Very prematurely born infants wheezing at follow-up: lung function and risk factors

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Objectives: To determine whether abnormalities of lung volume and/or airway function were associated with wheeze at follow-up in infants born very prematurely and to identify risk factors for wheeze.

Design: Lung function data obtained at 1 year of age were collated from two cohorts of infants recruited into the UKOS and an RSV study, respectively.

Setting: Infant pulmonary function laboratory.

Patients: 111 infants (mean gestational age 26.3 (SD 1.6) weeks).

Interventions: Lung function measurements at 1 year of age corrected for gestational age at birth. Diary cards and respiratory questionnaires were completed to document wheeze.

Main outcome measures: Functional residual capacity (FRC_{pleth} and FRC_{He}), airways resistance (R_{aw}), $FRC_{He}:FRC_{pleth}$ and tidal breathing parameters ($T_{PTEF}:T_E$).

Results: The 60 infants who wheezed at follow-up had significantly lower mean FRC_{He} , $FRC_{He}:FRC_{pleth}$ and $T_{PTEF}:T_E$, but higher mean R_{aw} than the 51 without wheeze. Regression analysis demonstrated that gestational age, length at assessment, family history of atopy and a low $FRC_{He}:FRC_{pleth}$ were significantly associated with wheeze.

Conclusions: Wheeze at follow-up in very prematurely born infants is associated with gas trapping, suggesting abnormalities of the small airways.

In the past, prematurely born children were reported to suffer frequent respiratory symptoms at follow-up.^{1–3} Such infants, particularly if they went on to develop bronchopulmonary dysplasia (BPD), had often been exposed to high peak inflating pressures and inspired oxygen concentrations and suffered severe lung injury. Nowadays, very prematurely born infants (that is, those born at <29 weeks of gestational age) may have mild or even no respiratory distress in the immediate neonatal period.⁴ Nevertheless, they are frequently wheezy at follow-up.⁵ The limited post-mortem data available from very prematurely born infants demonstrate that even those who had had BPD had minimal lung inflammation and fibrosis, but had evidence of arrest in alveolar development.^{6–7} Therefore, it cannot be assumed that such infants will have abnormalities of airway function at follow-up. Unfortunately, there is only one study⁸ exclusively reporting lung function at follow-up of very prematurely born infants (<29 weeks of gestational age) and as the infants were born approximately 15 years ago, they were exposed to different perinatal care practices. The aim, therefore, of this study was to characterise the lung function abnormalities of very prematurely born infants with wheeze at follow-up, as this will inform their optimum management. In addition, we wished to determine risk factors for wheeze at follow-up.

METHODS

Data from infants who had been recruited into either a randomised trial of ventilation strategies (UKOS)⁹ or a prospective follow-up study examining the impact of respiratory syncytial virus (RSV) infection in prematurely born infants (RSV study)¹⁰ and had lung function assessment at 1 year of age corrected for prematurity were analysed in this study. We combined the two datasets so that we were able to report lung function results from a large number ($n = 111$) of very prematurely born infants. All the infants entered into UKOS⁹ and assessed at 1 year corrected¹¹ were born prior to 29 weeks

of gestation. Only data from infants born prior to 29 weeks of gestation entered into the RSV study¹⁰ were analysed in this study.

The infants from both studies were examined in the Amanda Smith infant pulmonary function laboratory at King's College Hospital, London using the same equipment and techniques. No infant was tested within at least 2 weeks of a respiratory tract infection. Length was measured using a stadiometer (R511A Rollametre cm.100; Raven Equipment, Dunmow, Essex, UK) and weight using electronic scales (MPBT35 digital baby/toddler scale; Marsden Weighing Machine Group, Henley-on-Thames, Oxfordshire, UK) prior to lung function measurements. The Institute of Child Health Growth charts were used.¹² The infants were sedated with 80–120 mg/kg of chloral hydrate and monitored by pulse oximetry (Datex-Ohmeda 3800; Datex-Ohmeda, Hatfield, UK) throughout the pulmonary function testing and afterwards until they were awake. Once asleep, the infant was laid supine in the plethysmograph (Department of Medical Engineering, Hammersmith Hospital, London, UK), which had a total volume of 90 litres and included a heated, humidified rebreathing system. The infant breathed through an appropriately sized Rendell-Baker face mask, sealed around the nose and mouth with silicone putty. The mask deadspace was calculated as 50% of the water-displacement measurement with the silicone putty in situ.¹³ Pressure at the airway opening (P_{ao}) was measured using a differential pressure transducer (range ± 5 kPa; MP45, Validyne Engineering, Northridge, CA, USA) connected to a port in the mask support. The mask support also incorporated a thermistor measuring airway temperature and was connected to a heated pneumotachograph (Fleisch,

Abbreviations: 95% CI, 95% confidence intervals; BPD, bronchopulmonary dysplasia; FRC, functional residual capacity; OR, odds ratio; PMA, post-menstrual age; RSV, respiratory syncytial virus; SGA, small for gestational age

Lausanne, Switzerland) to measure airflow. The pneumotachograph was attached to a differential pressure transducer (range ± 0.2 kPa; MP45, Validyne). The total deadspace of the breathing apparatus, including the mask and all tubing connecting the transducers, measured by water displacement,¹³ was 31 ml. Pressure changes within the plethysmograph were measured using a differential pressure transducer (range ± 0.2 kPa; MP45, Validyne). All signals were amplified (CD18 carrier amplifiers; Validyne) and the flow signal integrated electrically to give tidal volume (FV156 integrator; Validyne). The resultant four channels of data were acquired, analysed and displayed in real time on a personal computer (Gateway GP7-500; Gateway, Dublin, Ireland) running a computer program custom-designed using LabWindows software (National Instruments, Austin, TX, USA) with analogue-to-digital sampling at 200 Hz (PC-LPM-16PnP; National Instruments). All channels were calibrated prior to each patient test, as previously described.¹¹

Following application of the face mask, time was allowed for the infant to settle and tidal breathing was then recorded for 1 min, from which a minimum of 20 breaths were recorded for analysis of tidal breathing, including calculation of the time taken to achieve peak expiratory flow, expressed as a proportion of expiratory time ($T_{PEF}:T_E$), and respiratory rate. At least 20 acceptable breaths were analysed (median 28, range 24–36). Plethysmographic estimation of lung volume (plethysmographic functional residual capacity, FRC_{pleth}) was then undertaken. FRC_{pleth} was calculated from a minimum of three end-inspiratory occlusions. A time-based trace of all four data channels and an x/y plot of V_{pleth}/P_{ao} during each occlusion were displayed by the computer. Occlusions were considered acceptable if V_{pleth} and P_{ao} were in phase and no airflow was evident. The infant was then switched to the rebreathing bag. Individual breaths acquired during periods of rebreathing were displayed as x/y plots of $V_{pleth}/flow$ by the computer. Only technically acceptable breaths, that is, the loop was closed or nearly closed at points of zero flow, were used in the analysis. Airways resistance (R_{aw}) was calculated electronically using an established formula by applying a regression line to the selected portion of the loop. R_{aw} was calculated during initial inspiration between 0 and 50% maximal inspiratory flow, and during expiration between 0 and 50% maximal expiratory flow.¹⁴ During all R_{aw} measurements, the computer calculated the apparatus resistance of the selected portion of the individual breath by relating ΔP_{ao} to $\Delta flow$ and then subtracted this value from the total measured resistance.

On completion of the plethysmographic measurements, lung volume was estimated by a helium gas dilution technique (FRC_{He}). FRC_{He} was measured whilst the infant lay undisturbed on the base of the plethysmograph, using the same mask with silicone putty. During the initial stages of the study, FRC_{He} was determined using a water-sealed spirometer (Pulmonet III; Gould, Bilthoven, The Netherlands), as described previously.¹¹ The deadspace of the breathing apparatus, including the mask and filter, was 66 ml. Most infants in the UKOS respiratory follow-up study¹¹ and all in the RSV study¹⁰ were tested using the EBS 2615 system (Equilibrated Bio Systems, New York, USA), which consisted of a 500-ml rebreathing bag in a closed heliox circuit. The deadspace of this system, including mask and filter, was 22 ml. The system was modified to produce a time-based display of flow and tidal volume, allowing accurate switching into the circuit at end expiration. An online display of the helium dilution curve allowed precise determination of gas equilibration. For both FRC_{He} techniques, the mean of two recordings that were within 10% of each other was taken. The FRC_{He} of 12 infants was measured using both devices in order to assess comparability.

The agreement between the two devices was assessed using the Bland-Altman method.¹⁵ The mean (SD) difference in measured FRC_{He} was 3.4 (12.5) ml (1.76% of the mean measured FRC_{He}) with 95% limits of agreement of 21.2 to 27.9 ml.¹¹ The FRC_{He} results from the EBS 2615 from these 12 infants were included in the study.

Diary cards were completed by the parents when the infants were 11 months of age corrected for gestational age at birth. The parents recorded on a daily basis for a 2-week period in the UKOS study and for a 4-week period in the RSV study; for the purpose of this analysis only the first 2 weeks of the RSV diary cards were analysed. Questionnaires also were administered to the parents at follow-up to further document wheeze, family history of atopy (parents or siblings with asthma, eczema or hay-fever) and smoke exposure at home. Data were obtained from the medical records regarding maternal smoking in pregnancy, gestation and weight at birth, from which birth centile was calculated. Small for gestational age (SGA) was diagnosed if the infant was less than the tenth percentile in weight for gestational age. In addition, the duration of ventilation and whether the infants had had BPD (oxygen dependency beyond 36 weeks post-menstrual age (PMA)) were determined.

Analysis

The infants were divided into two groups according to whether they wheezed on at least 1 day in a 2-week period (see above) (wheeze group) or did not wheeze during that period (no wheeze group). Comparisons were made using *t* tests (continuous data) and χ^2 tests (categorical data). The two data sets were combined for analysis by wheeze status and allowance was made for the two different source data sets in the modelling. Logistic regression was used to model factors associated with wheeze at age 1 year in two stages: (i) using antenatal and postnatal factors that were significant in unifactorial analyses and (ii) using factors measured at age 1 year that were significant in unifactorial analyses. Backward elimination was used to remove non-significant factors at each stage. Variables which remained significant in each of stages (i) and (ii) were then modelled together to give a final model. $p < 0.05$ was used to define statistical significance. Results are presented as odds ratios (OR) and 95% confidence intervals (95% CI).

Patients

All 76 infants from UKOS who had pulmonary function studies at 1 year of corrected age¹⁰ and 35 infants from the RSV study¹¹ were included in this study (table 1). UKOS was approved by the South Thames Multicentre Research Ethics Committee and the King's College Hospital Research Ethics Committee. The RSV study was approved by the King's College Hospital and Guy's and St Thomas' Hospital Research Ethics Committees. Parents gave informed written consent for their infant to take part in the studies.

RESULTS

Comparison of the demographics of the two study groups revealed that the only significant differences between them was that the infants in the UKOS study were shorter ($p = 0.03$) and lighter ($p = 0.001$) at 12 months corrected age than those in the RSV study (table 1).

Sixty infants wheezed at follow-up (median number of days of wheeze was 4 (range 1–14)) (fig 1). The infants who wheezed at follow-up compared to those who did not were of lower mean birth weight ($p = 0.05$), more immature at birth ($p < 0.001$), had required a longer duration of ventilation ($p = 0.003$), more had had BPD ($p = 0.003$) and more had a

Table 1 Demographics of the study populations

	All	UKOS study group	RSV study group	p Value
n	111	76	35	
Sex (% male)	63 (57%)	44 (53%)	19 (66%)	0.19
Gestational age (weeks)	26.5 (1.5)	26.4 (1.5)	26.8 (1.5)	0.29
Birth weight (g)	867 (202)	855 (176)	894 (245)	0.35
SGA	23 (21%)	17 (22%)	6 (17%)	0.53
BPD	70 (63%)	44 (58%)	26 (74%)	0.10
Days ventilated*	13 (4, 29)	14 (5, 32)	10 (3, 24)	0.23
At lung function assessment				
Length (cm)	74.6 (2.9)	74.2 (3.0)	75.5 (2.8)	0.03
Weight (g)	9.1 (1.3)	8.9 (1.3)	9.7 (1.4)	0.001
Wheeze (at 11–12 months)	60 (54%)	43 (57%)	17 (49%)	0.43

*The days of ventilation data are skewed, hence the median (interquartile range) is reported.

Data are presented as mean (SD) or n (%) unless otherwise stated. BPD, bronchopulmonary dysplasia; SGA, small for gestational age (<9th centile).

family history of atopy ($p = 0.004$) (table 2). The infants who wheezed were also shorter at follow-up ($p = 0.001$) and had a lower mean FRC_{He} (ml) ($p < 0.02$), mean $FRC_{He}:FRC_{pleth}$ ($p = 0.001$) and mean $T_{PTEF}:T_E$ ($p = 0.04$) but a higher mean R_{aw} ($p = 0.04$) (table 3).

Regression analysis demonstrated that the factors significantly related to wheeze were gestational age ($p = 0.005$), family history of atopy ($p = 0.009$), length at assessment ($p = 0.016$) and $FRC_{He}:FRC_{pleth}$ ($p = 0.005$) (table 4). Days of wheeze were significantly correlated to $FRC_{He}:FRC_{pleth}$ ($p = 0.015$).

DISCUSSION

We have demonstrated that very prematurely born infants who wheeze at follow-up have greater evidence of gas trapping than infants without wheeze, as they have a significantly lower $FRC_{He}:FRC_{pleth}$. These data suggest the very prematurely born infants who wheeze have abnormalities of the small airways.

Infants were entered into the wheeze group if they wheezed on at least 1 day in a 2-week period of diary card completion. Using such a definition, it is possible that we included some infants who had very mild symptoms, yet there were significant differences between the groups. In addition, we highlight a significant correlation between days of wheeze and $FRC_{He}:FRC_{pleth}$ in these very prematurely born infants.

There have been few reports of lung function at follow-up of infants born very prematurely. Doyle *et al*⁸ demonstrated that children born prior to 28 weeks of gestation and/or with a birth weight of <1000 g, when studied at 8–9 years of age, had diminished respiratory function variables reflecting air flow abnormalities. Their cohort, however, received only rescue surfactant and maternal smoking data were not reported. Others reported findings consistent with signs of dysfunction of the terminal respiratory units, that is, impaired gas mixing.¹⁶ That

study, however, included more mature infants, the gestational age range of the study population being 25–33 weeks.

On univariate analysis, the infants who wheezed had a significantly higher mean R_{aw} and a lower mean $T_{PTEF}:T_E$, suggesting they had large airways abnormalities. R_{aw} , however, is significantly related to length and as the infants who wheezed were significantly shorter at assessment, this may explain the relationship with wheeze. Indeed, regression analysis demonstrated length at assessment was significantly associated with wheeze, whereas R_{aw} and $T_{PTEF}:T_E$ were not. FRC_{He} (ml) was significantly lower in the wheeze group. As FRC_{pleth} did not differ significantly between the two groups, it is likely that the lower FRC_{He} in the wheeze group indicated the presence of gas trapping. BPD was significantly more common in the wheeze group. Decreased alveolarisation is seen at post-mortem in infants with “new” BPD^{6,7} and in ventilator- and oxygen-exposed baboons.¹⁷ Those data would suggest that, as the wheeze group had a significantly greater proportion of BPD infants, they would have had lower lung volumes. Indeed, we have previously demonstrated¹⁸ that at 33–39 weeks PMA, infants with mild to moderate BPD had lower lung volumes than those without BPD. In the present study population, however, we saw only significantly low FRC_{He} , but not FRC_{pleth} , in the wheeze group. They were studied at 1 year of corrected age, so it is possible that abnormalities in lung volume may disappear with increasing postnatal age. Serial measurements are required to test such a hypothesis.

Our FRC_{pleth} results are higher than those reported by Hulskamp *et al*¹⁹ who used a Jaeger plethysmograph. They also documented plethysmographically determined FRC results in infants and children from a series of studies and interpreted the results, except from one report,²⁰ as demonstrating a progressive decline in plethysmographic lung volumes in infants. They

Table 2 Antenatal and postnatal factors according to wheeze status at follow-up

	Wheeze	No wheeze	OR (95% CI)	p Value
n	60	51		
Birth weight (g)	831 (198)	910 (199)	1.22 (1.00, 1.49)	0.05
Gestational age (weeks)	26.0 (1.5)	27.1 (1.2)	1.76 (1.30, 2.36)	<0.001
SGA	15% (9/60)	27% (14/51)	0.45 (0.18, 1.16)	0.10
Antenatal smoking	13% (8/60)	8% (4/51)	1.83 (0.51, 6.49)	0.35
Males	62% (37/60)	51% (26/51)	1.62 (0.75, 3.50)	0.22
Duration of ventilation (days), median (IQ)	17 (9, 35)	12 (3, 20)	1.43 (1.11, 1.84)	0.006
BPD	75% (45/60)	49% (25/51)	3.46 (1.51, 7.93)	0.003
Family history of atopy	55% (33/60)	29% (15/51)	3.35 (1.46, 7.64)	0.004
Parental smoking at home	37% (22/60)	25% (13/51)	1.66 (0.73, 3.77)	0.23

Odds ratio (OR) for birth weight is per 100 g decrease in birth weight. Odds ratio for gestational age is per week decrease in gestation. Odds ratio for duration of ventilation is per 10 days increase in duration. p Values are all adjusted for study to allow for differences in baseline factors between the two study groups. The data are presented as the mean (SD) or % (n) unless otherwise stated. BPD, bronchopulmonary dysplasia; IQ, interquartile range; SGA, small for gestational age (<9th centile).

Figure 1 Airway resistance results (individual results are displayed according to wheeze status).

hypothesised that the diminished values of plethysmographic lung volumes in healthy infants primarily reflected gradual technological advances and refinements in protocols over the last 30 years rather than any physiological changes in lung growth and development in early life or differences in background characteristics of the tested infants.¹⁹ The largest study ($n = 264$) included in their comparative data, however, reported a mean plethysmographic lung volume of 29.7 ml/kg²⁰ and we recently reported that very prematurely born infants examined using a Hammersmith plethysmograph at a corrected age of 1 year had a mean FRC_{pleth} of 26.7 ml/kg.¹¹ In an in vitro study, we compared results given by the Hammersmith and Jaeger plethysmographs to a lung model and found that the Hammersmith, but not the Jaeger, plethysmograph gave results which were similar to those of the lung model.²¹ The significantly lower mean FRC_{pleth} results obtained using the Jaeger, compared to the Hammersmith, plethysmograph we therefore interpret as representing under-recording by the Jaeger plethysmograph.²¹

There are limitations to our study. In particular, the infants were not recruited a priori to determine lung function abnormalities in very prematurely born infants who were wheezy at follow-up, but rather into two separate studies. The demographics of the two study populations, however, were very similar and only differed significantly with regard to length and weight at follow-up (table 1). Also, as the majority of infants were studied using the same equipment and all using the same plethysmograph, we feel our results are valid. The analysis undertaken specifically looked to see if differences in lung

Table 4 Factors related to wheeze according to logistic regression analysis

	OR (95% CI)	p Value
Gestational age (weeks)	1.64 (1.16 to 2.30)	0.005
Family history of atopy	3.81 (1.40 to 10.40)	0.009
Length at assessment (cm)	1.26 (1.04 to 1.51)	0.016
Length z score	1.89 (1.30 to 2.69)	0.001
$FRC_{He}:FRC_{pleth}$	1.84 (1.20 to 2.83)	0.005

Odds ratios for gestational age and length are per unit decrease in factor. Odds ratio for $FRC_{He}:FRC_{pleth}$ is per 0.1 decrease in $FRC_{He}:FRC_{pleth}$. Pseudo R-squared = 27%. p Values are all adjusted for study to allow for differences in baseline factors between the two study groups.

function between wheezy and non-wheezy infants differed by study, demonstrated no significant effect by study. A further possible limitation was that we did not have information for infants entered into UKOS regarding whether they had had an RSV infection. Children born at term²² or prematurely¹¹ have an excess of wheeze at follow-up following RSV infection and RSV infection has been associated with lung function abnormalities in infants born at term.^{23–26} The abnormalities reported, however, are hyperinflation,^{23–26} elevated resistance²³ and reduced $T_{PTEF}:T_E$.²⁴ Regression analysis demonstrated that neither R_{aw} nor $T_{PTEF}:T_E$ was significantly associated with wheeze in the very prematurely born infants we assessed. We would also emphasise that our study was not designed to identify the mechanism of wheeze at follow-up but rather to determine the lung function abnormalities associated with wheeze in very prematurely born infants, as this could have implications for treatment.

In this population, wheezing at follow-up was not associated with intrauterine growth retardation or antenatal smoking. Previous studies have demonstrated that wheezing is increased in children who were SGA.²⁷ The present population, however, was born at a very early gestation and it is possible that growth retardation may have less impact on the lung function of such infants. In infants born at term,²⁸ exposure to antenatal smoking has been significantly associated with wheeze and abnormal lung function. The incidence of maternal smoking in that study,²⁸ however, was 44%, whereas only 11% of those infants presently studied were exposed in utero to maternal smoking. Although univariate analysis demonstrated that the infants who wheezed differed significantly from those who did not wheeze with regard to their gestational age, duration of ventilation, BPD status and a family history of atopy, only gestational age and a family history of atopy remained significant factors for wheeze following regression analysis. Duration of ventilation and BPD status are highly negatively

Table 3 Lung function at follow-up according to wheeze status

	Wheeze	No wheeze	OR (95% CI)	p Value
n	60	51		
Length at assessment (cm)	73.7 (3.15)	75.7 (2.47)	1.27 (1.10 to 1.47)	0.001
Length z score	-0.67 (1.20)	0.12 (1.04)	1.89 (1.30 to 2.69)	0.001
Weight at assessment (kg)	8.94 (1.30)	9.38 (1.43)	1.26 (0.94 to 1.69)	0.13
Weight z score	-1.16 (1.40)	-0.55 (1.53)	1.20 (0.92 to 1.48)	0.21
FRC_{pleth} (ml)	250.5 (61.4)	251.1 (71.6)	1.01 (0.99 to 1.02)	0.10
FRC_{pleth} (ml/kg)	28.3 (6.4)	27.7 (5.8)	0.98 (0.92 to 1.04)	0.48
FRC_{He} (ml)	199.8 (66.4)	228.5 (68.0)	0.98 (0.97 to 0.99)	0.02
FRC_{He} (ml/kg)	23.3 (4.6)	25.1 (5.3)	1.07 (0.99 to 1.16)	0.08
$FRC_{He}:FRC_{pleth}$	0.83 (0.13)	0.91 (0.11)	1.84 (1.27 to 2.65)	0.001
R_{aw} (kPa/l/s)	3.34 (1.58)	2.65 (0.96)	1.57 (1.09 to 2.26)	0.02
$T_{PTEF}:T_E$	0.24 (0.08)	0.28 (0.11)	1.68 (1.03 to 2.74)	0.04
Respiratory rate (breaths per minute)	32.7 (7.5)	32.2 (5.2)	1.01 (0.95 to 1.07)	0.65

Odds ratios for length, weight, FRC_{pleth} and FRC_{He} are all per unit decrease in the "factor", eg, odds ratio for length is per cm decrease in length. Odds ratios for $FRC_{He}:FRC_{pleth}$ and $T_{PTEF}:T_E$ are per 0.1 decrease in $FRC_{He}:FRC_{pleth}$ or $T_{PTEF}:T_E$. Odds ratio for R_{aw} is per unit increase in R_{aw} . p Values are all adjusted for study to allow for differences in baseline factors between the two study groups. The data are presented as the mean (SD).

What is already known on this topic

- There are no data documenting the lung function of very prematurely born infants wheezy at follow-up.
- Very prematurely born infants with BPD are frequently wheezy at follow-up; limited post-mortem data suggest that they have minimal lung inflammation and fibrosis but have evidence of arrest of alveolar development.

What this study adds

- We have demonstrated, in infants born prior to 29 weeks of gestational age, that gestational age, length at assessment, family history of atopy and a low functional to total lung volume were significantly associated with wheeze at follow-up.
- These data highlight that wheeze at follow-up in very prematurely born infants is associated with gas trapping, suggesting abnormalities of the small airways.

correlated with gestational age at birth.¹⁰ Their elimination from the multifactorial model suggests that the adverse effect on respiratory health is primarily due to low gestational age rather than its consequences.

In conclusion, we have demonstrated that very prematurely born infants who have wheeze at follow-up have evidence of gas trapping, suggesting they have abnormalities of small airway function. As it is not certain that such infants would respond to bronchodilator therapy, appropriately designed studies are required to determine whether bronchodilator and/or prophylactic anti-asthma therapy have benefits in wheezy, very prematurely born infants.

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