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Repaired oesophageal atresia: respiratory morbidity and pulmonary function in adults

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ABSTRACT: Although after oesophageal atresia (OA) repair in infancy, respiratory problems are common, their natural history remains unclear. We assessed morbidity, pulmonary function (PF), and bronchial hyperresponsiveness (BHR) in adults with repaired OA respiratory.

588 patients who underwent surgery for OA during 1947–1985 were identified and those 262 who were alive and had their native oesophagus were included. Respiratory symptoms and respiratory symptom-related quality of life (RSRQoL) were assessed by questionnaire and interview, and the patients underwent spirometry, a histamine challenge test, and an exhaled nitric oxide test. For the questionnaires, we added 287 carefully matched general population-derived controls.

Among the 101 (58 male) patients, median age 36 yrs (range 22–56 yrs), respiratory morbidity was significantly increased compared to controls. Patients had more respiratory symptoms and infections, as well as asthma and allergies, and more often impaired RSRQoL ($p<0.001$ for all). PF tests revealed restrictive ventilatory defect in 21 (21%) patients, obstructive ventilatroy defect in 21 (21%) patients, and both in 36 (36%) patients. A total of 41 (41%) had BHR, and in 15 (15%), it was consistent with asthma. The most significant risk factors for restrictive ventilatory defect were thoracotomy-induced rib fusions (OR 3.4, 95% CI 1.3–8.7; $p=0.01$) and oesophageal epithelial metaplasia (OR 3.0, 95% CI 1.0–8.9; $p=0.05$).

After repair of OA, respiratory-related morbidity, restrictive ventilatory defect and BHR extended into adulthood. Nearly half the patients had BHR and over half had a restrictive ventilatory defect. Thoracotomy-induced rib fusions and gastro-oesophageal reflux-associated oesophageal epithelial metaplasia were the strongest risk factors for restrictive ventilatory defect.

KEYWORDS: Atopy, bronchial hyperresponsiveness, long-term outcome, oesophageal atresia, pulmonary function, tracheo-oesophageal fistula

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The most common congenital anomaly of the oesophagus is oesophageal atresia (OA). It is usually associated with a tracheo-oesophageal fistula (TOF) [1, 2] and affects approximately one in 2,500 live births [3]. The embryology of OA is incompletely understood [4], and over half these infants have associated anomalies [3, 5]. The malformation itself and surgical trauma result in impaired oesophageal motility, a dysmotility predisposing to gastro-oesophageal reflux (GOR) and its complications [6, 7]. A strong connection exists between severity of GOR and persistence of respiratory symptoms among OA survivors [4], but respiratory problems become less frequent with time.

After repair of OA, approximately one-third of these patients suffer respiratory symptoms in adolescence and adulthood [8–12]. Prevalence of wheeze ranges 26–43% [10, 13, 14], and that of doctor-diagnosed asthma (DDA) 12–29% [9, 10, 12, 14, 15]. This is generally higher than in children (8.8%) [16] and adults (6%) [17]. Additionally, pulmonary function (PF) abnormalities, mostly mild restrictive disease [14, 18, 19], occur after repair of OA in childhood [14], adolescence [9, 18, 20, 21] and adulthood [12, 19, 21]. Restriction may result from surgical trauma, repeated aspiration or recurrent chest infections, as well as from associated thoracic musculoskeletal defects, such as postoperative rib fusions, scoliosis or other chest deformities.

Although after repair of OA, respiratory symptoms are common, the long-term outcome of PF and respiratory morbidity remain unclear. As growing numbers of OA survivors are reaching adulthood, interest in their long-term outcome is increasing. To this end, we performed a population-based, long-term follow-up study in

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adults with repaired OA, assessing respiratory morbidity, respiratory symptom-related quality of life (RSRQoL), PF, bronchial responsiveness and atopy. The predictive factors for restrictive ventilation in adulthood were also studied.

PATIENTS AND METHODS

The hospital records of all 588 patients treated for OA at the Hospital for Children and Adolescents, Helsinki University Central Hospital (Helsinki, Finland) between 1947–1985 were reviewed. Vital status and postal addresses came from the database of the Population Register Centre of Finland based on a personal identification code given to all residents of Finland. Of the 588 infants who underwent surgery for OA, 296 were alive at the beginning of the study in November 2005. The 34 who had undergone oesophageal replacement were excluded. 16 patients had emigrated, and the postal addresses of 11 were unknown. The remaining 235 (90%) eligible survivors with a native oesophagus were contacted by mail. Letters described the study protocol and purpose. Those returning signed consent forms received invitations to enter the study. Data drawn from the hospital records included survival, type of OA, associated anomalies, surgical treatment and complications.

During their outpatient visit, each participant filled in a symptom questionnaire and underwent an interview, clinical assessment, flow–volume spirometry for PF, histamine challenge test (HCT) for bronchial responsiveness, exhaled nitric oxide fraction (F_{ENO}) for airway inflammation, skin prick test (SPT) for common allergens, and measurement of serum level of immunoglobulin (Ig)E.

The present study is part of a larger evaluation of the long-term outcomes of OA. Findings concerning oesophageal morbidity and function [22], incidence of cancer [23], and natural history of spinal anomalies and scoliosis [24] among adults with repaired OA have already been published. GOR symptoms occurred in 34 of the study participants, and 85 had symptoms of dysphagia due to oesophageal dysmotility after repair of OA; these occurrences were significantly more frequent than among the general population-derived controls [22]. A total of 21 adults with repaired OA had oesophageal epithelial metaplasia in their oesophageal biopsy samples [22]. In addition, chest wall deformities were noted in 15 study participants [24].

Interview and questionnaires

All participants were interviewed by the same investigator with a structured form, providing information on medical history, respiratory symptoms and diseases, symptoms of allergy, need for asthma medication, and smoking habits. Symptoms of respiration included wheeze, attacks of shortness of breath, recurrent cough and respiratory infections. Symptoms of allergy included allergic rhinitis, conjunctivitis, rash and atopic eczema. The questionnaire was a modification of validated questionnaires on asthma and allergy symptoms [25] as well as on RSRQoL [26]. The identical symptom questionnaire was sent to a group of 915 controls randomly chosen from the Population Register Centre of Finland, matched for age, sex and municipality of residence.

Pulmonary function, histamine provocation and exhaled nitric oxide

Flow–volume spirometry was performed according to the guidelines of the European Respiratory Society (ERS) [27], and bronchial hyperresponsiveness (BHR) was estimated using a validated dosimetric HCT [28]. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded, as well as their reference value percentages. We used national reference values for spirometry published previously [29]. Ventilatory function was defined as restrictive when FVC was $<80\%$, which corresponds to a z-score of -2.0, and obstructive when FEV_1/FVC was $<87\%$ predicted, which also corresponds to a z-score of -2.0. Defects were classified as mild (z-score -2.0– -3.5), moderate (z-score -3.5– -5.5), or severe (z-score -5.5– -7.5). Through use of the dose–response curve, the provocative dose of inhaled histamine producing a decrease of 15% in FEV_1 (PD_{15}) could be determined, and, based on bronchial hyperreactivity, was graded as mild (0.41–1.60 mg), moderate (0.11–0.40 mg) or severe ($\leqslant$0.1 mg) [30]. Patients with PD_{15} $\leqslant$1.6 mg were considered to have increased bronchial responsiveness. Previous study has shown that moderate to severe BHR (PD_{15} $\leqslant$0.40 mg) has a high specificity for asthma [28].

F_{ENO} was measured using computerised equipment with a chemiluminescence analyser (Niox; Aerocrine AB, Sweden), according to American Thoracic Society (ATS) recommendations [30]. The patients were seated, wore no nose clip, and were asked to fill their lungs completely with NO-free air, and thereafter to exhale with a mean$\pm$10% and instantaneous flow of 50 ± 5 mL·s^{-1}. An exhalation time of 10 s served as the default. The system was calibrated with a certified NO calibration gas mixture according to manufacturer's instructions. Exhalations not meeting ATS requirements were rejected by the system, and the patient was asked to perform new exhalation manoeuvres, until providing three reproducible F_{ENO} values within 10% of each other. The mean F_{ENO} of three acceptable end-expiratory plateau measurements was calculated and recorded [31, 32]. Previously specified reference values for adult lifelong never-smokers, according to the distribution of F_{ENO} by similar technique, and exhalation rate depending on age and height, were used [33].

Atopy

Atopy was defined by a positive SPT to common allergens. To evaluate sensitisation to common allergens, SPTs were carried out for the following common allergens: birch, grass, mugwort, cat, dog, cow, horse, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus* (Soluprick SQ; ALK, Horsholm, Denmark). The patient was regarded as atopic if one or more reactions were positive, determined as a wheal diameter of $\geqslant$3 mm in the presence of an expected response to control solutions; the positive control was histamine dihydrochloride (10 mg·mL^{-1}) and as the negative control was saline. The level of serum IgE was determined based on the standard values of our laboratory, 0–110 kU·L^{-1} for adults.

Statistical analysis

Data was analysed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis used the Chi-squared and Kruskal–Wallis tests. Data are given as frequencies or as mean and

range. The multivariate logistic regression model for occurrence of restrictive ventilation defect, included age, any other associated anomaly, rethoracotomies, thoracotomy-induced rib fusions, oesophageal anastomotic leakage, recurrent TOF, primary pulmonary complications, oesophageal epithelial metaplasia and smoking. A study of the urban adult population of Helsinki served as a comparison group for SPTs [34]. Level of significance was set at $p<0.05$.

Ethics

The ethics committee of the Hospital for Children and Adolescents, Helsinki University Central Hospital approved this study. Written informed consent was obtained from each participant.

RESULTS

Subjects

A total of 72% of the 235 subjects contacted replied, and the first 101 (43%) patients who returned the signed informed consent form were invited to enter the study (fig. 1). Most of those participating (91%) had OA with distal TOF. Because patients who had undergone oesophageal replacement were excluded, each patient had a native oesophagus. Of the 101 participating patients, 95 had undergone primary oesophageal anastomosis, two had undergone a staged anastomosis, and three had undergone a closure of an isolated H-type fistula. Myotomy of the proximal oesophageal pouch to enable primary anastomosis was employed in five subjects. Of the 101 participants, 58 were male, and the mean follow-up time was 36 yrs (range 21–57 yrs) (table 1). Participants and nonparticipants were comparable in terms of age, sex, type of OA, associated anomalies and surgical complications ($p>0.05$). A total of 287 (31%) of the controls responded to the mail questionnaires (table 1).

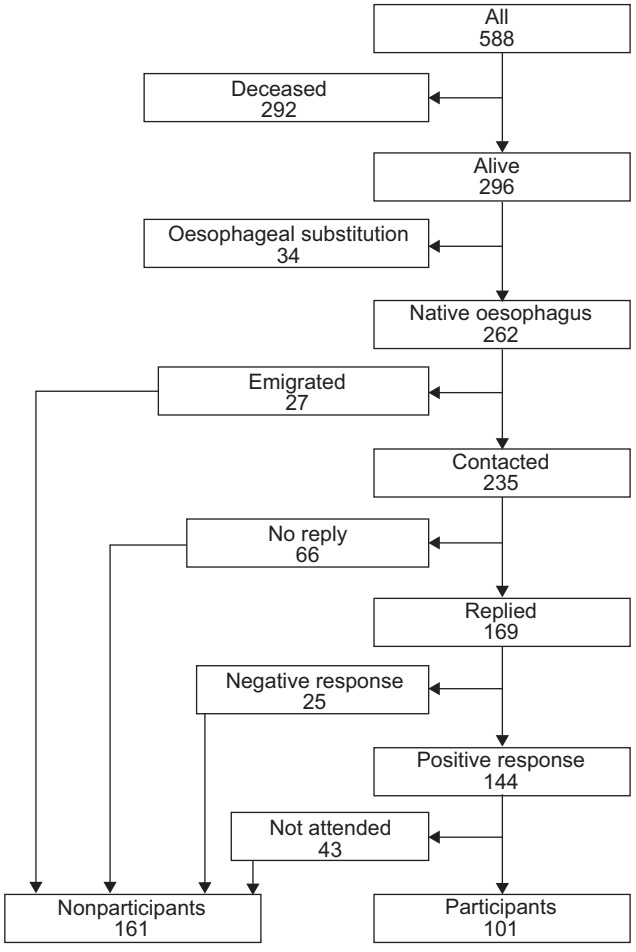

FIGURE 1. Flow chart of study design and patient characteristics.

Tracheopulmonary morbidity in infancy

Of the patients, 34 had suffered pneumonia as a primary pulmonary complication and 32 needed no postoperative ventilation, with the mean postoperative ventilation time being 2.6 days (range 0–7 days) (table 2). During childhood, tracheomalacia was diagnosed in 15 of the patients, but only one had undergone aortopexy. A total of 10 patients had recurrent TOF.

Questionnaires

Participants reported increased incidence of allergy, pneumonia, bronchitis, repeated childhood infections, persistent cough and DDA in relation to controls ($p<0.001$ for all). Among the patients, RSRQoL was significantly decreased ($p<0.001$). Occurrence of tracheomalacia in infancy was associated with neither current respiratory symptoms nor with tendency to respiratory infections ($p>0.05$) (table 3).

Pulmonary function, histamine provocation and exhaled nitric oxide

In flow–volume spirometry, 21 patients had restriction only, 21 had only obstruction only and 36 had both. Accordingly, 57% of the patients had restrictive ventilatory defect. The PF test (PFT) results were similar in males and females ($p>0.05$) (table 4). A total of 41 had BHR. BHR was mild in 26 patients, moderate in 11 and severe in four; 15 patients had moderate to severe BHR compatible with asthma. BHR was associated with atopy ($p<0.007$) and with current respiratory symptoms ($p<0.03$). F_{ENO} was clearly elevated only in four patients, and slightly elevated in seven of the patients, but was associated neither with BHR, atopy, current respiratory symptoms, nor PF abnormalities.

Atopy

37 patients had at least one positive reaction to common allergens in SPT, and sensitisation to multiple allergens was evident in 22. Positive SPT reactions to the most common allergens were dog (28%), cat (22%), birch (23%), mugwort (22%), and timothy grass (21%). Elevated levels of serum IgE >110 kU·L^{-1} occurred in 20 patients (median 285 kU·L^{-1}, range 126–2,436 kU·L^{-1}). Elevated IgE was associated with multiple sensitisations ($p<0.001$), current respiratory symptoms ($p=0.015$) and BHR ($p<0.007$), whereas multiple sensitisations were associated with current respiratory symptoms ($p=0.008$).

Predictors of restrictive ventilation

Restrictive ventilation defect was only associated with the occurrence of oesophageal epithelial metaplasia in adulthood ($p=0.038$), but not with tracheomalacia in infancy, history of primary pneumonia, age, airway inflammation in adulthood, or current respiratory symptoms ($p>0.05$ for each). In a multivariate logistic regression analysis, thoracotomy-induced

TABLE 1 Characteristics of the participants and nonparticipants with repaired oesophageal atresia (OA) and tracheo-oesophageal fistula (TOF), and general population-derived controls

	Participants	Nonparticipants	Controls
Subjects	101	161	287
Males	58 (58)	83 (64)	117 (41)
Age yrs	36 (22–56)	37 (22–56)	36 (22–56)
BMI kg·m^{-2}	24 (21–45)		25 (21–46)
OA			
With proximal TOF	2 (2)	3 (2)	
With distal TOF	91 (91)	120 (89)	
With double TOF	5 (5)	10 (7)	
TOF only	3 (3)	3 (2)	
Associated anomalies			
Primarily	30 (30)	56 (35)	
Currently	72 (72)		
VACTERL			
Primarily	5 (5)	8 (5)	
Currently	23 (23)		
Anastomotic complications			
Leak	4 (4)	4 (3)	
Recurrent TOF	10 (10)	10 (7)	
Stricture requiring early resection	3 (3)	3 (2)	
Oesophageal epithelial metaplasia in adulthood	21 (21)		
GOR			
Antireflux medication	10 (10)		
Antireflux surgery	10 (10)	8 (6)	

Data are presented as n, n (%) or mean (range). BMI: body mass index; VACTERL: vertebral defects, anal atresia, cardiovascular anomalies, TOF with OA, renal dysplasia and limb anomalies; GOR: gastro-oesophageal reflux. No significant differences between the groups (Chi-squared test p>0.1).

rib fusions (OR 3.4, 95% CI 1.3–8.7; p=0.01) and GOR-associated oesophageal epithelial metaplasia in adulthood (OR 3.0, 95% CI 1.0–8.9; p=0.05) were the most significant risk factors for restrictive ventilation defect. Neither increasing age, sex, other associated anomalies, primary lung complications, primary surgical complications, nor number of thoracotomies, predicted the incidence of restriction.

TABLE 2 Tracheo-pulmonary morbidity at primary repair of oesophageal atresia among participants and nonparticipants

	Participants	Nonparticipants
Subjects	101	161
Primary pneumonia	34 (34)	47 (33)
Need for postoperative ventilation		
None	33 (33)	66 (41)
1 day	6 (6)	25 (16)
2 days	22 (22)	27 (17)
3–6 days	26 (26)	31 (19)
>7 days	13 (13)	15 (9)
Tracheostomy	1 (1)	0
Tracheomalacia	15 (15)	13 (8)
Aortopexy	1 (1)	4 (2)
Recurrent TOF	10 (10)	10 (7)

Data are presented as n or n (%). TOF: tracheo-oesophageal fistula. No significant differences (Chi-squared test p>0.076).

DISCUSSION

To the best of our knowledge, this is the largest and only population-based study on respiratory morbidity and PF in adults with repaired OA. We used validated questionnaires with controls derived from the general population that were carefully matched for age, sex, and municipalities of residency. A drop-out analysis between participants and nonparticipants suggested that the two groups were comparable with respect to primary disease characteristics, minimising the risk of selection bias. We found an increased incidence of daily respiratory symptoms and asthma, as well as decreased RSRQoL. PF abnormalities were detectable in 78% of the patients: restriction in 57%, obstruction in 55% and both these ventilation defects in 36%. Occurrence of restrictive PF after repair of OA was associated with thoracotomy-induced rib fusion, which was present in one-third, and GOR-associated oesophageal epithelial metaplasia in one-fifth of the patients. However, the restrictive ventilation defect showed no association with current respiratory symptoms.

Environmental factors, such as cold climate, and inhaled allergens and irritants, have a substantial effect on respiratory symptoms among the general population [35]. In Finland, prevalence of DDA among children is 8.8% [16] and is 6%

TABLE 3 Self-reported occurrence of asthma, allergy and symptoms of the adult patients with repaired oesophageal atresia (n=101) who participated the clinical studies, and of controls (n=287)

	Patients	Controls	p-value
Impaired RSRQoL	11	6	0.001
Current respiratory symptoms	11	2	0.001
DDA	16	6	0.001
Wheeze	37	30	NS
Allergy	42	11	0.002
Persistent cough	31	8	0.001
Pneumonia	56	20	0.001
Bronchitis	70	50	0.001
Recurrent respiratory infections	52	23	0.001
Childhood respiratory infections	35	13	0.001

Data are presented as %, unless otherwise stated. RSRQoL: respiratory symptom-related quality of life index, as defined in [27]; DDA: doctor-diagnosed asthma.

among adults [17], whereas in patients with OA it is even higher [9, 10, 12, 14, 15]. In the present study, 16% of the adult patients with repaired OA and 6% of the general population-derived controls have DDA. These figures are in line with other findings [9, 10, 12, 14, 15]. Self-reported wheeze occurred in 37% of the patients and in 30% of the controls. Self-reported wheeze usually occurs in ~37% of the survivors of OA with no tendency toward improvement with age [4, 10, 11, 13, 14].

In the present study, occurrence of respiratory symptoms was clearly lower among the adult study population than in children and adolescents with repaired OA [9, 10, 12], suggesting that prevalence of respiratory problems decreases with age. Nevertheless, decreased RSRQoL and daily respiratory symptoms were still significantly more common among patients than among controls. Incidences of asthma and BHR were in line with previous results, whereas the PF abnormalities were more common among our adults than in children and adolescents [9, 14, 18, 20, 21, 36], in accordance with other findings among adults [19].

The proportion of children and adolescents with repaired OA having a restrictive PF defect has ranged 21–40%, and 16–54% with obstructive ventilation defect [9, 18, 20, 21, 36]. Our respective figures were 57% and 55%. PF abnormalities have not shown a correlation with respiratory or oesophageal symptoms [9, 21, 36]. Although a clear link exists between severity of GOR and persistence of respiratory symptoms among OA survivors [4], the reason for PF abnormalities is unclear. They have been suggested to result from recurrent aspiration [21], from poor tracheal clearance leading to recurrent episodes of bronchitis and pneumonia causing lung damage [15, 36], or from poor lung growth during infancy [18]. In the present study, thoracotomy-induced rib fusion and GOR-associated epithelial metaplasia of the oesophagus were significant predictors of restrictive ventilation defect. Thus, epithelial metaplasia served as a surrogate marker for significant GOR, which may result in repeated aspiration and lung damage. However, rib fusion leads to an immobile and thus restrictive thoracic cage.

TABLE 4 Pulmonary function, bronchial hyperresponsiveness, exhaled nitric oxide, and skin prick test (SPT) among adult patients with repaired oesophageal atresia (n=101)

Variable	Result	Abnormal	Grade		
			Mild	Moderate	Severe
Age yrs	36 (21–57)				
BMI kg·m^{-2}	24 (21–45)				
Spirometry					
FVC % pred	77 (53–120)	57	28	28	1
FEV_1 % of FVC pred	100 (72–119)	57	25	29	3
Restriction[#]		21	18	3	0
Obstruction[¶]		21	15	4	2
Both restriction and obstruction		36	10	25	1
Any abnormality		78			
Histamine challenge test					
PD_{15} mg	0.65 (0.03–1.60)	41	26	11	4
PD_{15} <0.4 mg		15			
Exhaled nitric oxide elevated		11	7	4	0
Positive SPT		37	15		22

Data are presented as mean (range) or %. BMI: body mass index; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; PD_{15}: provocative dose of histamine causing a 15% fall in FEV_1. [#]: restriction is defined as FVC <80%, z-score < -2.0; [¶]: obstruction is defined as FEV_1/FVC <87%, z-score < -2.0.

Prevalence of BHR in the general Finnish population with no previous diagnosis of asthma or chronic bronchitis and with normal lung volumes is 17% [37]. In our study population, BHR occurred markedly more frequently in 41%, which is in accordance with the results of other studies [9, 18, 20, 36]. It has been postulated that increased bronchial reactivity in these patients would merely reflect sequalae of chronic lung disease from damaged epithelium in the airways caused by recurrent aspiration of acidic gastric contents [18]. Severe or moderate BHR has been associated with a more restrictive ventilatory defect among adolescents [9], but no correlation has emerged between increased BHR and history of asthma or atopic eczema [9, 36]. In the present study, BHR was associated with current respiratory symptoms and atopy. Atopy prevalence was 37%, and 22% had multiple sensitisations, in accordance with incidences of 34–47% and 16–42% among the general population, respectively [34].

Increased F_{ENO} is associated with the steroid-responsive eosinophilic airway inflammation, higher particularly in patients with atopic asthma [32]. Elevated F_{ENO} was detectable in 23% of the adolescents with repaired OA [9]. Elevated values were detectable only in patients with atopy and increased BR, but with no relation to respiratory symptoms [9]. Among the present study population, elevated F_{ENO} occurred in 11% of subjects. F_{ENO} was associated with neither current respiratory symptoms, atopy, nor pulmonary abnormalities. In short, in adult patients with repaired OA, airway inflammation was uncommon in the absence of atopy.

In conclusion, respiratory-related morbidity, restrictive ventilatory defect and BHR extend into adulthood after repair of OA in a significant number of patients, whereas obstructive ventilatory defect is not the main pulmonary problem. Nearly half the patients had BHR and over half had restrictive ventilatory defect. Thoracotomy-induced postoperative rib fusions and GOR-associated oesophageal epithelial metaplasia in adulthood were the strongest risk factors for restrictive ventilatory defect.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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