of nonionic iodinated contrast medium (Isovue 370; Bracco Diagnostics, Princeton, New Jersey, USA) through an antecubital vein at a rate of 3–5 ml/s instillation of 20 ml of normal saline at the same rate before and after administration of contrast to check the intravenous line to avoid saline extravasation and to washout the bolus. After start of contrast medium injection, CT scanning was performed by the bolus-tracking technique. The time delay for scanning was determined using the (bolus-tracking technique) in the pulmonary artery trunk. Threshold value selection was at 120 HU. Total time for scanning was 4–5 s.

Image interpretation

Images were reviewed at a workstation, reconstructed using a mediastinum/soft tissue algorithm to reduce the edge-enhancing artifacts that may mimic emboli when bone algorithms are utilized. Multiplanar reconstruction images were generated along the long axis of vessels.

Measurment of clot burden in the pulmonary vascular tree was measured by using the Qanadli score [9] and by calculation of the obstruction index. Also, right to left ventricular (LV) diameter ratio was calculated. Calculation of PAOI and right ventricular (RV) diameter ratios in all patients was performed apart from their clinical assessment or results of diagnostic examination.

Computed tomography pulmonary angiography diagnostic criteria for acute pulmonary embolism included:

(1) Complete occlusion of the arterial lumen with failure to opacify the whole lumen and enlargement of the artery in comparison with the pulmonary arteries of the same branching order.

(2) Central defect of arterial filling which is surrounded by contrast materials.
(3) Intraluminal filling defect in the periphery with an acute angle with the wall of the artery [10].

Pulmonary artery obstructive index measurement

Definition of PAOI as NXDN was the clot site value and D was the obstruction degree as 1 for partial obstruction and 2 for total obstruction. Definition of the N, the arterial tree for each lung was observed as having 10 segmental arteries (three to the upper lobes, two to the middle lobe, two to the lingula, and five to the lower lobes). The presence of embolus in a segmental artery is scored as 1 point. Emboli in the most proximal arterial level had a value equal to the number of segmental arteries arising distally.

In the pulmonary arterial tree, the thrombus in the most proximal branch was counted as a maximum of six (3×2) for the upper lobe arteries, for the middle lobe four (2×2) and the lingual arteries, for the lower lobe arteries 10 (5×2), for the intermediate arteries 14 (7×2), and 20 (10×2) for the main pulmonary artery, so 40 was the maximal PAOI. The final PAOI for each patient was expressed as percent (score/40×100) [9].

Statistical analysis

Methods of statistical analysis

Data were collected, revised, verified, coded, and then entered into a PC for statistical analysis which was done using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL, USA), version 22.

Continuous data were presented in the form of Mean ± stander deviation.

Analytical statistics: independent sample *t* test for the analysis of quantitative data. χ^2 test and Fisher's exact test for analysis of qualitative data.

For all *P* was considered: nonsignificant if more than 0.05, significant if less than 0.05, highly significant if less than 0.01, and very highly significant if less than 0.001.

Results

Seventy patients presented with signs or symptoms suspecting acute PE were included in the current study. The final diagnosis as regarding the diagnosis of PE was based on the result of multidetector CTPA.

Fifty patients proved to have PE by CTPA; men were 19 and women were 31 whereas 20 patients were negative for PE. The average age of the patients was 48±17 years. In the patients that proved to have PE (50 patients) 12 (24%) patients had hypertension, seven (14%) patients had chronic obstructive pulmonary disease, three patients had ischemic heart diseases, two patients had idiopathic pulmonary fibrosis (IPF), 11 patients had more than one comorbidity and no comorbidity was found in 24 (48%) patients. The risk factors for PE within the study population were evaluated. Deep vein thrombosis was present in 38.5% of patients while immobility was present in 40% of patients; surgery was present in 15% of patients while the presence of malignancy and antiphospholipid syndrome was equal (2.8%). Four percent of patients were in the postpartum period and 20% of the patients had no identifiable risk factor.

The patients were evaluated according to Wells score and revised Geneva score. According to Wells score the mean was 6 in the nonhigh-risk group and was 7.8 in the high-risk group and the *P* value was highly significant. As regards revised Geneva score the mean was 9 in the nonhigh-risk group and 11 in the high-risk group and the *P* value is significant.

The patients were divided into (a) nonhigh-risk and (b) high-risk groups according to systolic blood pressure:

The first group included nonhigh-risk patients who had normal blood pressure. They were 15 patients, with a mean age of 48±18 years and mean systolic blood pressure of 120±15 mmHg. The mean PAOI for the first group was 36±13%, ranging between 12.5 and 60%.

The second group included high-risk patients who were presented by shock or hypotension. They were 35 patients with a mean age of 47±12 years and a mean systolic blood pressure of 80±5 mmHg. Mean PAOI for the second group was 66±13%. Significant difference was present between two groups regarding vital data as the blood pressure was in group I 120±15 and in group II was 80±5 and the *P* value less than or equal to 0.0001. Table 1 shows the summary of descriptive statistics for the studied groups.

A significant difference was present between the two groups regarding PAOI ($P<0.0001$). Also, there were significant differences regarding revised Geneva score, systolic blood pressure, length of hospital stay, Systolic pulmonary Artery Pressure (sPAP), PAOI, RV/LV ratio, ($P=0.0003$, $P<0.0001$, $P<0.0001$, $P=0.0006$, $P=0.001$, 0.017, and respectively).

Although A-a O_2 gradient was high in all studied patients with positive PE, there was no significant difference between high-risk/nonhigh-risk groups

Table 1 Comparison between high-risk and nonhigh-risk groups, demographic data, hospital length of stay, laboratory data, pulmonary artery obstructive index, and echocardiography

	Nonhigh-risk PE group I (*N*=35)	High-risk PE group II (*N*=15)	Negative PE group III (*N*=20)	*P*1 value	*P*2 value
Demographic findings					
Age (years)	48±18	47±12	50±18	0.626	0.23
Sex (M/F) (%)	37/63	31/69	45/55	0.32	0.53
Hospital length of stay (days)	9±2	14±3	8±1.5	0.0001	0.0001
Mortality rate	0	2 (13)	0	0.0003	0.0003
Wells scores	6±2	7.8±.3	2.5±1	0.023	0.0001
Revised Geneva scores	9±3	11±2.5	5±2	0.000	0.000
Systolic arterial pressure (mmHg)	120±15	80±5	120±15	0.001	0.002
Laboratory findings					
PaO_2 (mmHg)	65±15	61±13	68±16	0.354	0.05
SaO_2 %	90±10	87±13	89±9	0.324	0.08
A-a O_2	43±19	49±14	29±15	0.259	0.004
$PaCO_2$	33±6	30±12	42±11	0.409	0.002
Echocardiography findings					
sPAP (mmHg)	48±15	63±12	21±9	0.0006	0.0003
CTPA					
PAOI	36±13	66±13	–	0.0001	0.000
RV/LV	0.9±0.2	1.2±0.2	0.8±0.1	0.001	0.001

A-a, alveolar–arterial; CTPA, computed tomography pulmonary angiography; LV, left ventricular; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PAOI, pulmonary artery obstructive index; PE, pulmonary embolism; RV, right ventricular; SaO_2, arterial oxygen saturation; sPAP, Systolic pulmonary Artery Pressure. *P*1, *P* value between nonhigh-risk and high-risk groups. *P*2, *P* value between all positive PE and negative PE patients.

Table 2 Correlations between pulmonary artery obstructive index and arterial-blood gas parameters

ABG parameters	Correlations with PAOI	
	R^2	*P* value
PaO_2	0.033	0.202
$PaCO_2$	0.012	0.44
SaO_2	0.011	0.461
A-a O_2	0.041	0.161

A-a, alveolar–arterial; ABG, arterial-blood gas; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; PAOI, pulmonary artery obstructive index; SaO_2, arterial oxygen saturation.

regarding PaO_2 (mmHg), SaO_2 (%), A-a O_2, $PaCO_2$ (*P*=0.354, 0.324, 0.259, 0.409, respectively). In addition, there was no significant relationship detected between ABG parameters regarding PaO_2 (*r*=0.033, *P*=0.202) and SO_2 (*r*=0.011, *P*=0.461) with PAOI, also $PaCO_2$ and A-a O_2 gradients were nonsignificant (Table 2, Figs 1 and 2).

Discussion

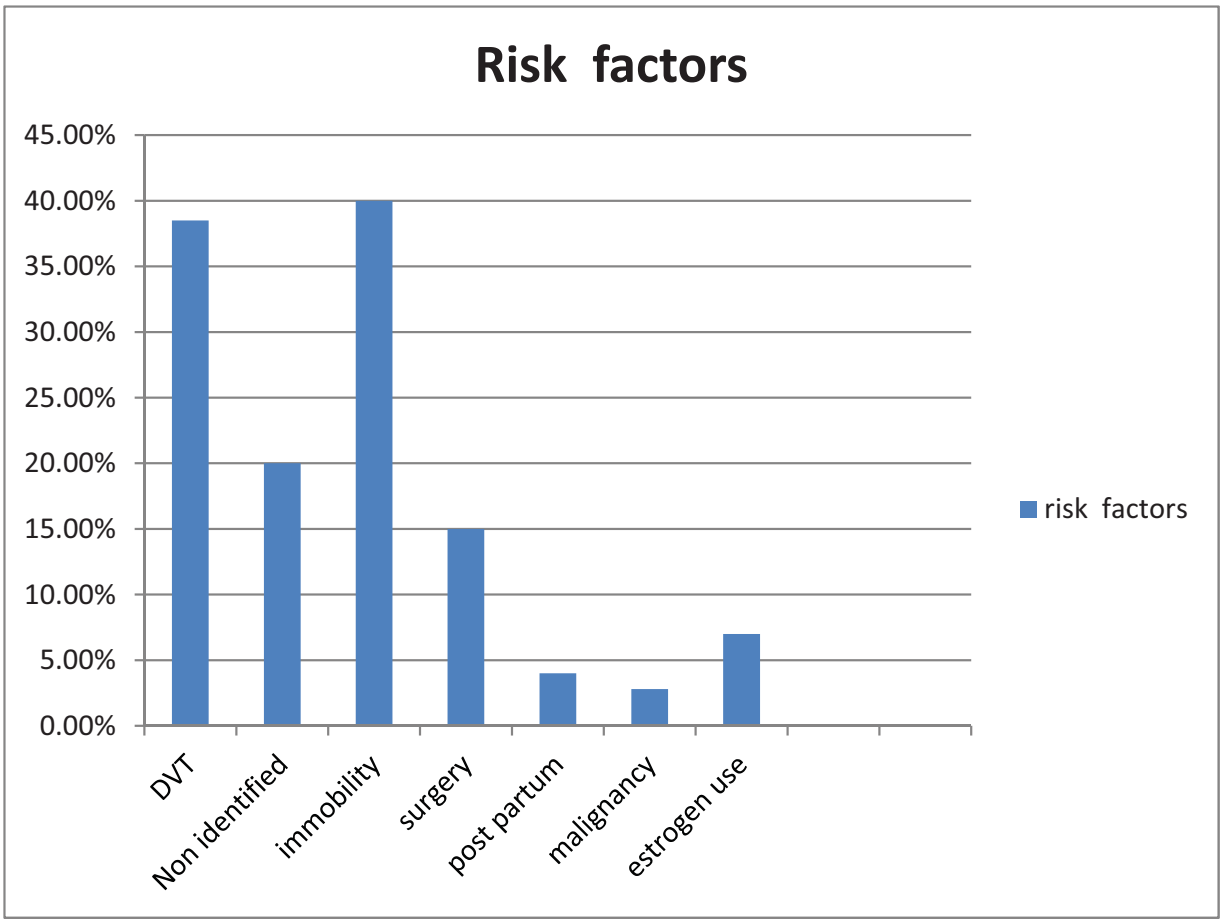
Specifically, in patients with extensive PE and RV dysfunction acute PE is a high mortality disorder. Evaluation of severity in PE patients is necessary as it provides patient classification into those who could get benefit from the use of interventional managements as thrombolysis and those with low risk; so it may be no fear from postpone outpatient investigation or management [11].

Stratification of risk can be made by detecting the evidence of RV dysfunction and ECG. But these methods may be undependable for the assessment of PE severity [12] Prediction of patient outcome can give a more accurate prognostic information [13]. However, there are difficulties in techniques of right heart imaging, especially if less experienced operators perform the imaging. As radiological tests have some delays in patients undergoing CTPA more accurate prognostic risk stratification may not be available [14].

Diagnosis and follow-up of PE can be made by blood gas analysis as it is a bedside test. In acute PE patients of hypoxemia may be related to different mechanisms including ventilation/perfusion mismatch (V/Q), shunt percent (right to left), cardiac output, and impairment of diffusion. The most important mechanism of hypoxemia is V/Q abnormalities while diffusion impairment had a limited role. V/Q mismatch and intrapulmonary shunt is the main cause of disturbed PaO_2–PaO_2 [15].

In the current study, chronic obstructive pulmonary disease was present in 14% of cases of PE with no cases of IPF. In contrast, Farghaly and El-Abdin [16] found that IPF, especially in women, is associated with increased risk for VTE.

Figure 1



Illustrates risk factors of pulmonary embolism within study population.

Regarding ABG results in our study, the mean A–a O_2 gradient was high in both groups but it is higher in the high-risk group. But no difference was present when comparing the two groups in the mean A–a O_2 gradient, mean PaO_2, or the SaO_2 but high-risk patients were more hypocapnic and this may be explained by hyperventilation stimulated by decreased O_2 and reflexes from the parenchyma of the lung and has wide A-a O_2 gradient and this is agreed upon by Günay *et al.* [17] but different studies show a limited role of ABG analysis in diagnostic utility in suspected PE. Cvitanic and Marino [18] had a trial of sensitivity optimization of the A-a O_2 gradient to exclude PE by adding the normal arterial carbon dioxide tension ($PaCO_2$) and McFarlane and Imperiale [19] tried to improve the sensitivity of the A-a O_2 gradient in excluding PE by regarding absence of previous history of thromboembolism, but neither McFarlane and Imperiale's nor Cvitanic and Marino's recorded results have a sensitivity of 100%.

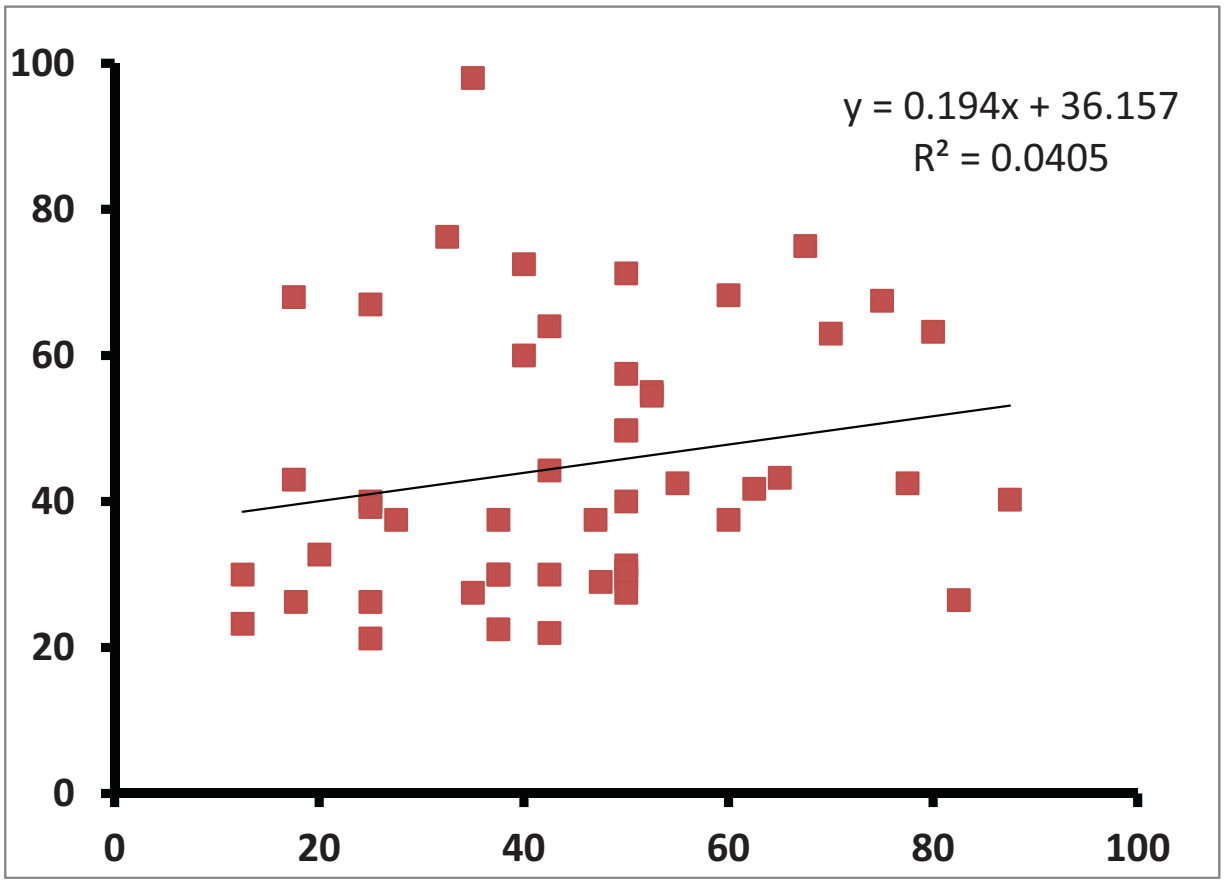
Stein *et al.* [20] found that a normal A-a O_2 gradient in no previous thromboembolism with a sensitivity of 89%, while a normal A-a O_2 gradient and a $PaCO_2$ 35 mmHg had a sensitivity of 92% in PE exclusion.

This study found non statistically significant relation between ABGs parameters regarding PaO_2 (r=0.033, P=0.202), $PaCO_2$, A-a O_2 gradient (r=0.041, P=0.161) and SaO_2 (r=0.011, P=0.461) with PAOI. This is in contrast to the results of Karakayalı et al. [2] who found a positive (but weak) correlation present between the PAOI and the A-a O_2 gradient. (r=0.400, P<0.001). This may be explained by the difference in study population number, as in the current study we have a smaller number of patients as well as the number of patients was different in each group, as a larger number of low-risk patients were included in this study. Also, Karakayalı et al. [2] had many patients with no underlying cardiopulmonary disease which is not present in our study.

Conclusion

Evaluation of A-a O_2 gradient values may be helpful for the diagnosis of patients with PE because it is easy to perform and is a bedside test. However, it may be

Figure 2



Illustrates non-significant correlation between A-a O_2 & PAIO.

incapable of detection of severity of PE. Further larger studies are recommended for more justification of the role of A-a O_2 gradient for a triage of patients of PE.

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Conflicts of interest
There are no conflicts of interest.

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