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ORIGINAL PAPER

Factors associated with SiPAP failure in late preterm infants with respiratory insufficiency

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ABSTRACT

Introduction: SiPAP is a popular method of non-invasive respiratory support in Polish NICUs. Risk factors associated with treatment failure in late preterm infants are poorly understood. Aim of the study was to delineate risk factors of treatment failure when SiPAP is used as a primary modality of respiratory support following delivery.

Material and methods: This is a retrospective study that included 184 neonates born between 2009 and 2014 with a mean gestational age (GA) of 34 3/7 weeks, and mean birth weight of 2200 grams. The parameters of ventilation during the use of SIPAP method, neonatal status and complications were compared between the failure and the success group. Success was defined as possibility of discharging from SiPAP. Failure of SiPAP method was defined as necessity for intubation with applying invasive mechanical ventilation or occurrence of pneumothorax. Logistic regression models were used to determine which factors had a significant impact on SiPAP failure.

Results: Treatment failure was noted in 28.8% of infants. Pneumothorax was found in 4.9% of newborns treated with SiPAP. There were no significant differences in GA, birth weight, Apgar score between the groups. In the failure group, the newborns were significantly later connected to the SiPAP device; they also had significantly higher Silverman score. Congenital pneumonia (OR = 2.45), respiratory distress syndrome (RDS) grade II (OR = 5.97), intracranial hemorrhage (IVH) grade II–IV (OR = 3.29), necessity to use sedation drugs (OR = 6.05) and increase of FiO_2 as well as breath rates with SiPAP (OR = 2.85; OR = 16.0) are in relation to the failure of the SIPAP.

Conclusions: Factors associated with SiPAP failure among late preterm infants were a delay in initiation of SiPAP, severity of RDS, high oxygen requirements, and presence of grade II IVH.

KEY WORDS:

infants, non-invasive ventilation, SiPAP failure.

INTRODUCTION

Non-invasive ventilation is currently the preferred method of respiratory support in premature infants with respiratory failure [1–5]. Nasal continuous positive airway pressure (CPAP) and bi-level modalities are both frequently used [2, 5]. Nasal CPAP is a commonly used mode of respiratory support for infants with mild to moderate respiratory distress that increases functional residual capacity by providing a continuous pressure to recruit collapsed alveoli and improve gas exchange in the lungs [1, 2, 5–9]. Bi-level pressure, including the Infant Flow SiPAP system (CareFusion, Yorba Linda, CA) is a modality used for infants that require more respiratory support than CPAP can provide [2, 10–13]. In this mode, the respiratory rate, inspiratory time, and peak inspira-

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tory pressures are present and not synchronized with the breathing effort [1, 2].

The use of non-invasive ventilation is increasing in premature infants of all gestational ages [10–12]. Its popularity is likely related to the overall reduction in the incidence of severe complications, both respiratory and non-respiratory ones [14–16]. However, failure of non-invasive ventilation has been associated with life-threatening complications including pneumothorax and massive haemorrhage within the central nervous system, which suggests further investigation into patient-specific risk factors is needed [17, 18]. Although a review of the literature shows several well-defined risk factors associated with failure of non-invasive ventilation in immature newborns born before 32 week of gestation [18, 19], data regarding more mature infants are less conclusive. Therefore, the aim of this study was to identify risk factors associated with failure of the non-invasive bi-phasic Infant-Flow SiPAP method of respiratory support in a single-centre study of late-preterm infants.

MATERIAL AND METHODS

This retrospective, single center study analyzes the results of treatment with a non-invasive SiPAP ventilation Infant Flow device (CareFusion, Yorba Linda, USA) used in a group of 184 newborns as a first respiratory support after delivery, in the period 2009–2014. The decision to use SiPAP at birth or later during observation of the newborns in the observation room was due to neonatal respiratory inssuficiency. For children who were not immediate on SiPAP, oxygen therapy was applied.

Inclusion criteria: infants treated with SiPAP, gestational age ≥ 32 weeks/birth weight ≥ 1500 g, parents consent to use non-invasive ventilation. Exclusion criteria: intubation/surfactant in delivery room, congenital anomalies.

Demographic data, gestational age, births weight, Apgar score, and laboratory tests such as blood gas analysis, C-reactive protein (CRP), complete blood count (CBC), blood culture, hospitalization time, were extracted from the medical record by the study team.

The variables that were additional obtained and analyzed for the purpose of the study covered also parameters such as: Silverman score, SiPAP application time, the period of time (hours) of SiPAP treatment, Pethidine/Meperidine used for sedation due to anxiety of the newborns on SiPAP, as well as neonatal complications: grade of respiratory distress syndrome (RDS), neonatal pneumonia, and intraventricul hemorhages (IVH) – in all treated patients cerebral ultrasound was performed in the first day after delivery. Necrotizing enterocolitis diagnosed in the following days after SiPAP application was also taken into account.

Respiratory insufficiency was determined by the specialist of pediatric or neonatology providing care to the infants. All clinical symptoms included in the Silverman score and results of blood gas analysis as well as the results of the chest X-ray described by the radiologist were noted in a neonatal observational chart.

Respiratory insufficiency was diagnosed mainly on the basis of clinical symptoms included in the Silverman scale – the score comprises 4 inspiratory categories of movements (thoraco-abdominal, intercostal, sternum, and chin movements) and one expiratory category (grunting). More than 5 points were considered as severe respiratory failure [1]. In addition blood gas analysis taken from arterial cord blood at the delivery room from all patients treated and capillary blood during SiPAP therapy (reduced pH < 7.25, increased pCO_2 > 45 cm H_2O) were taken into account. Because most of our patients did not have arterial blood taken for blood gas analysis within the first hours after delivery, capillary pO_2 were not taken into statistical analysis. Surfactant was not used in any of the analysed patient before or during SiPAP therapy.

RDS or congenital pneumonia was recognised as a reason for respiratory insufficiency. The diagnosis was determined on the basis of chest X-ray examination. Four gradations in the progression and severity of X-ray changes seen in RDS have been outlined [20]. The first, Grade 1, consisted of a fine granularity with some air bronchograms visible. Grade 2 was characterized by a more apparent, distinct, and coarse granularity to the lung fields, with more extensive air bronchograms. Grade 3 was characterized by increasing opacity, with decreasing air bronchograms and granularity. Heart borders were still visible in Grade 3. In Grade 4, diffuse bilateral opacification was present, with lack of apparent heart borders and loss of air bronchograms – a "whiteout" on the chest X-ray [20]. Congenital pneumonia was recognized usually up to 24 hours of life on the basis of clinical and chest X-ray examinations as well as data from maternal perinatal anamnesis.

Parameters for respiratory support such as: FiO_2, positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), mean airway pressure (MAP), number of SiPAP breaths were set by the physician to the patients and noted every hour in the special respiratory support chart from the beginning of application of SiPAP methods as well as anytime of changing the set parameters. Initial parameters of ventilation, 1 hour after SiPAP application and final, before SiPAP was discharged, were compared depending on the achieved effect (success, failure). Success was defined as possibility of newborn's own breath without support. Failure of SiPAP method was defined as necessity for intubation with applying invasive mechanical ventilation or occurrence of pneumothorax (after diagnosis neonate was intubated). Indications for intubation were as follows: respiratory acidosis (pH < 7.20 and PCO_2 > 65 mm Hg), apnoea and bradycardia in spite of noninvasive ventilation; and hypoxia (PaO_2 < 50 mm Hg, SpO_2 < 87%) in spite of non-invasive ventilation with FiO_2 > 0.6 or pneumothorax.

The primary outcome of interest was the necessity for intubation due to failure of SiPAP treatment and a secondary outcome was occurrence of pneumothorax.

The study was approved by the Pomeranian Medical University Ethical Committee (decision No KB – 0012/45/01/2013).

STATISTICAL ANALYSIS

The obtained values of the particular parameters were compared between the subgroups with appropriate statistical analysis tools. Continuous variables were checked for normality of distribution with a Kolmogorov-Smirnov test. Median, minimum and maximum values were used to describe the variables (in cases when the normal distribution assumptions were not met), while in other cases the mean and standard deviation were calculated. Discrete variables were described by the frequency of their occurrence (number, percentage). χ^2 Pearson, χ^2 Yates and χ^2 NW tests were used to study statistical differences or to check the homogeneity of the groups. Statistical differences between continuous variables of the different groups were checked with a Mann-Whitney *U* test. Logistic regression models were used to determine which factors had a significant impact on SiPAP failure. In all the tests conducted, those for which the confidence level was $p < 0.05$ were considered statistically significant.

Statistical analyzes were carried out with the help of the STATA 11 statistical program, license number 30110532736.

RESULTS

184 newborns fulfilled the inclusion criteria, 100 infants males and 84 infant females, 141 born by caesarean section and 43 born spontaneously, on mean 34.3 weeks of pregnancy, and with a mean body weight of 2200 grams.

In 77 (43%) cases, respiratory insufficiency was caused by congenital pneumonia, and in 62 (34.6%) by grade I respiratory distress syndrome (RDS). In 28 newborns grade II RDS, in 11 newborns grade III RDS was diagnosed, and in three newborns, grade IV RDS.

Treatment failure was noted in 28.8% of infants. A single doses of Pethidine was applied during SiPAP therapy in 61.2% patients due to inability to calm a newborn baby through non-pharmacological actions. In the analyzed period of time, this method of sedation was accepted in our neonatology department. Pethidine was used in 45 (34.6%) patients from the success group and in 51 (98.1%) from the failure group (Table 1). There were no significant differences in gestational age, birth weight and Apgar score between the group of infants successfully treated with the SiPAP method, and the group of infants for which the method was unsuccessful (Table 1). In the group of successful intervention, the newborns were connected to the SiPAP significantly ($p < 0.05$) earlier (mean 3.69 h vs. 4.50 h); they also had a significantly lower severity of respiratory insufficiency ($p < 0.001$), because the level of symptoms in the Silverman score was up to 5 points during the time of decision-making regarding non-invasive ventilation, whereas in the group with failure, the most common score was 6 points (Table 1).

A significantly higher pH and significantly lower pCO_2 were found in the group with successful intervention than for failure of the SiPAP therapy (Table 2). There were also significantly lower SiPAP FiO_2 ($p < 0.05$) and breaths rate ($p < 0.01$) (Table 3), and lower PEEP, PIP, MAP values at the final stage of I-F therapy (Fig. 1) compare to initial stage of SiPAP in the group with success noted than for failure.

It was determined that congenital pneumonia (OR = 2.45), grade II and III RDS (OR = 5.97; OR = 7.29), grade II–IV IVH (OR = 3.29), the necessity to use sedation drugs (OR = 6.05), desaturation (OR = 15.83) as well as necessity of increasing SiPAP breaths rate (OR = 16.47) and FiO2 (OR = 2.85), were all more likely to cause ineffective treatment with the SiPAP method (Table 4).

In the course of this study, pneumothorax was found in 4.9% of newborns treated with SiPAP. There was higher intensification of symptoms of respiratory insufficiency defined as 8 points in the Silverman score (in the group without pneumothorax it was ≤ 5), and a tendency to later incorporation time of SiPAP – 2.5 hours compared to

TABLE 1. General characteristics of the groups with success or failure of SIPAP treatment

Evaluated features	Success ($n = 131$)	Failure ($n = 53$)	p
Gestational age**	34.0 (32–36)	34.0 (32–36)	$> 0.20^{\#}$
Birth weight (g)**	2000 (1700–2750)	2200 (1700–2590)	$> 0.90^{\#}$
Apgar 1 min**	7 (1–10)	7 (2–10)	$> 0.70^{\#}$
Apgar 5 min**	8 (5–10)	7 (5–10)	$> 0.51^{\#}$
Silverman scale**	5 (0–10)	6 (2–10)	$\mathbf{< 0.001}^{\#}$
SiPAP application time (h)*	3.69 ±2.8	4.50 ±4.0	$\mathbf{< 0.01}^{\#}$
Period of time of SiPAP treatment (h)**	31 (16–68)	9 (3–30)	$\mathbf{< 0.001}^{\#}$
Pethidine for sedation on SiPAP	45 (34.6%)	51 (98.1%)	$< 0.001^{\#\#}$
Hospitalization (day)**	15.5 (11–27)	19 (13–34)	$> 0.08^{\#}$

**Mean ± SD. **Median (ranges). #Mann-Whitney test. ##χ^2 test*

TABLE 2. Comparison of pH and pCO_2 values in the groups with success and failure

Features	Group	*n*	Mean	SD	*I**
Arterial cord blood pH	Failure	44	7.283	0.077	> 0.81
	Success	110	7.277	0.097	
Initial pH on SiPAP	Failure	44	7.274	0.064	< 0.001
	Success	119	7.319	0.065	
Final pH on SiPAP	Failure	41	7.296	0.088	> 0.001
	Success	117	7.376	0.064	
Arterial cord blood pCO_2	Failure	43	52.17	8.06	> 0.62
	Success	110	54.13	12.89	
Initial pCO_2 on SiPAP	Failure	44	52.52	8.20	> 0.001
	Success	118	47.01	9.78	
Final pCO_2 on SiPAP	Failure	41	52.15	10.94	> 0.001
	Success	117	41.28	8.87	

**Mann-Whitney test*

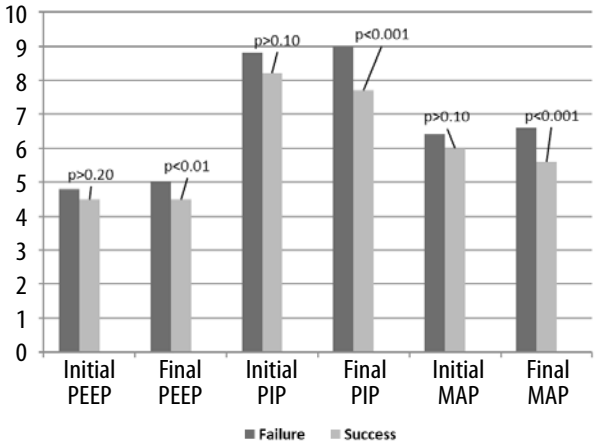

FIGURE 1. Initial and final PEEP (cmH_2O), PIP (cmH_2O), and MAP (cmH_2O) in accordance to success or failure non-invasive ventilation

TABLE 5. Comparison of the general characteristic of the group with or without pneumothorax

Evaluated features	Pneumothorax		*p****
	Yes, *n* = 9	No, *n* = 174	
Gestational age (weeks)*	32.2 ±2.6	34.1 ±3.1	> 0.52
Birth weight (g)*	2108 ±501	2235 ±755	> 0.91
Apgar 1 min**	7 (3-8)	7 (1-10)	> 0.72
Apgar 5 min**	7 (5-8)	8 (5-10)	> 0.06
Silverman score**	8 (0-10)	5 (2-10)	< 0.05
SiPAP application time (h)**	2.5 (1-11)	1 (1-98)	> 0.06
Period of time of SiPAP treatment (h)**	11 (0.25-76)	24 (1-792)	> 0.12
Length of stay (day)*	27.22 ±18.32	20.58 ±13.19	> 0.09

**Mean ± SD. **Median (ranges). ***Mann-Whitney test*

TABLE 3. Initial and final SiPAP FiO_2, and number of SiPAP breaths in accordance to success or failure

Features	Group	*n**	Mean	SD	***p*
Intial FiO_2	Failure	52	0.49	0.17	< 0.05
	Success	131	0.44	0.15	
Final FiO_2	Failure	52	0.45	0.18	< 0.001
	Success	131	0.30	0.11	
Intial number of breaths	Failure	52	59.13	11.51	< 0.001
	Success	124	52.98	11.35	
Final number of breaths	Failure	52	73.04	20.55	< 0.001
	Success	124	46.79	15.83	
	Success	110	5.55	1.34	

**Number of patients. **Test Mann-Whitney*

TABLE 4. Significant risk factors in relation to failure of SIPAP therapy

Features	OR	95% CI	*p*
Pneumothorax	22.93	2.79–188.47	< 0.01
Increasing SIPAP rate	16.47	345.24–649.08	< 0.001
Desaturation	15.83	40.07–650.84	< 0.001
Respiratory acidosis in blood gas evaluation	10.80	27.54–448.51	< 0.001
Grade III RDS	7.29	1.85–28.70	< 0.01
Pethidine for sedation	6.05	2.09–12.58	< 0.001
Grade II RDS	5.97	2.52–14.10	< 0.001
Grade 2–4 IVH	3.29	1.57–6.92	< 0.01
NEC grade II	3.03	1.44–6.41	< 0.01
Increasing FiO_2	2.85	1.26–6.44	< 0.01
Pneumonia	2.45	1.27–4.72	< 0.01

TABLE 6. Significant risk factors in relation to occurrence of pneumothorax during SIPAP therapy

Features	OR	95% CI	*p*
Increase of PIP	26.78	5.20–137.90	< 0.001
Increasing SIPAP rate	25.95	3.15–213.65	< 0.001
Increasing SiPAP FiO_2 due to desaturation	24.18	4.72–123.90	< 0.001
Grade 2–4 IVH	5.55	1.41–21.82	< 0.01
Grade II RDS	4.83	1.21–19.26	< 0.01
Pethidine	4.33	1.11–16.90	< 0.05

1 hour in the group without pneumothorax (Table 5), but that difference was not significant ($p > 0.06$). The study showed that the following factors increased the risk of pneumothorax: grade II RDS (OR = 4.83), necessity of increasing SiPAP breaths rate (OR = 25.95), and FiO_2 concentration at the end-stage of using this method OR = 24.18), and the necessity to use pethidine for sedation of the treated newborns (OR = 6.05) (Table 6).

DISCUSSION

For many years SIPAP has been a form of neonatal respiratory insufficiency treatment in Poland thanks to the program of non-invasive ventilation of newborns of the Great Orchestra of Christmas Charity, which financed the purchase of this medical equipment for neonatal units in Poland.

This is a single-center, retrospective, observational study of late preterm infants admitted to the NICU with respiratory failure over a five-year study period treated with SiPAP ventilation. The primary outcome was treatment failure, which was defined as necessity for intubation or the occurrence of pneumothorax. Treatment failure was observed in 28.8% of newborns; 4.9% of children developed a pneumothorax. SiPAP failure has been reported to be as high as 29% by Binmanee *et al.* which is in keeping with the results of this study [8]. Whereas failure rates have also been reported to be as low as 4% in premature Chinese neonates born before 37 weeks of pregnancy [17]. Resnick and Sokol, in a group of 166 Australian infants born later than 32 weeks of gestation observed a 13% of failure using CPAP from birth [16]. Bhatti *et al.* in a group of babies born earlier than 34 weeks of gestation reported a 21% of failure using the SiPAP method [9].

The analysis of our material showed that the decision to use respiratory support was most often guided by the results of capillary blood gas analysis. The average pH before switching on the SiPAP method was 7.28 and the pCO_2 was 53 mm Hg. In the study by Salvio *et al.* pH was lower (7.21) and pCO_2 was at a similar level [3].

This study showed that the factors that increase the chances of SiPAP failure include: a late decision to non-invasive breathing support application and higher score on the Silverman scale. In a group born before 28 weeks of pregnancy, it is usually easy to decide to use SiPAP in the delivery room, while in later deliveries, especially those after 32–34 weeks, this decision is often preceded by observation of the severity of the respiratory failure and the moment of implementation of respiratory support is delayed, which is not always a good predictor of the success of non-invasive ventilation, and sometimes results in the occurrence of pneumothorax after a few hours.

The analysis carried out in the course of this study showed that the failure of SiPAP was significantly influenced by the delay in initiated non-invasive ventilation. The average time of implementation of SiPAP in the group with success of therapy was 3.7 hours, while in the group with failure it was significantly longer at 4.5 hours. In the observations of Tagare *et al.* in a group with successful intervention, SiPAP was most often used in the 1st hour of life, and in cases of failure most often after 1.5 hour of life [21].

It should be emphasized that failure of non-invasive ventilation in late preterm infants is mainly dependent on the severity of RDS [18, 21]. As a rule, the more intense symptoms according to the Silverman scale (≥ 4 points) with grade II RDS symptoms in the chest X-ray examination, the greater the chance of failure of the non-invasive ventilation [18, 21]. In this study, the severity of symptoms on the Silverman scale was most often at 5 points at the time of making the decision to use SiPAP, and in the group with failure, it was most often 6 points. The grade II RDS is also a prognostic factor, which was confirmed in the course of this study (OR = 5.97).

Newborns requiring oxygen therapy FiO_2 higher than 40–50% often require intubation and mechanical ventilation [16]. This was confirmed by the analysis carried out in the course of this study; in the group with SiPAP success, the concentration of FiO_2 was significantly lower in both the initial (0.44 vs. 0.49) and the final (0.30 vs. 0.45) stage of non-invasive ventilation compared to the group where this type of respiratory support ended in failure. It should also be emphasized that newborns treated in our Department of Neonatology required the use of relatively high FiO_2 values at the beginning of treatment. SiPAP was not always used in the delivery room, often the decision was preceded by the observation of a newborn in an incubator with oxygen therapy. Salvio *et al.* described a lower concentration of FiO_2 – 0.35 at the start of non-invasive ventilation [3], and Soleväg and Kann described higher FiO_2 application – 0.45 [22].

A complication that adversely affects a newborn is the occurrence of pneumothorax. It has been shown that the factors that increase the risk of its occurrence is the severity of symptoms of respiratory failure defined as 8 points on the Silverman scale (in the group without pneumothorax it was ≤ 5), later time of inclusion of respiratory support – 2.5 hours in relation to 1 hour in the group without pneumothorax, grade II RDS (OR = 4.8), the need to increase SIPAP breaths (OR = 26), FiO_2 at the final stage of applying SiPAP (OR = 24) and the necessity of using sedation drugs (OR = 4.3). Iyer and Mhanna in an editorial based on the analysis of data from publications included in PubMed, assessed the risk factors leading to the occurrence of pneumothorax during non-invasive ventilation [23]. These were: CPAP value ≥ 8 cm H_2O, pCO_2 > 75 mm Hg and FiO_2 > 0.6 [23].

Necessity to use sedation with pethidine was found among factors that increase the chance of SiPAP failure (OR = 6.05). One can say it is very rare to use sedative/analgesics for non-invasive respiratory support. There is likely to be variability in use of sedatives between different hospitals and regions of the world. There is also great variability among reports of sedation rates, with one review conducted by Longrois *et al.* finding a sedation rate of 25% of all non-invasive ventilated patients, and 40% of critically ill patients [24]. Matsumoto *et al.* concluded that sedation may help avoid non-invasive ventilation failure in agitated patients [25]. The lung-protective effects of non-invasive ventilation should not prompt disregard for the possible

pain and discomfort it can generate. As for the breathing modes, bilevel positive airway pressure often produces a need for anxiolysis or sedation [24, 26]. However, the use of opioids will definitely put the babies at risk for respiratory failure and subsequent intubation. According to European recommendations opioids should be used selectively when indicated by clinical judgment and evaluation of pain indicator [5]. Sedation is not mandatory for SiPAP but it may help in specific situations, when anxiety of the late preterm infants may lead to pneumothorax [24, 27].

Among factors associated with increased risk of SiPAP failure grade II IVH were also found (OR = 3.29). IVH is associated with prematurity and mechanical ventilation [28]. Early non-invasive ventilation is associated with decreasing the risk of severe IVH [28].

The analysis of the results of SiPAP non-invasive ventilation performed in this study and comparison of our own results with data from other researchers from many regions of the world allowed us to determine what was done well and what should be changed to achieve better results for the benefit of the patients. Some factors have also been defined that *a priori* may lead to the failure of non-invasive ventilation, and thus to prolong the hospitalization time. Nowadays, the trend and emphasis to begin therapy of respiratory insufficiency with non-invasive ventilation is not always beneficial for the fate of the child. Sometimes intubation, lung expansion, possible administration of a surfactant at grade II RDS, is associated with a lower risk of complications such as pneumothorax or bleeding to the central nervous system [4]. European recommendations and updated standards of the Polish Neonatological Society are currently in force in Poland [5]. SIPAP is still popular but progressively being suppressed by other forms of non-invasive ventilation.

There are some limitations of this study which include retrospective nature, and no standardized guidelines at the period of our study for applying non-invasive ventilation after delivery.

CONCLUSIONS

A delay in initiation of SiPAP, higher RDS scores, higher FiO_2 requirements, and development of IVH grade II were the factors associated with failure of SiPAP therapy among late preterm infants.

DISCLOSURE

The authors declare no conflict of interest.

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