

Improved Surgical Outcome After Fetal Diagnosis of Hypoplastic Left Heart Syndrome

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Background—Hypoplastic left heart syndrome (HLHS) is frequently diagnosed prenatally, but this has not been shown to improve surgical outcome.

Methods and Results—We reviewed patients with HLHS between July 1992 and March 1999 to determine the influence of prenatal diagnosis on preoperative clinical status, outcomes of stage 1 surgery, and parental decisions regarding care. Of 88 patients, 33 were diagnosed prenatally and 55 after birth. Of 33 prenatally diagnosed patients, 22 were live-born, and pregnancy was terminated in 11. Of 22 prenatally diagnosed patients who were live-born, 14 underwent surgery, and parents elected to forego treatment in 8. Of 55 patients diagnosed postnatally, 38 underwent surgery, and 17 did not because of parental decisions or clinical considerations. Prenatally diagnosed patients were less likely to undergo surgery than patients diagnosed after birth ($P=0.008$). Among live-born infants, there was a similar rate of nonintervention. Among patients who underwent surgery, survival was 75% (39/52). All patients who had a prenatal diagnosis and underwent surgery survived, whereas only 25 of 38 postnatally diagnosed patients survived ($P=0.009$). Patients diagnosed prenatally had a lower incidence of preoperative acidosis ($P=0.02$), tricuspid regurgitation ($P=0.001$), and ventricular dysfunction ($P=0.004$). They were also less likely to need preoperative inotropic medications or bicarbonate ($P=0.005$). Preoperative factors correlating with early mortality included postnatal diagnosis ($P=0.009$), more severe acidosis ($P=0.03$), need for bicarbonate or inotropes ($P=0.008$ and 0.04), and ventricular dysfunction ($P=0.05$).

Conclusions—Prenatal diagnosis of HLHS was associated with improved preoperative clinical status and with improved survival after first-stage palliation in comparison with patients diagnosed after birth. (*Circulation*. 2001;103:1269-1273.)

Key Words: prenatal diagnosis ■ hypoplastic left heart syndrome ■ heart diseases

Hypoplastic left heart syndrome (HLHS) can be easily recognized on prenatal ultrasound and is proportionately one of the most common serious cardiac defects diagnosed prenatally.^{1,2} The standard “4-chamber cardiac view” used by obstetricians for screening of congenital heart disease demonstrates either a small left side or an echogenic left ventricle from endocardial fibroelastosis. Prenatal diagnosis of HLHS, however, has not been demonstrated to improve surgical outcomes.³⁻⁵

In HLHS, the left heart complex is underdeveloped and unable to support the systemic circulation. Newborns with HLHS may be asymptomatic but become severely ill as the ductus arteriosus closes. Without treatment, this defect is almost certainly lethal. Current surgical strategy for infants with HLHS includes staged palliative surgery, culminating with total cavopulmonary connection (Fontan operation) or cardiac transplantation.⁶⁻⁸ Despite refinements in surgical technique and postoperative care for infants with HLHS, the

first stage of surgical palliation continues to have significant mortality compared with other neonatal cardiac operations.⁸

Prenatal diagnosis of HLHS affords time for physicians both to counsel parents and to plan perinatal management. Without the benefit of prenatal diagnosis, most infants with HLHS are born outside of tertiary care centers, which delays diagnosis and appropriate resuscitation. The delay in diagnosis, in turn, may lead to systemic hypoperfusion, shock, and multiorgan damage, which can diminish chances for surgical success and lead to long-term sequelae.⁹⁻¹⁴

Previous smaller studies have failed to demonstrate a positive impact of prenatal diagnosis on the surgical outcomes of patients with HLHS.³⁻⁵ Furthermore, the different influences of prenatal and postnatal diagnoses on either parental decisions or preoperative clinical status have not been fully addressed. The aims of the present study were to compare the impact of prenatal and postnatal diagnosis on (1) the preoperative clinical status of these infants, (2) outcomes

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after first-stage palliative surgery, and (3) parental decisions to pursue surgical options.

Methods

Patients

We reviewed all patients with HLHS who were evaluated at our institution between July 1992 and March 1999. We included all fetuses and newborn infants with HLHS, which we defined as normal cardiac topology with concordant atrioventricular and ventriculoarterial relationships, an intact ventricular septum, and hypoplasia of the left ventricle and left heart complex sufficient to preclude biventricular repair. Thus, we did not include patients with other forms of functionally univentricular cardiac defects who underwent a Norwood or Damus type of palliative procedure, such as unbalanced atrioventricular septal defect, double-outlet right ventricle with mitral valve atresia, and aortic atresia with ventricular septal defect. Patients with low birth weight (<2000 g) and patients with associated potentially lethal noncardiac congenital defects were also excluded. At diagnosis, the parents were counseled by an attending pediatric cardiologist and cardiac surgeon. Although cardiac transplantation was mentioned in postdiagnosis counseling as a therapeutic option that could be pursued at other institutions, it was not offered as an option at our institution. To obtain clinical and laboratory data, we reviewed patient records and departmental databases, including records from the referring hospital and transport team for patients referred from other institutions.

Diagnosis and Preoperative Evaluation

Diagnosis was made by standard echocardiography. In patients diagnosed prenatally, the diagnosis was confirmed with postnatal echocardiography. In patients transported to our center after being diagnosed with HLHS elsewhere, the diagnosis was confirmed with echocardiography at our institution. Not all of the postnatally diagnosed infants in this study underwent an echocardiogram before referral. For this reason, the first postnatal echocardiogram performed in our institution was used for analysis of anatomic and functional data, such as assessment of tricuspid regurgitation, ventricular dysfunction, and the degree of restriction of the interatrial communication. Right ventricular function was reported as normal if normal or mildly depressed and as abnormal if moderately or severely depressed by qualitative analysis. Similarly, the degree of tricuspid regurgitation was assessed as being normal if absent or mild and as clinically significant (abnormal) if moderate or severe. Because the echocardiograms were performed on the patient's admission to the hospital, the cardiologist who interpreted the echocardiogram was blinded to the final outcome.

Operative Management

Stage 1 palliation for HLHS was performed in the standard fashion, with side-to-side anastomosis of the pulmonary trunk and ascending aorta, reconstruction of the ascending aorta and aortic arch with a patch of allograft tissue, atrial septectomy, and placement of a 3.0-, 3.5-, or 4.0-mm systemic-to-pulmonary-arterial shunt from the innominate or right subclavian artery to the right pulmonary artery. The diameter of the ascending aorta was measured intraoperatively.

Data Analysis

Data are presented as median and range or mean \pm SD. Data analysis was conducted for 2 different cohorts: (1) all patients with HLHS, with comparisons made between those diagnosed prenatally and those diagnosed postnatally, and (2) only patients who underwent stage 1 palliative surgery, with comparisons made between those diagnosed prenatally and postnatally, as well as between surgical survivors and nonsurvivors.

Among the entire cohort of patients diagnosed with HLHS, the parental decision regarding treatment (ie, termination of pregnancy, no treatment after birth, or stage 1 palliative surgery) was the primary outcome assessed.

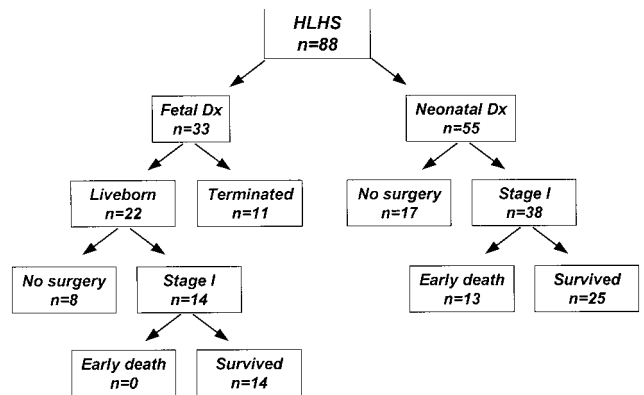


Figure 1. Flow diagram depicting outcomes of patients with prenatal or postnatal diagnosis (Dx) of HLHS.

Among patients who underwent stage 1 palliative surgery, the primary outcome measure was early survival, defined as survival to hospital discharge.

Preoperative variables analyzed in surgical patients included whether the patient had a prenatal diagnosis, gestational age at birth, severity of preoperative acidosis (lowest arterial pH), the need for inotropic or bicarbonate medications, the degree of ventricular dysfunction and tricuspid valvar regurgitation, and the need for an atrial septostomy or septectomy. The patient's degree of acidosis was used as a marker for systemic hypoperfusion, frequently observed in this group of patients when the ductus arteriosus is closing.

Operative variables analyzed included the year of surgery, age at surgery, duration of cardiopulmonary bypass, duration of deep hypothermic circulatory arrest, diameter of the ascending aorta, and diameter of the inserted systemic-to-pulmonary-arterial shunt.

SPSS for Windows version 7.0 (SPSS Inc) was used for statistical analysis. Continuous variables were compared between 2 groups with independent-samples *t* test. Dichotomous variables were compared between groups with χ^2 analysis or Fisher's exact test. Variables found to be significant by univariate analysis were entered into multivariate analysis with logistic regression. Odds ratios (ORs) are presented with 95% confidence intervals (CIs).

Results

Overall Cohort

Of the 88 patients with HLHS in our study, 33 (37%) were diagnosed prenatally and 55 (63%) were diagnosed in the newborn period. There was no significant year-to-year variation in the proportion of patients diagnosed prenatally during the period of our study. Of the 33 patients who were diagnosed prenatally, 66% ($n=22$) were live-born, whereas 11 parents elected to terminate the pregnancy. In 8 (35%) of the 22 prenatally diagnosed patients who were live-born, the parents elected to forego surgery. Thus, of the 33 fetuses diagnosed with HLHS prenatally, 14 (42%) underwent first-stage palliation (Figure 1). None of the parents of patients diagnosed prenatally transferred care to an institution that offered transplantation as a primary treatment for HLHS.

Of the 55 patients diagnosed with HLHS in the newborn period, 17 (31%) did not undergo surgery. In these 17 patients, the decision not to perform surgery was based on parental wishes, clinical considerations (such as severe acidosis and multiorgan dysfunction), or a combination thereof. Prenatally diagnosed patients were significantly less likely to undergo stage 1 palliation than patients diagnosed postnatally (OR 0.31 [95% CI 0.13 to 0.75], $P=0.008$, Figure 1). Among live-born infants,

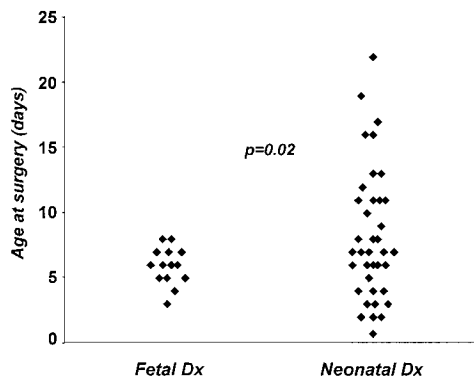


Figure 2. Comparison of age at repair between prenatally and postnatally diagnosed (Dx) patients. Each diamond represents a single patient. There is greater scatter among postnatally diagnosed patients, with some needing repair very early and others undergoing surgery later, after delayed presentation.

however, there was a similar rate of nonintervention between the 2 groups (8 of 22 versus 17 of 55, $P>0.5$). All patients who did not undergo surgery died within 7 days and therefore were not included in further analysis.

Surgical Cohort

Overall, 52 (60%) of the 88 patients underwent stage 1 palliation. Age at repair was more uniform and significantly younger in those diagnosed prenatally than those diagnosed after birth (5.9 ± 1.4 versus 8.2 ± 5.1 days, $P=0.02$) (Figure 2). Overall survival to hospital discharge was 75% (n=39). All of the patients who had a prenatal diagnosis and underwent stage 1 palliative surgery (n=14) survived to hospital discharge, which contrasted with a survival rate of 66% (25/38) among the postnatally diagnosed patients ($P=0.009$). The 13 postnatally diagnosed patients who did not survive died a median of 5 days after surgery (0 to 34 days).

Among the 52 patients who underwent surgery, those diagnosed prenatally had a significantly lower incidence of preoperative acidosis (lowest arterial pH 7.29 ± 0.1 versus 7.19 ± 0.1 , $P=0.02$), tricuspid regurgitation ($P=0.001$), and ventricular dysfunction ($P=0.004$) (Figures 3 and 4). They were also significantly less likely to need preoperative inotropic medications or bicarbonate (both OR 0.08 [95% CI 0.01 to 0.69], $P=0.005$) (Figure 4). Only 1 prenatally diagnosed patient

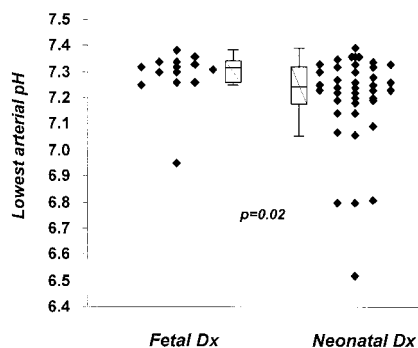


Figure 3. Comparison of lowest preoperative systemic arterial pH between prenatally and postnatally diagnosed (Dx) patients. Each diamond represents a single patient. Box plots depict median, quartiles, and highest and lowest nonoutlier values.

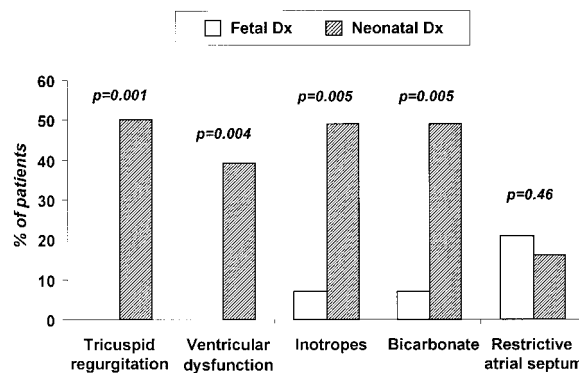


Figure 4. Percentage of prenatally and postnatally diagnosed (Dx) patients who were found to have tricuspid regurgitation of mild or greater degree, right ventricular dysfunction, or a significantly (needing intervention) restrictive interatrial septum on first postnatal echocardiogram and who needed preoperative bicarbonate or inotropic medications.

became significantly acidotic before surgery, most likely as a result of pulmonary overcirculation and systemic hypoperfusion, and needed bicarbonate and inotropic medication. The acidosis was treated rapidly, and the patient underwent surgery the following day. None of the other preoperative or operative variables analyzed were found to differ significantly between prenatally and postnatally diagnosed patients (Table).

In addition to postnatal diagnosis (OR 1.6 [95% CI 1.2 to 2.0], $P=0.009$), factors that correlated significantly with early mortality included greater preoperative acidosis (arterial pH 7.13 ± 0.2 versus 7.25 ± 0.1 , $P=0.03$), need for bicarbonate medication preoperatively (OR 2.6 [95% CI 1.4 to 5.0], $P=0.008$), need for inotropic medications preoperatively (OR 2.1 [95% CI 1.1 to 4.1], $P=0.04$), and preoperative ventricular dysfunction (OR 2.4 [95% CI 1.03 to 5.5], $P=0.05$) (Figure 5). Aside from the aforementioned variables, none of the other preoperative or surgical variables analyzed were found to correlate significantly with early mortality. By multivariable logistic regression analysis of the above factors that were significant by univariable analysis, only postnatal diagnosis remained significantly associated with early mortality ($P=0.04$).

Two patients, both of whom were diagnosed postnatally, had an intact atrial septum. After cardiovascular collapse and trans-

Demographic and Surgical Variables in Prenatally and Postnatally Diagnosed Patients Undergoing Stage 1 Palliation of HLHS

Variable	Fetal Diagnosis (n=14)	Postnatal Diagnosis (n=38)	P
Age at repair, d	5.9±1.4	8.2±5.1	0.02
Weight at repair, kg	3.2±0.4	3.4±0.5	0.16
Gestational age at birth, wk	38.9±1.1	39.6±1.4	0.11
Ascending aortic diameter, mm	3.0±1.5	3.4±1.7	0.45
Total support time, min*	134±46	158±52	0.13
Circulatory arrest time, min	48±8	43±17	0.57
Diameter of systemic-to-pulmonary-artery shunt, mm	3.4±0.3	3.4±0.2	0.89

*Sum of cardiopulmonary bypass time and circulatory arrest time.

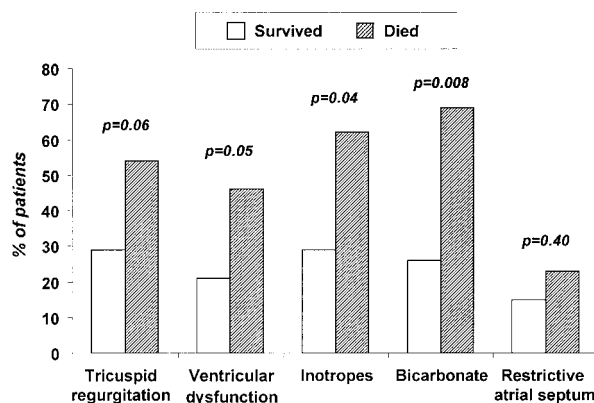


Figure 5. Data only from patients who underwent surgery depict difference between those who survived and those who did not. Bars represent percentage of patients who were found to have tricuspid regurgitation of mild or greater degree, right ventricular dysfunction, or a significantly (needing intervention) restrictive interatrial septum on first postnatal echocardiogram and who needed preoperative bicarbonate or inotropic medications.

port from an outside institution, both were taken emergently to the operating room. One patient had an atrial septectomy, followed several days later by first-stage palliation. The other patient underwent an atrial septectomy and a Norwood procedure on the first day of life. Both subsequently died in the early postoperative period. Analysis conducted excluding these 2 patients did not alter our findings significantly. Although there were no such patients among those diagnosed prenatally, 2 prenatally diagnosed patients did undergo a bedside atrial septostomy to relieve moderate to severe atrial restriction.

Discussion

Results and Implications of the Study

This is the first study to demonstrate that patients with HLHS who are diagnosed prenatally have improved survival after first-stage palliative surgery compared with those diagnosed after birth. In our cohort, the improved early survival can most likely be attributed to the more stable preoperative clinical condition of our prenatally diagnosed patients.^{7,10,11} HLHS is proportionately one of the most common congenital cardiac defects diagnosed prenatally, because standard 4-chamber views obtained during routine obstetrical ultrasounds demonstrate hallmark findings of either a small left side or an echogenic left ventricle.^{1,2} In addition, there is usually reversal (left to right) of shunting across the foramen ovale and often retrograde aortic arch flow, all easily recognized by color-flow Doppler.¹⁵

Prenatal diagnosis of HLHS has clear advantages. It allows time to counsel parents and time for both parents and physicians caring for the patient to plan perinatal management. As at other centers, patients diagnosed prenatally in our experience were found to have a more stable preoperative course.^{5,10} All of the prenatally diagnosed patients were born at our institution or another nearby tertiary care facility and did not endure the stress of delay in diagnosis and transport. All underwent echocardiographic confirmation of the diagnosis and the initiation of prostaglandin therapy from birth. In contrast, patients in our study who were diagnosed postnatally had worse surgical

outcomes and were more likely to be sick at presentation, as demonstrated by greater preoperative acidosis, an increased need for inotropic and bicarbonate medication, and more severe right ventricular dysfunction and tricuspid regurgitation.

Despite substantial improvements in surgical survival, patients with HLHS remain at risk for a number of problems.^{8,12-14,16} Ultimately, children born with HLHS are left with a single, morphologically right ventricle and a Fontan circulation, with its well-described long-term complications. Furthermore, early and medium-term survival after palliative surgery in infants with HLHS remain suboptimal, with a combined surgical and nonsurgical mortality of $\approx 50\%$ to 60% by the time the patient has undergone all 3 stages.^{6,8,14} In addition, studies of neurodevelopmental outcome in survivors have demonstrated that patients with palliated HLHS perform below average in various areas.^{12,13,16} On the basis of such historical data, parents may also choose to forego surgery for their infants, as we observed in our study.

For parents who choose to have a prenatally diagnosed infant undergo surgery, elective delivery at a tertiary care center can be planned.¹⁷⁻¹⁹ This ensures appropriate multidisciplinary management from the delivery room to the operating room, including confirmation of the diagnosis by echocardiography, prompt initiation of prostaglandin therapy, and maintenance of a normal acid-base status by delicate manipulation of systemic and pulmonary blood flows and mechanical ventilation in a neonatal intensive care setting.

In addition, there are other issues specific to patients with HLHS in which prenatal diagnosis and early intervention may help. For example, a small percentage of patients with HLHS have an intact or severely restrictive atrial septum.²⁰ Patients with this variation are the sickest of all and need immediate intervention, such as balloon atrial septostomy or surgical septectomy, an advantage afforded by birthing in a tertiary care setting that should not be underestimated.

Despite the many potential benefits, the increasing frequency of prenatal diagnosis of HLHS has not previously been shown to result in significant improvements in outcome.³⁻⁵ In fact, several previous studies have not found a significant difference in survival between infants with HLHS diagnosed prenatally and those diagnosed after birth, although they may not have been designed to detect such differences or had sufficient statistical power to do so and in several cases reflected more diverse study populations that may have obscured the impact of prenatal diagnosis on the management of HLHS in particular. In addition, they were conducted several years earlier than our series. Therefore, they may not reflect recent advances in optimal management of infants with HLHS. Importantly, several earlier studies, as well as ours, found that fetal diagnosis and subsequent planned delivery of patients with severe left ventricular outflow tract obstruction is an effective strategy for minimizing preoperative acidosis.^{5,10,11} In addition, fetal diagnosis has been associated with improved surgical outcome for some biventricular heart defects.^{18,19} The present study reinforces the hypothesis that prenatal diagnosis has the potential to improve surgical outcomes, presumably by means of ensuring a more stable preoperative status.

The long-term implications of prenatal diagnosis of HLHS or other forms of congenital heart disease have not been elucidated. Although 1 retrospective study found no difference in neurode-

velopmental outcome in patients with HLHS diagnosed in utero, the long-term effects of the potential advantages of fetal diagnosis are not known.²⁰ Many of the long-term issues facing these patients are complex, multifactorial issues, and an even larger cohort will most likely be necessary to address this question adequately.

Limitations of the Study

There are several limitations to our retrospective study. First, we conducted an institutional rather than a population-based study. Therefore, data regarding the rate of termination of pregnancy for this defect and the decision to pursue surgery at birth in our region are most likely underestimated, because patients may have been diagnosed and counseled elsewhere and may not have been evaluated at our institution. Despite this limitation, we think that a study of this nature can be performed adequately with a retrospective design, insofar as its being conducted at a single center limits the impact of investigator bias that might be introduced in counseling of parents, evaluation of clinical data, and management of patients.

Also, because we were able to evaluate only patients who were referred to our institution, there was the potential for a selection bias. It is possible that only fetal patients with the most optimal cardiac function and anatomy were referred for surgery, whereas the group with a postnatal diagnosis included all comers. For example, a fetus with significant tricuspid regurgitation might not have been referred for surgery because of prenatal counseling at another institution. In the group of patients who were prenatally diagnosed at our institution, however, there were no differences in anatomy or fetal tricuspid regurgitation between patients who ultimately did and did not undergo surgery. The anatomic similarities between the surgical and nonsurgical groups suggest that these factors did not substantially influence counseling or parental decision-making in these patients.

Finally, we acknowledge that right ventricular function is difficult to assess quantitatively by means of echocardiography, and therefore we relied on qualitative assessment of function. Because the data for the study were collected retrospectively, the echocardiographers were essentially blinded to patient outcome, insofar as the studies were performed preoperatively. The echocardiograms used in this study were uniformly the first ones performed at our institution. Patients who were diagnosed prenatally and born at our institution usually underwent an echocardiogram in the first few hours of life. Postnatally diagnosed infants, however, were usually resuscitated before being transferred to our institution. If anything, this reliance on our own institution's first echocardiogram allowed time for resuscitation, treatment of acidosis, and inotropic support in postnatally diagnosed patients, all factors that may have improved ventricular function before arrival at our center. Nevertheless, patients diagnosed postnatally still had worse ventricular function and more severe tricuspid regurgitation.

Conclusions

Prenatal diagnosis of HLHS affords the opportunity for counseling and perinatal planning.²¹ For patients in whom

surgical palliation is elected, prenatal diagnosis provides an opportunity to avoid the preoperative hemodynamic and metabolic insult so frequently seen in those diagnosed postnatally. This improved preoperative state may, in turn, contribute to improved survival after first-stage palliation, as was seen to be the case in our experience.

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