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Prognostic significance of oscillatory ventilation at rest in patients with advanced heart failure undergoing cardiopulmonary exercise testing

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ABSTRACT

Background: Among heart failure patients diagnosed as having exertional oscillatory ventilation (OV), some present with OV at rest that persists during exercise, and others develop OV only after the onset of exercise during cardiopulmonary exercise (CPX) testing. We tested whether or not there was any difference in the prognostic significance between the two abnormal breathing patterns.

Methods: Patients with New York Heart Association class III-heart failure were categorized into the following 3 groups according to their ventilation pattern during the CPX: patients with an OV pattern at rest that persisted for ≥60% of the exercise test at an amplitude of ≥15% of the average resting value (group 1), patients with the same abnormal ventilatory pattern as group 1 that was observed only during exercise (group 2), and patients without any OV (group 3). The patients were followed-up for at least 2 years to assess the composite outcome of cardiac death or hospitalization for worsening heart failure.

Results: The occurrence of the composite outcome differed significantly across the groups with its highest occurrence in group 1 (21/29 [72.4%], 15/38 [39.5%] and 48/167 [28.7%]; log-rank $P < 0.001$). In multivariate hazard analyses, an N-terminal pro-brain natriuretic peptide of >900 pg/mL (hazard ratio [HR] = 1.72, $P = 0.04$), and group 1 (HR 2.03, $P = 0.02$) were independently associated with the composite outcome.

Conclusions: Checking for the resting OV prior to incremental exercise during CPX testing may be helpful in risk-stratification among subjects with advanced heart failure.

1. Introduction

Exertional oscillatory ventilation (EOV) is an abnormal ventilatory response to exercise, and is characterized by cyclic fluctuations in minute ventilation during incremental exercise [1]. EOV is recognized as reflecting advanced disease severity and a poor prognosis in patients with heart failure [2,3]. Despite its prognostic significance, there is currently no gold standard definition of the EOV, and therefore, a wide variety of EOV patterns have been reported [4–6]. The newest scientific statement from the American Heart Association [2,3] recommends the following EOV definition: an oscillatory pattern at rest that persists for ≥60% of the exercise test at an amplitude of ≥15% of the average resting value. Importantly, this definition indicates that the OV must be observed at rest before starting the exercise as well as during the exercise. Nevertheless, in the majority of the studies on EOV, no resting phase prior to the warm-up has been included in the cardiopulmonary exercise (CPX) protocol or has been mentioned, if any [4]. Probably because of that, in a considerable number of the studies, if the OV was observed during exercise, it was considered the EOV regardless of whether or not any resting OV was confirmed. In fact, even representative images of the EOV in some articles [1,6–8] have shown a phenomenon in which the OV is never observed during the resting

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phase, however, it emerges shortly after the onset of exercise. Therefore, it is safely said that this OV pattern is not uncommon in clinical practice. The goal of the present study was to test the hypothesis that the OV seen both at rest and during exercise would have a different prognostic significance as compared to the OV seen only during exercise in patients with advanced heart failure.

2. Methods

2.1. Study population

This study was designed as a prospective observational study. Patients were recruited in Hiroshima University Hospital and Onomichi General Hospital from January 2013 to December 2014. Patients were eligible for inclusion if they were on a stable medical therapy for New York Heart Association (NYHA) class III heart failure. Patients were excluded from consideration if they were unable to exercise or had experienced a major cardiovascular event in the previous 6 weeks [9]. Eligible patients were enrolled after giving informed consent. All patients underwent laboratory testing and an echocardiogram with the standard measurements [10,11] after the inclusion. The study protocol was approved by the research committee of each institution.

2.2. CPX procedure

A symptom-limited CPX was performed on an electromagnetically braked cycle ergometer (Aerobike 75XLIII; Combi Wellness Co., Ltd., Tokyo, Japan) with the use of a conservative ramp protocol. The exercise test was initiated with a 3-minute rest on the ergometer followed by a 3-minute warm-up at 10 W, 50 rpm. The work rate was then increased incrementally by 1 W every 6 s. The test termination criteria consisted of symptoms such as dyspnea or fatigue, ventricular tachycardia, a horizontal or downsloping ST-segment depression of ≥2 mm, or a drop in the systolic blood pressure of ≥20 mm Hg [12]. During the exercise test, a 12-lead electrocardiogram and pulse oximeter were continuously monitored, and the blood pressure was manually measured every minute. The breath-by-breath minute ventilation (V_E), carbon dioxide production (VCO_2), and oxygen consumption (VO_2) were measured with the use of a metabolic cart (AE310; Minato Medical Science Co., Ltd., Osaka, Japan). The following 3 valuables were reported [2]. The peak VO_2 was calculated as the highest consecutive 30-second averaged value during the last minute of exercise or early recovery. The V_E/VCO_2 slope was obtained by a linear regression analysis of the data acquired throughout the entire period of exercise. The respiratory exchange ratio was defined as the VCO_2/VO_2 ratio, and its peak value was reported.

2.3. Oscillatory ventilation and patient grouping

The term OV has been used as a synonym of periodic breathing defined as cyclic waxing and waning of the tidal volume without apnea [13]. The most recent scientific statement [2,3] defined EOV as an OV pattern at rest that persists for ≥60% of the exercise test at an amplitude of ≥15% of the average resting value. The subjects were categorized into the following 3 groups according to the breathing pattern during the CPX: patients with the scientific statement-defined EOV (i.e. OV observed at rest as well as during exercise; group 1, Fig. 1A), patients in whom the same abnormal ventilatory pattern as in group 1 was observed only during warm-up or incremental exercise and was never noted during the resting phase (group 2, Fig. 1B), and patients without any OV (group 3, Fig. 1C). OV was visually determined by 2 experienced cardiologists.

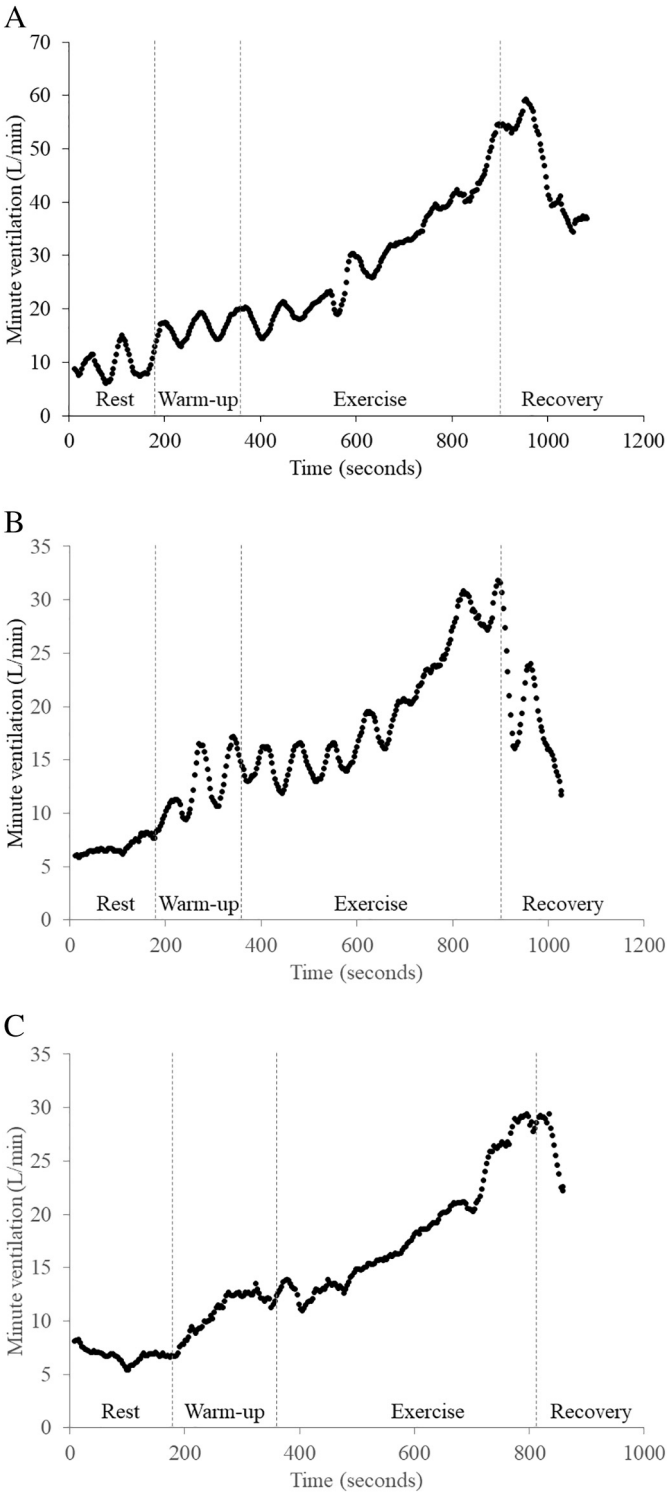

Fig. 1. Representative example of the ventilatory pattern during the cardiopulmonary exercise (CPX) testing in each patient group. The oscillatory ventilation (OV) was observed both during the resting phase and incremental exercise in a group 1 patient (panel A). The OV was not seen at rest, however, it emerged after the start of pedaling in a subject in group 2 (panel B). The OV was not noted throughout the CPX protocol in a group 3 patient (panel C).

2.4. Outcome measure

The primary endpoint was a composite of cardiac death and hospitalization for worsening heart failure.

Cardiac death included any death due to a proximate cardiac cause (e.g., myocardial infarction, heart failure, or fatal arrhythmia),

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unwitnessed death or death of unknown cause, and all cardiac procedure-related deaths [14,15]. Patients were followed-up for at least 2 years after the recruitment, and the follow-up information was obtained through clinical visits, medical chart reviews, or telephone interviews.

2.5. Statistical analysis

The continuous variables were summarized as the mean ± SD or median with the interquartile range, and categorical variables as proportions. The differences in the categorical variables across the 3 groups were examined with the use of a Pearson chi-square test'. A one-way analysis of variance was used to compare the normally distributed variables. Event-free survivals were compared with the use of a log-rank test, followed by a Bonferroni correction for multiple comparisons. Univariate and multivariate Cox proportional hazard models were used to determine the predictors of the primary endpoint. Likely parameters were included as explanatory variables in the models on the basis of a comparison of the baseline characteristics across the groups. For some continuous variables included in the models (left ventricular ejection fraction [16], left ventricular end-systolic volume [16], N-terminal pro-brain natriuretic peptide [17], Peak VO_2 [12,18], and V_E/VCO_2 slope [12,18]), the cut-off points were determined according to the current guidelines or landmark trials. Variables with statistical significance in the univariate analysis were included in the multivariate models. All statistical analyses were performed with the use of JMP software version 13.0 (SAS Institute, Cary, North Carolina). With Bonferroni corrections, a P value of <0.016 was considered statistically significant. Otherwise, a P value of <0.05 was considered significant.

3. Results

3.1. Patients

A total of 261 patients were eligible for inclusion. Among them, 17 patients met the exclusion criteria: 12 were unable to exercise, and 3 and 2 had experienced myocardial infarction or ischemic stroke, respectively, within 6 weeks before the consideration of inclusion. Another 10 patients were lost to follow-up. Finally, 234 patients were studied. We found the newest scientific statement-defined EOV in 29 patients (12.4%, group 1), the OV seen only during exercise in 38 (16.2%, group 2), and no OV pattern in 167 (71.4%, group 3) during CPX testing. The baseline clinical characteristics and CPX parameters of each patient group are presented in Table 1.

Table 1
Baseline characteristics of the study subjects (N = 234).

	Group 1	Group 2	Group 3	P-value
	N = 29	N = 38	N = 167	
Age (years)	65.3 ± 12.9	68 ± 10.7	68.7 ± 11.7	0.35
Male	19 (65.5)	26 (68.4)	89 (53.3)	0.15
Body mass index (kg/m^2)	23.2 ± 4.1	24.2 ± 4.8	23.1 ± 4.3	0.35
Ischemic etiology	6 (20.7)	13 (34.2)	63 (37.7)	0.21
Valvular insufficiency	8 (27.6)	9 (23.7)	49 (29.3)	0.78
Medical history				
Hypertension	20 (69)	33 (86.8)	117 (70.1)	0.1
Diabetes mellitus	8 (27.6)	15 (39.5)	58 (34.7)	0.6
Dyslipidemia	10 (34.5)	24 (63.2)	91 (54.5)	0.06
Myocardial infarction	6 (21.4)	13 (34.2)	49 (29.3)	0.53
Peripheral vascular disease	0	2 (5.3)	5 (3)	0.47
Atrial fibrillation	10 (34.5)	5 (13.2)	24 (14.4)	0.02
Chronic obstructive pulmonary disease	5 (17.2)	5 (13.2)	11 (6.6)	0.11
Echocardiographic parameters				
Left ventricular ejection fraction (%)	40.2 ± 14.3	48 ± 14.1	54.3 ± 13.5	<0.001
Left ventricular end-systolic volume (mL/m^2)	62.8 ± 42.1	38 ± 23.8	32.1 ± 25.5	<0.001
Average E/e′ ratio	17.8 ± 10.3	18.7 ± 9.4	15.9 ± 7.8	0.15
Laboratory data				
Hemoglobin (g/dL)	12.4 ± 2.3	13.2 ± 2.2	12.4 ± 1.7	0.04
eGFR (mL/min/1.73 m^2)	52.1 ± 19.3	50.4 ± 22.6	56.5 ± 21.7	0.22
NT pro-BNP (pg/mL)	1749 [898.5–3054]	806 [485–2035]	715 [375–1636]	0.003
Medical therapy				
ACE-I or ARB	23 (79.3)	28 (73.7)	119 (71.3)	0.66
Diuretic	25 (86.2)	31 (81.6)	123 (73.7)	0.24
β-Blocker				0.29
β1–β2 unselective blocker	20 (69)	20 (52.6)	97 (58.1)	
β1 selective blocker	7 (24.1)	11 (29)	33 (19.8)	
None	2 (6.9)	7 (18.4)	37 (22.2)	
Cardiopulmonary exercise testing parameters				
Peak respiratory exchange ratio	1.16 ± 0.16	1.13 ± 0.14	1.16 ± 0.13	0.43
Peak VO_2 (mL/min/kg)	11.6 ± 2.9	11.9 ± 3.1	13.4 ± 3.4	0.004
V_E/VCO_2 slope	35.1 ± 5	37.6 ± 11.1	32.9 ± 8	0.006

The values are the means ± SDs, n (%), or median [interquartile range] as appropriate. Valvular insufficiency includes moderate or severe aortic or mitral valve insufficiencies. E/e′ = peak early mitral inflow velocity / early diastolic mitral annulus velocity, eGFR = estimated glomerular filtration rate, NT pro-BNP = N-terminal pro-brain natriuretic peptide, ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, VO_2 = oxygen consumption, V_E = minute ventilation, VCO_2 = carbon dioxide production.

3.2. Outcomes

We found 10 (34.5%), 4 (10.5%), and 7 (4.2%) cardiac deaths (log-rank P < 0.001, Fig. 2A) during the follow-up period (mean ± SD, 3.4 ± 1.8, 3.7 ± 1.8, 3.6 ± 1.7 years; P = 0.71) in groups 1, 2, and 3 respectively. Worsening heart failure was the most common cause of cardiac death (8 [80%], 1 [25%], 3 [42.9%]), and unwitnessed sudden death was the second (2 [20%], 2 [50%], 1[14.3%]). The rate of the composite outcome differed significantly across the groups (21 [72.4%], 15 [39.5%], and 48 [28.7%]; log-rank P < 0.001, Fig. 2B). With the multiple pairwise comparisons with Bonferroni corrections, group 1 had the highest occurrence of the composite outcome of cardiac death and hospitalization for worsening heart failure (vs. group 2; log-rank P = 0.015, vs. group 3, log-rank P < 0.001), however, no significant difference was found in its occurrence between groups 2 and 3 (log-rank P = 0.12). We found 11 patients with OV that persisted throughout a progressive exercise only among patients in group 1, and their incidence of a composite outcome (81.8%) was similar to that of patients in group 1 who presented with OV that ceased by the end of exercise (N = 18, 66.7%; P = 0.67).

In the multivariate hazard analyses, an N-terminal pro-brain natriuretic peptide of >900 pg/mL (P = 0.04) and group 1 (i.e. OV observed both at rest and during exercise, P = 0.02) were independently associated with the composite outcome (Table 2).

4. Discussion

The major findings of the present study were two-fold. (i) Patients with NYHA class III-heart failure who presented with OV both at rest and during exercise had more increased composite outcomes of cardiac death or hospitalization for worsening heart failure than those with the OV seen only during exercise or those without any OV. (ii) OV observed both at rest and during exercise was an independent predictor of the composite outcome among the NYHA class III-heart failure patients.

According to our major findings, OV seen both at rest and during exercise versus that observed only during exercise suggests more serious heart failure. The mechanism is yet hard to explain because no previous study has focused on the difference between the two OV patterns, and therefore, little data on it is currently available. Some clue, however, may come from a study [8], in which the cardiac output and intracardiac pressures were measured invasively during the CPX testing in patients

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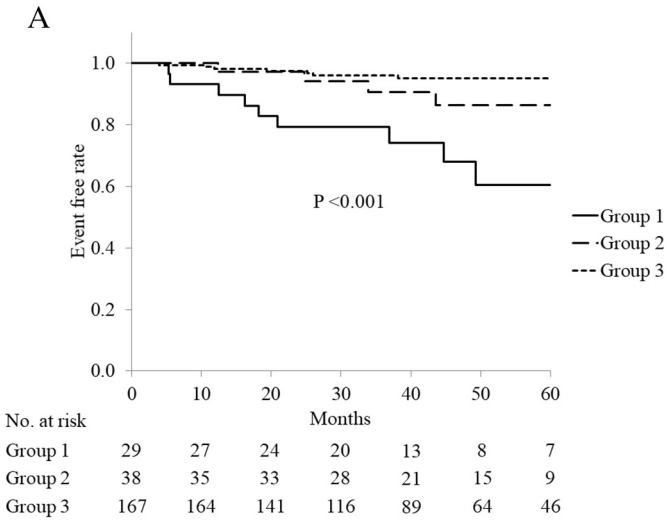

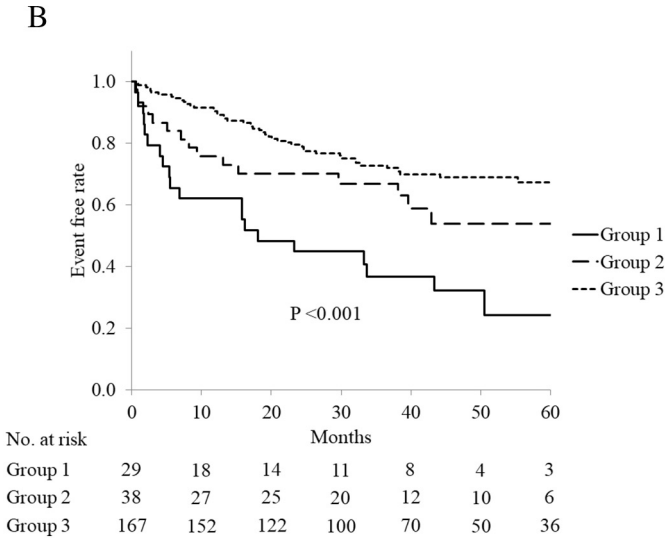

Fig. 2. Kaplan–Meier estimates comparing the survival free of cardiac death (panel A, group 1 vs. 2; log-rank P = 0.01, group 1 vs. 3; log-rank P < 0.001, and group 2 vs. 3; log-rank P = 0.36), and the primary composite outcome of cardiac death or hospitalization for worsening heart failure (panel B, group 1 vs. 2; log-rank P = 0.015, group 1 vs. 3; log-rank P < 0.001, and group 2 vs. 3; log-rank P = 0.12) in the 3 patient groups.

with heart failure and healthy control subjects. The authors found that a low cardiac index during exercise rather than the PO_2 or PCO_2 was the only single independent predictor of the EOV. They also demonstrated a reduced ability to increase the cardiac index during incremental exercise in patients with EOV. On the basis of the findings, they concluded that an inadequate cardiac index at a given exercise intensity is likely to lead to EOV. With this concept, the following is possible. Patients who had an adequate cardiac output to meet the resting oxygen demand did not present with OV during the resting phase in the CPX protocol. If their cardiac function was not good enough to increase the stroke volume adequately in response to the increase in the exercise intensity, they developed OV after the start of the incremental exercise. Patients with more advanced heart failure were unable to preserve an adequate peripheral organ perfusion even at rest, and thus they had OV constantly at rest and it was continuously observed or was even enhanced during exercise. Of course, this speculation may not solely explain our major findings because some putative mechanisms responsible for the EOV other than the reduced cardiac index have been known, such as an increased chemosensitivity to PaCO2 and PaO2, or baroreflex impairment [5,19]. For instance, Apostolo et al. [20] successfully demonstrated that a modification of the chemosensitivity to carbon dioxide with the use of acetazolamide reduced the EOV.

We failed to find any statistical significance in adverse outcomes between patients with OV seen only during exercise and those without any OV. That might be apparently different from the finding of previous studies [7,21] that heart failure patients with EOV had several times higher mortality compared to those without it. The potential explanations are as follows: (1) It is possible that patients were considered as having EOV as long as the OV pattern was observed during their incremental exercise, and little attention was paid to whether or not it was also seen during resting phase in the previous studies [4,21]. On the other hand, we in the present study checked for the resting OV, which might have contributed to the identification of potential "benign EOV". (2) Unlike many previous studies, we recruited patients with "heart failure with preserved ejection fraction (HFpEF)" as well. Patients with HFpEF generally have a better prognosis than those with "heart failure with reduced ejection fraction" [16]. That might have contributed to the statistical insignificance.

4.1. Clinical implications

It has long been known that the daytime resting OV also predicts an increased mortality among heart failure patients [13]. To the best of our knowledge, however, the present study is the first to compare the OV at rest that persists during exercise and the OV observed only during exercise among heart failure patients undergoing CPX. Our major findings suggest that checking for the resting OV before incremental exercise during the CPX testing may be helpful in assessing the severity of heart failure. Further, they may confirm the validity of the currently recommended EOV definition.

Table 2
Hazard ratio for cardiac death or hospitalization for worsening heart failure (N = 234).

Variables	Univariate		Multivariate	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age ≥ 75 years	1.23 (0.77–1.92)	0.37		
Male	1.42 (0.92–2.23)	0.12		
Diabetes mellitus	0.89 (0.56–1.39)	0.62		
Atrial fibrillation	1.3 (0.74–2.15)	0.35		
Left ventricular ejection fraction < 50%	1.71 (1.11–2.62)	0.02	0.84 (0.46–1.53)	0.58
Left ventricular end-systolic volume > 43 mL/m^2	2.48 (1.59–3.83)	<0.001	1.72 (0.91–3.33)	0.1
Hemoglobin < 12 g/dL	1.09 (0.83–1.42)	0.53		
NT pro-BNP > 900 pg/mL	2.45 (1.58–3.86)	<0.001	1.72 (1.04–2.89)	0.04
Peak VO_2 < 14 mL/min/kg	1.88 (1.16–3.19)	0.001	1.47 (0.88–2.54)	0.15
V_E/VCO_2 slope > 34	0.94 (0.59–1.45)	0.77		
Group 1	3.3 (1.96–5.31)	<0.001	2.03 (1.12–3.56)	0.02
Group 2	1.22 (0.67–2.07)	0.5		

CI = confidence interval. The other abbreviations are the same as in Table 1.

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A circadian variation in the prevalence of Cheyne-Stokes respiration has been suggested in patients with advanced heart failure [22,23]. Given that OV is considered to be less severe form of Cheyne-Stokes respiration [24], to determine its diurnal pattern in those subjects is a future challenge.

4.2. Limitations

We determined the OV visually as in the previous studies [4,5], which made it difficult to remove the subjectivity entirely. Exertional OV and sleep apnea often coexist, and the combination has a strong prognostic value [25]. However, that was not examined in our series. The present study was a single-center and observational study with a limited number of participants, and therefore, the statistical power and its impact on clinical practice are limited.

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Declaration of competing interest

None declared.

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