Left Ventricular Functional Reserve in Adult Patients with Atrial Septal Defect: Pre- and Postoperative Studies

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SUMMARY To assess left ventricular (LV) function in patients with atrial septal defect (ASD), we used radionuclide cineangiography at rest and during exercise in 11 patients (ages 16–59 years, mean 36 years) without other cardiac abnormalities. All patients had normal LV ejection fraction (EF) at rest (mean 59 ± 3% vs normal 57 ± 1%; NS); during exercise, four patients increased LVEF normally, four had no change in LVEF with exercise, and three decreased LVEF to 56%, 54%, and 44% (lower limit of normal 55%). These three patients had orthopena and paroxysmal nocturnal dyspnea; the other eight were asymptomatic or mildly symptomatic. While the LVEF response to exercise did not correlate directly with hemodynamic or echo data, the two patients with the greatest decrease in LVEF during exercise had higher pulmonary-to-systemic flow ratios than the other nine patients (mean 4.8 vs 2.0, p < 0.001). All patients had abnormalities of ventricular septal motion on echocardiography with subnormal LV diastolic dimensions secondary to the right ventricular volume overload. Six months after operation, all 11 patients were asymptomatic and all had normal rest and exercise LVEFs (mean EF 58 ± 2% rest, 65 ± 3% exercise, p < 0.001), including the seven patients with abnormal preoperative LVEF responses to exercise. LV diastolic dimension by echocardiography, subnormal before operation in all 11 patients, increased into the normal range in all patients postoperatively. These data suggest that diminished LV functional reserve in adult patients with ASD is related, at least in part, to reversible mechanical factors related to right ventricular volume overload with abnormal diastolic–systolic relations of the interventricular septum, rather than to intrinsic, irreversible myocardial dysfunction.

ABNORMALITIES in left ventricular performance have been reported frequently in patients with ostium secundum atrial septal defect. However, the etiology of such abnormalities is unclear. Left ventricular dysfunction may occur only as a secondary mechanical response to chronic right ventricular volume overload, or may develop as a primary process. Assessment of the reversibility of functional abnormalities after closure of the defect might help to determine the etiology of left ventricular dysfunction, but such assessments have not been reported. Various investigators, using contrast angiography and echocardiography, have noted subnormal left ventricular volumes, stroke volume, and ejection fraction, as well as subnormal left ventricular distensibility. However, rotation of the left ventricle by the large right ventricle in patients with atrial septal defect might cause inaccuracies in contrast angiographic assessment of volumes, and hence, ejection fraction. Earlier studies have been performed at rest and have not evaluated the functional reserve of the left ventricle during exercise, a sensitive index of left ventricular dysfunction in patients with other forms of heart disease. Finally, the extent of reversibility of these abnormalities has not been reported.

To provide further information about the etiology and extent of left ventricular dysfunction, we used radionuclide cineangiography at rest and during exercise in 11 adult patients with atrial septal defect before and after operative closure of the defect.

Methods

Eleven patients (four men and seven women) with uncomplicated atrial septal defect, ages 16–59 years (mean 36 years), were evaluated before operation by history, physical examination, M-mode echocardiography, cardiac catheterization and radionuclide cineangiography. Five patients were asymptomatic, three complained of fatigue and mild dyspnea on exertion, and three were severely symptomatic with orthopena and paroxysmal nocturnal dyspnea (table 1).

Echocardiography

Echocardiograms were obtained in each patient using a 12.5-mm-diameter, 2.25-MHz, unfocused ultrasound transducer and a Hoffel 201 ultrasound transceiver interfaced with a Honeywell 1856 strip-chart recorder. Qualitative assessment of ventricular septal motion was uniformly made at a level in the left ventricle below the tips of the mitral leaflets, because the degree of abnormal septal motion in patients with right ventricular volume overload varies at different sites along the ventricular septum. Anterior

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systolic motion of the septum at this level was defined as "paradoxical." Right ventricular internal dimensions were measured at the level of the mitral leaflets during diastole. Left ventricular internal dimensions at end-diastole and end-systole, however, were made lower in the ventricular cavity caudal to the tips of the mitral leaflets, to facilitate comparison with normal subjects. The left ventricular end-diastolic dimension was taken at the beginning of the QRS complex and the end-systolic dimension, because of abnormal septal motion in all patients, at the maximal systolic anterior excursion of the left ventricular posterior wall. The ventricular measurements were plotted as a function of body surface area and compared with the 95% confidence limits previously described in our laboratory for 105 normal subjects. Left ventricular fractional shortening was computed as the quotient of the difference between the left ventricular diastolic and systolic dimensions divided by the diastolic dimension. Fractional shortening in this study was not computed to measure actual quantitative left ventricular systolic function (because of the presence of abnormal septal motion), but only to indicate changes that occurred in relative left ventricular dimensions before and after operation.

Cardiac Catheterization

Each patient underwent right-heart catheterization. The presence of an atrial septal defect was confirmed by increased oxygen saturation in right atrial blood compared with mixed venous blood; shunt flow across the defect was quantitated by oximetry in all patients and was validated by the krypton-85 inhalation technique in seven patients. Direct left atrial pressure measurements were recorded in all 11 patients, and left ventricular pressures in seven patients, with the right-heart catheter placed across the septal defect. Another patient underwent retrograde left ventricular catheterization. Cardiac output was determined in

these eight patients using indocyanine green dye injected into the left ventricle.

Ten patients, including the six with symptoms, had ostium secundum defects, and one asymptomatic patient had an ostium primum defect (table 1). In this asymptomatic patient, retrograde left-heart catheterization and ventriculography documented the absence of a ventricular septal defect and the presence of mild mitral regurgitation (dye clearing the left atrium with each cardiac cycle).

Gated Cardiac Scintigraphy

Radionuclide cineangiography was performed in the supine position. Before imaging, red blood cells were labeled in vivo with 10–15 mCi of technetium-99m. Imaging was accomplished using a conventional Anger camera equipped with a high-sensitivity parallel-hole collimator oriented in a modified left anterior oblique position to isolate the left ventricle. A computer-based procedure gated to the ECG, previously described, was used to collect and organize data into a series of images (framing rate up to 100 frames/sec), spanning the average cardiac cycle and displayed in rapid-sequence endless-loop movie format; simultaneously, high temporal (10 msec) resolution time-activity curves were generated. Blood radioactivity is proportional to blood volume, so after background correction, the time-activity curve represents a measure of relative left ventricular volume changes with time.

After images and time-activity curves were obtained at rest, imaging was repeated in each patient during supine bicycle exercise. Exercise loads were increased in a stepwise fashion at 2-minute intervals until the patient developed limiting fatigue (six patients) or limiting dyspnea (five patients). Analysis was performed using only images obtained during maximal exercise, always encompassing at least the last 1½ minutes of exercise.

After completion of imaging, left ventricular ejection fraction at rest and during exercise was determined by computer analysis of the time-activity curves, as previously described. The ejection fraction at rest and its response to exercise in patients with atrial septal defect were then compared with data obtained in 30 normal volunteers (ages 19–63 years) who had no clinical, electrocardiographic or echocardiographic evidence of cardiovascular or other systemic disease. Results in these normal subjects have been reported and have been used to define the range of normal for our laboratory.

Operative Findings and Postoperative Evaluation

Ten patients had patch closures of moderate-to-large ostium secundum atrial septal defects. The patient with the ostium primum defect also had a cleft anterior mitral leaflet with minimal mitral regurgitation and no ventricular septal defect. In addition to closure of the primum defect, two sutures were placed in the cleft mitral leaflet.

Each patient returned for evaluation 6 months after

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<th>Table 1. Preoperative Clinical Data</th>
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Mean = 36

Abbreviations: ASD = atrial septal defect; DOE = dyspnea on exertion; PND = paroxysmal nocturnal dyspnea.
operation; each was asymptomatic. M-mode echocardiography, right-heart catheterization, and radiouclide cineangiography at rest and during exercise were repeated. The patient with the repair of the ostium primum defect had a normal physical examination, without evidence of mitral valvular stenosis or regurgitation, and a mean pulmonary artery wedge pressure of 4 mm Hg, compared with a preoperative left atrial mean pressure of 7 mm Hg. On echocardiography, the mitral valve showed normal mobility. Left ventriculography was not performed to rule out occult mitral regurgitation.

Statistical Analysis

Data were analyzed by the t test, using unpaired and paired analysis as appropriate. Linear regression analysis of left ventricular ejection fractions and data from echocardiographic and hemodynamic studies was also performed.

Results

Preoperative Data

Preoperative left ventricular ejection fractions at rest and during maximal exercise obtained by radiouclide cineangiography are presented in table 2. These data are also shown in figure 1 for comparison with the data obtained in the 30 normal subjects. In the normal subjects, ejection fraction at rest ranged from 45-71% (mean ± SEM 57 ± 1%). In these subjects, ejection fraction increased during maximal exercise to 60-80% (mean ± SEM 65 ± 3%).

**Table 2. Left Ventricular Ejection Fraction**

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<td>Exercise EF</td>
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Mean ± SEM: EF = ejection fraction (%) by radionuclide angiography; HR = heart rate (beats/min).

FIGURE 1. Effect of maximal exercise on left ventricular ejection fraction in normal subjects (left) and in patients with atrial septal defect before operation (right). Open circles with bars indicate mean values.
exercise, to a mean of 71 ± 2% (range 58–93%), significantly greater than the value at rest (p < 0.001). All 11 patients with atrial septal defect had normal ejection fractions at rest, ranging from 47–72%. During maximal exercise, however, there was no significant change in ejection fraction, which averaged 59 ± 3% at rest and 60 ± 3% during exercise. For the group with atrial septal defect, ejection fraction during exercise was significantly lower than that in normal subjects (p < 0.001). Four patients demonstrated increases in ejection fraction with exercise that were at least as great as in our normal subjects (increase of 5% or greater), but four patients showed almost no change in ejection fraction with exercise, and all three patients with severe symptoms (patients 1, 3, and 9) had substantial decreases in ejection fraction to 56%, 54% and 44%. The lower limit of normal for left ventricular ejection fraction at heart rates of 90 beats/min or greater during exercise, previously determined in our laboratory, is 55%.10

Preoperative clinical and catheterization data (table 3) were examined to determine whether any variable might predict the changes observed in left ventricular ejection fraction with exercise. The absolute value of resting ejection fraction did not correlate directly with any hemodynamic variable. Ejection fraction during exercise did correlate with pulmonary artery systolic pressure, but with a low correlation coefficient (r = 0.67, p < 0.05). The change in ejection fraction correlated only with the magnitude of the left-to-right shunt, but again with a low correlation coefficient (r = 0.69, p < 0.05). Moreover, the three symptomatic patients with marked decreases in ejection fraction with exercise did not differ from the other seven with respect to age, right or left atrial pressures, right or left ventricular end-diastolic pressures, or cardiac index. However, patients 1 and 3, who had the greatest decrease in ejection fraction with exercise, had higher pulmonary-to-systemic flow ratios, 4.3 and 5.3, than the other nine patients, whose pulmonary-to-systemic flow ratios ranged from 1.6–2.4 (average 2.0); patients 3 and 9, who had the subnormal ejection fractions during exercise, had the highest pulmonary arterial pressures.

None of the preoperative echocardiographic variables (table 4) correlated with radionuclide left ventricular ejection fraction at rest or during exercise using linear regression analysis. Moreover, the echocardiographic data of the three patients with the marked fall in radionuclide ejection fraction during exercise did not differ from data of the other eight.

Ten of 11 patients demonstrated paradoxical septal motion by echocardiography (table 4); the eleventh patient had abnormal flat septal motion. When corrected for body surface area, none of the 11 patients fell within the 95% normal confidence limits for left ventricular systolic dimension (fig. 2), using regression equations developed in our laboratory for normal subjects.14 However, all 11 patients had subnormal left ventricular end-diastolic dimensions, with values below the 95% confidence limit (p < 0.01).

**Postoperative Data**

At right-heart catheterization 6 months after operation, no residual left-to-right shunt was detected in any patient using the krypton-85 technique.18 Only patient 9 had persistent pulmonary hypertension (table 3).

Left ventricular ejection fractions determined by radionuclide cineangiography 6 months after operation were normal at rest for all patients (table 2, fig. 3), ranging from 47–74%, (mean 58 ± 2%). During exercise (to the same work load and heart rate at which

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**Table 3. Hemodynamic Data**

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<th>Pt</th>
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<th>PA (mm Hg)</th>
<th>LA (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>CI (l/min/m²)</th>
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Mean 6 9 35/13 7 8 2.9 2.5 42/9 2.7

± = SEM ± 1 ± 1 ± 4/2 ± 1 ± 1 ± 0.2 ± 0.2

Abbreviations: CI = cardiac index; LA = mean left atrial pressure; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary arterial pressure; Qp/Qs = pulmonary-to-systemic flow ratio (computed by oximetry); RA = mean right atrial pressure; RVEDP = right ventricular end-diastolic pressure.
the preoperative data were computed), ejection fractions increased in all patients (p < 0.001), to 55–85% (mean 64 ± 3%). The exercise ejection fractions after operation did not differ significantly from normal.

Echocardiographic data obtained at the 6-month postoperative study (table 4) revealed persistent paradoxical septal motion in two patients. Six patients had abnormal flat septal motion and three had normal septal motion. Right ventricular internal dimension significantly decreased (fig. 4), from a mean of 44 mm before operation to 31 mm after operation (p < 0.001). Left ventricular end-diastolic dimension significantly increased in all patients as a result of operation (39 ± 1 mm before operation to 45 ± 1 mm after operation, p < 0.001), and fell within the 95% normal confidence limits after operation in all patients. There was no significant change in left ventricular end-systolic dimension as a result of operation. When corrected for body surface area, all 10 patients were within the 95% confidence limits\textsuperscript{14} for normal systolic dimension after operation. Calculated left ventricular fractional shortening was normal in all patients after operation.

\section*{Discussion}

The status of left ventricular function in patients with atrial septal defect and the mechanism and clinical importance of apparent dysfunction is controversial. Dexter\textsuperscript{1} and Tikoff et al.\textsuperscript{2} postulated that the left ventricle was hypoplastic because of relative underfilling, but many of the patients with left ventricular dysfunction presented in their studies either had associated lesions (rheumatic mitral regurgitation, systemic hypertension, endocardial fibroelastosis or severe hypoxia) that might alter left ventricular function\textsuperscript{1, 2} or had evidence of advanced right ventricular failure.\textsuperscript{3} Thus, the effect of atrial septal defect per se on left ventricular function was unresolved in these studies.

Popio et al. reported abnormal left ventricular pressure-volume relationships plus abnormal sequences of contraction in patients with isolated atrial septal defect; but left ventricular ejection fractions, assessed by biplane cineangiography, were normal.\textsuperscript{4} Conversely, cineangiographic left ventricular ejection fractions were subnormal in the studies of Mathew et al.\textsuperscript{5} and Altieri et al.\textsuperscript{7} However, in patients with atrial septal defect, assessment of ventricular volumes and ejection fraction by contrast angiographic techniques is difficult, and comparison with studies in normal subjects is potentially inaccurate because of rotation of the left ventricle caused by the enlarged right ventricle.\textsuperscript{5, 8}

To avoid these problems, we used radionuclide cineangiography to evaluate left ventricular systolic function in patients without other cardiac diseases and without objective right or left ventricular failure. This method does not depend on geometric formulations of left ventricular volume or the orientation of the ventricle or motion of the ventricle within the chest and does not require precise delineation of the left ventricle.\textsuperscript{5, 10, 13} Thus, it is well suited for use in patients with irregularly shaped or unusually oriented ventricles.

Using the radionuclide-based technique, we could not demonstrate subnormal left ventricular ejection fractions at rest in any of our patients with isolated atrial septal defect. However, during maximal exercise, seven of 11 patients manifested evidence of depressed left ventricular functional reserve, and for the group as a whole, ejection fraction response to exercise was significantly lower than that observed in normal sub-

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\begin{table}
\centering
\caption{Echocardiographic Data}
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& & \multicolumn{3}{c|}{Preoperative} & & \multicolumn{3}{c|}{Postoperative} \\
& & RVID & LVID (D) & LVID (S) & & RVID & LVID (D) & LVID (S) \\
Pt & BSA & (mm) & (mm) & (mm) & & (mm) & (mm) & (mm) & \multirow{2}{*}{Septal motion} \\
& (m\textsuperscript{2}) & & & & & & & & \\
\hline
1 & 1.51 & 50 & 38 & 28 & Paradoxical & 27 & 50 & 34 & Paradoxical \\
2 & 1.51 & 47 & 40 & 31 & Paradoxical & 32 & 46 & 31 & Flat \\
3 & 1.92 & 55 & 38 & 28 & Paradoxical & 36 & 44 & 26 & Flat \\
4 & 1.80 & 52 & 42 & 27 & Paradoxical & 30 & 48 & 28 & Flat \\
5 & 1.37 & 30 & 36 & 26 & Paradoxical & 27 & 40 & 23 & Normal \\
6 & 1.88 & 32 & 42 & 25 & Flat & 30 & 46 & 27 & Normal \\
7 & 1.64 & 45 & 42 & 30 & Paradoxical & 30 & 48 & 34 & Paradoxical \\
8 & 2.12 & 51 & 40 & 27 & Paradoxical & 35 & 51 & 30 & Normal \\
9 & 1.60 & 46 & 36 & 25 & Paradoxical & 35 & 44 & 26 & Flat \\
10 & 1.47 & 36 & 32 & 26 & Paradoxical & 28 & 40 & 26 & Flat \\
11 & 1.34 & 42 & 30 & 17 & Paradoxical & 28 & 39 & 22 & Flat \\
\hline
Mean & & 44 & 39 & 26 & & 31 & 45 & 28 & \\
\pm SEM & & ±3 & ±1 & ±1 & & ±1 & ±1 & ±1 & \\
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Abbreviations: BSA = body surface area; LVID = left ventricular internal dimension at end-diastole (D) and end-systole (S); RVID = right ventricular internal dimension.

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\textsuperscript{9} LV FUNCTION IN ASD/Bonow et al.
FIGURE 2. Preoperative echocardiographic left ventricular dimensions at end-diastole and end-systole, plotted as a function of body surface area. The stippled region within the dashed lines represents the 95% confidence limits previously described for 105 normal subjects.14 Nine of 11 patients had normal systolic dimensions, but all 11 patients had subnormal diastolic dimensions. The three symptomatic patients with the marked fall in ejection fraction during exercise are represented by the solid symbols.

PROJECTS. The finding of exercise-induced dysfunction is consistent with the earlier observation of Flamm et al., that adult patients with atrial septal defect can have normal ventricular hemodynamics at rest but can develop abnormalities during exercise.4 Many of their patients had evidence of biventricular or isolated right ventricular dysfunction, but no patient had isolated abnormalities of the left ventricle, suggesting that left ventricular dysfunction occurred only as a generalized myocardial response to chronic right ventricular dysfunction.4

In the present study, clinical and hemodynamic evidence of right ventricular failure was lacking in the patients with exercise-induced left ventricular dysfunction. However, both clinical and experimental evidence suggest that even in the absence of overt right ventricular failure, left ventricular structure and function in atrial septal defect may be influenced by right ventricular dilatation.5-21 Posterior displacement of the interventricular septum by the volume-loaded right ventricle, as reported by Weyman et al.,5 may create distortion of left ventricular diastolic size and geometry. This might explain reports of diminished left ventricular end-diastolic volumes and decreased left ventricular distensibility.2, 3 In addition, systolic anterior motion of the septum, characteristic of atrial septal defect,5, 8, 12 may affect systolic function in the
superior septal region and may be seen in the absence of right heart failure.

The animal studies of Kelly et al.\textsuperscript{21} emphasize the complex interrelationship of the right and left ventricles. The development of chronic right ventricular volume and pressure overload in dogs produced left ventricular dysfunction, manifested by decreased left ventricular peak systolic pressure, peak dP/dt, and calculated peak systolic wall stress developed during an isovolumetric contraction over a wide range of left ventricular end-diastolic pressures. In vitro passive left ventricular pressure-volume relationships in the excised hearts of these animals remained abnormal when the right ventricle was filled to match the in vivo conditions, but the left ventricular pressure-volume curve was normal when the right ventricle was emptied. Thus, the intrinsic compliance of the left ventricle was not altered.\textsuperscript{21}

Postoperative assessments in the present study support the concept that left ventricular dysfunction in patients with atrial septal defect is at least in part a reversible response to mechanical factors associated with the left-to-right shunt and right ventricular volume overload. Thus, 6 months after successful closure of the septal defect, at a time when all patients were asymptomatic and had no demonstrable residual shunt, left ventricular ejection fractions were again normal at rest for all patients and showed a normal increase during exercise.

Reversal of mechanical effects of the volume-loaded right ventricle upon the left ventricle, and perhaps also of the effects of underfilling of the left ventricle, are also evident in the echocardiographic data. After operation, the right ventricular internal dimension decreased in all patients but remained dilated.\textsuperscript{6, 22-24} Abnormal septal motion persisted in eight of 11 patients,\textsuperscript{9, 22-25} although there was a trend toward normalization of septal relations in diastole and systole. Left ventricular end-diastolic dimensions, subnormal in all patients before operation, increased significantly after operation\textsuperscript{23, 24} and were within the normal range for body surface area in all patients. Calculated left ventricular fractional shortening, subnormal in half the patients before operation, increased significantly after operation and was within the normal range for all patients.

Because of paradoxical septal motion and distortion of the left ventricular cavity, M-mode echocardiography does not permit accurate quantitation of left ventricular volumes in patients with right ventricular volume overload. Therefore, our preoperative data, although abnormal and suggestive of subnormal left ventricular end-diastolic volume, cannot be translated quantitatively into left ventricular volumes or indexes of left ventricular function. However, the changes from before to after operation demonstrate reversal of preoperative abnormalities upon correction of the right ventricular volume overload.

Our results demonstrate that although left ventricular ejection fraction is normal in adult patients with atrial septal defect without hemodynamically severe right or left ventricular failure, ejection fraction may exhibit an abnormal response to exercise. The impairment in the left ventricular exercise response appears to be correlated with the severity of symptoms and with the magnitude of the left-to-right shunt.
After operative closure of the defect, with obliteration of the shunt, the abnormalities of left ventricular ejection fraction are reversed. Concomitantly, septal relations in diastole and systole improve and subnormal echocardiographic left ventricular end-diastolic dimensions increase to normal. These findings are consistent with the concept that left ventricular dysfunction in patients with atrial septal defect is in many cases the result of reversible mechanical factors related to right ventricular volume overload, with abnormal diastolic-systolic relations of the interventricular septum and, perhaps, left ventricular underfilling, rather than to intrinsic, irreversible myocardial dysfunction.

Only one of the patients in our series had hemodynamic evidence of fixed pulmonary hypertension. None had hemodynamic evidence of right or left ventricular failure. Left ventricular ejection fraction might be abnormal at rest in patients with such complications, and postoperative ejection fractions might manifest persistent abnormalities. Further studies are required to test if this is so and to assess the severity and reversibility of such abnormalities.

Acknowledgment

We gratefully acknowledge the excellent technical assistance of Bonnie Mack, Susan Farkas and Joyce McKay.

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Left ventricular functional reserve in adult patients with atrial septal defect: pre- and postoperative studies.
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