Intravenous digital subtraction angiography to assess pulmonary artery anatomy in patients with the Alagille syndrome[1]

Debra Brindza, M.D.
Douglas S. Moodie, M.D.
Robert Wyllie, M.D.
Richard Sterba, M.D.

The authors present three cases of the Alagille syndrome in which the pulmonary artery anatomy was well defined by intravenous digital subtraction angiography (DSA). The degree of pulmonary artery hypoplasia varied in all three patients and was readily identified by digital techniques. DSA provides an easy, safe method to study the intracardiac and pulmonary artery abnormalities in patients with this syndrome.

Index terms: Angiography • Pulmonary artery, abnormalities • Subtraction technic

Cleve Clin Q 51:493–497, Fall 1984

The association between arteriohepatic dysplasia and pulmonary artery stenosis with characteristic facies was first noted by Watson and Miller in 1973.[1] Alagille et al[2] described a syndrome which, in addition to the above abnormalities, included growth retardation and hypogonadism.

Previous studies to evaluate the degree of cardiovascular involvement in arteriohepatic dysplasia have included electrocardiography (ECG), echocardiography, and angiography.[3] With the development of intravenous digital subtraction angiography (DSA), an accurate assessment of intracardiac and pulmonary artery anatomy has been possible which has a spatial resolution comparable to that of direct contrast angiography. No reports appear in the literature concerning the use of DSA for the evaluation of pulmonary artery abnormalities in patients with the Alagille syndrome. We describe three cases in which this technique was used to define cardiovascular abnormalities in young patients having this unusual syndrome.

[1] Department of Cardiology, The Cleveland Clinic Foundation. Submitted for publication Mar 1984; accepted June 1984. jw

0009-8787/84/03/493/05/$2.25/0

A, B

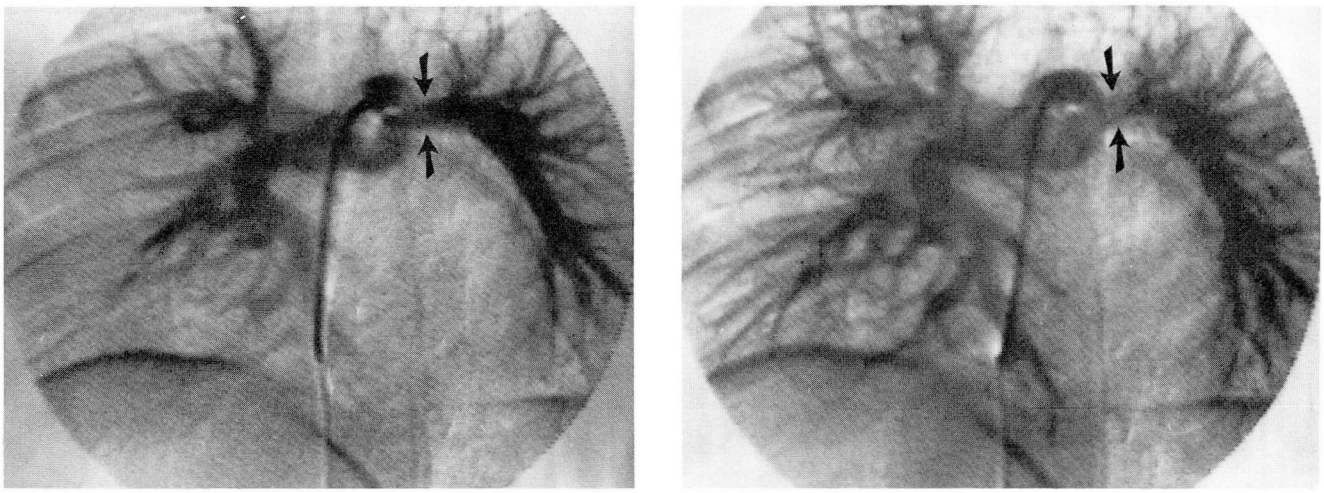

Fig. 1. Case 1.
A. Intravenous DSA (shallow left anterior oblique view) with the catheter placed in the proximal main pulmonary artery, demonstrating mild hypoplasia of the proximal left pulmonary artery (*arrows*) with mild distal pulmonary artery hypoplasia.
B. Intravenous DSA (shallow left anterior oblique view), further demonstrating the pulmonary artery anatomy with mild hypoplasia of the proximal left pulmonary artery and distal pulmonary artery.

Case reports

Case 1. A white boy was noted at age 11 months to have hepatomegaly. At that time, he was described as having an elfin facies, and his liver was palpated 3 cm below the mid-costal margin. Abnormal blood chemistries included serum glutamic-oxaloacetic transaminase (SGOT), 380 U/L; serum glutamic-pyruvic transaminase (SGPT), 720 U/L;

A, B

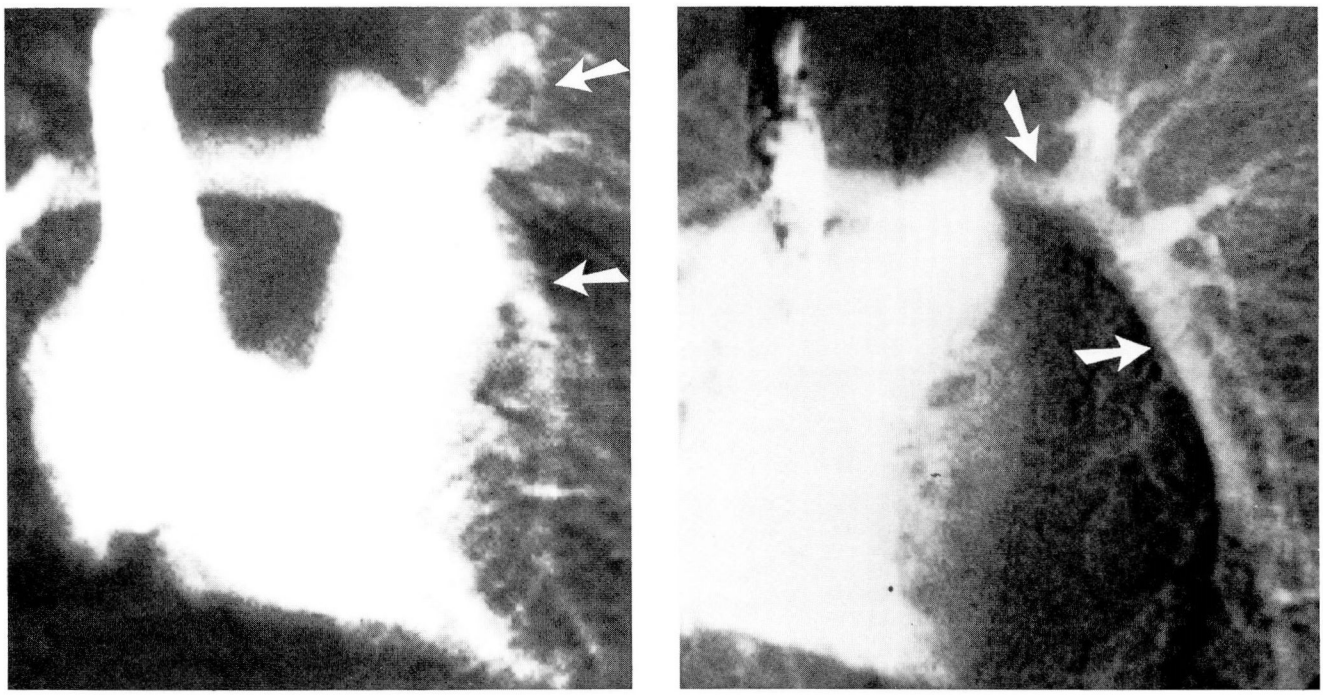

Fig. 2. Case 2.
A. Intravenous DSA (anteroposterior view), demonstrating severe hypoplasia of the proximal and distal left pulmonary artery (*arrows*) as well as of the proximal right pulmonary artery.
B. Intravenous DSA (left anterior oblique view), further demonstrating the pulmonary artery hypoplasia (*arrows*).

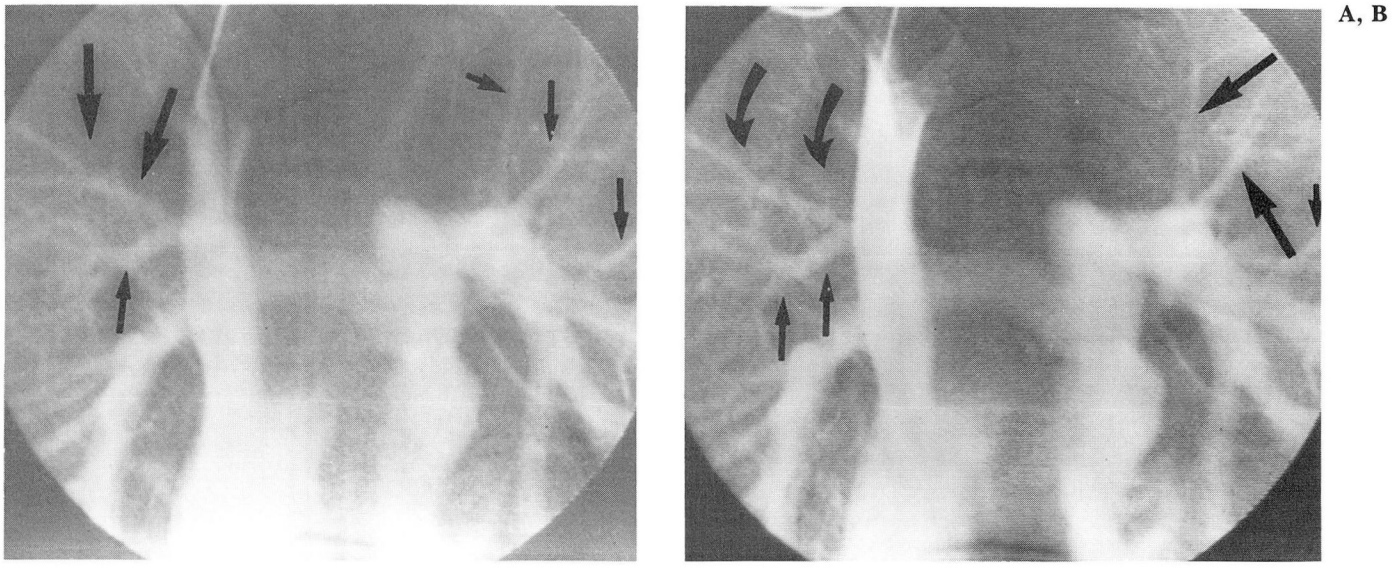

Fig. 3. Case 3.

A. Intravenous DSA (anteroposterior view), demonstrating mild hypoplasia of the distal pulmonary arteries in the right and left lung (*arrows*).

B. Intravenous DSA (anteroposterior view, further frame), demonstrating mild hypoplasia of the distal pulmonary arteries bilaterally (*arrows*).

alkaline phosphatase, 1,780 U/L; triglycerides, 1,337 mg/dL; and cholesterol, 520 mg/dL. At age 16 months, he was referred for further evaluation. Significant physical findings included triangular facies with a prominent forehead, a grade II/VI short systolic murmur at the left lower sternal border radiating to the left mid-sternal border, and hepatomegaly. Biopsy of the liver showed a paucity of intrahepatic bile ducts, a finding consistent with arteriohepatic dysplasia. The eye examination was normal. The electrocardiogram (ECG) and echocardiogram were normal. DSA showed mild hypoplasia of the proximal left pulmonary artery with distal pulmonary artery hypoplasia (*Fig. 1*).

Case 2. A one-month-old white girl was noted to be jaundiced. Biopsy of the liver at that time demonstrated giant cell transformation. At the age of 11 months, she was referred to us for failure to thrive. The physical examination showed a prominent forehead, deep-set eyes, a grade III/VI systolic murmur, and hepatomegaly. Significant blood chemistries were total bilirubin, 3.7 mg/dL; direct bilirubin, 2.0 mg/dL; SGOT, 228 U/L; and alkaline phosphatase, 327.3 Bodansky units. Liver and small bowel biopsies were interpreted as being normal. When the patient was 10½ years old, repeated biopsy demonstrated a paucity of intrahepatic bile ducts, a finding consistent with arteriohepatic dysplasia. Abnormal blood chemistries included cholesterol, >500 mg/dL; alkaline phosphatase, >350 BU/L; lactate dehydrogenase (LDH), 340 U/L; and SGOT, >300 U/L. When she was 14 years old, she was readmitted for further evaluation of growth retardation and hepatomegaly. The physical examination showed a height of 116 cm (50th percentile for six years) and weight of 23.5 kg (50th percentile for 7½ years). The patient was Tanner stage I. Her heart murmur was unchanged. Abnormal blood chemistries included total bilirubin, 1.4 mg/dL; cholesterol, 915 mg/dL; alkaline phosphatase, 1,560 U/L; creatine phosphokinase (CPK), 286 U/L; lactic (acid) dehydrogenase (LDH), 343 U/L; SGOT, 300 U/L; SGPT, 341 U/L. The free thyroxin (T_4) was 8.4 and thyroid-stimulating hormone (TSH) was 3.8, which are normal for our laboratory. The ECG showed right ventricular hypertrophy with a QRS axis in the frontal plane of +90°. The chest radiograph also suggested right ventricular enlargement. A two-dimensional echocardiogram was normal. Intravenous DSA showed main, proximal, and distal pulmonary artery hypoplasia (*Fig. 2*).

Case 3. A white boy, when one day old, was noted to be jaundiced and to have a heart murmur. When he was 2½ months old, liver biopsy results were thought to be consistent with postnecrotic cirrhosis. A later review revealed changes characteristic of arteriohepatic dysplasia. At age four years, he was referred for evaluation of jaundice and eruptive xanthomas. A grade IV/VI systolic ejection murmur at the left upper sternal border was noted at this time. A chest radiograph and ECG showed right ventricular hypertrophy. Significant blood chemistries included the following values: total bilirubin, 7.8 mg/dL; direct bilirubin, 3.0 mg/dL; cholesterol, 490 mg/dL; triglycerides, 265 mg/dL, SGOT, 190 U/L; LDH, 240 U/L. An ECG, obtained when the boy was 10 years old, was normal. Six years later, the clinical diagnosis of arteriohepatic dysplasia was made. When he was 16½ years old, intestinal obstruction secondary to adhesions developed. Post-surgical recovery was complicated by a right subphrenic abscess. After the patient recovered, DSA was performed to further evaluate his cardiac status; it demonstrated mild bilateral peripheral pulmonary artery hypoplasia (*Fig. 3*). Intracardiac structures

were normal. Repeat echocardiography demonstrated a mildly deformed aortic valve.

Results

Interesting differences appeared in the pulmonary artery anatomy of the three patients. The infant had the least pulmonary hypoplasia. The 15-year-old patient had the most severe proximal and distal pulmonary artery stenosis, whereas the 17-year-old patient was somewhere in between with only mildly hypoplastic distal pulmonary arteries. Intravenous DSA affords an ideal method to follow the natural progression in the development of the pulmonary arteries in these patients. In addition, intravenous DSA also allowed us to evaluate intracardiac anatomy in these patients, and except for the involvement of the pulmonary arteries, the intracardiac anatomy in all three cases was normal aside from a mildly dysplastic aortic valve in Case 3.

Discussion

The syndrome of neonatal jaundice with cardiac malformations was first recognized by Watson and Miller.[1] Other associated features of arteriohepatic dysplasia include characteristic facies, skeletal anomalies, ocular changes, growth retardation, endocrine abnormalities, and hypogonadism.[2,3] Recent evidence indicates the presence of intralobular bile ducts in infancy, with progressive inflammatory changes, and later in childhood, a paucity or absence of intralobular bile ducts.[4]

The cardiovascular malformations most commonly described in this syndrome have been peripheral pulmonary artery stenosis and hypoplasia and patent ductus arteriosus.[5] Other intracardiac malformations reported include atrial septal defect,[5] ventricular septal defect,[5,6] aortic coarctation,[2] stenosis of the right coronary artery ostium,[6] and pulmonary valvular atresia.[7] The etiology of arteriohepatic dysplasia has yet to be determined. Alagille et al[2] described a positive family history for neonatal cholestasis in three out of 15 reported cases. Riely et al[8] reported a father and son with cholestasis and peripheral pulmonic stenosis, and they speculated that the cause was an inborn error of metabolism. Although an infectious agent has not been isolated, other investigators have suggested intrauterine infection.[3,6–8] Intrauterine rubella infections have been shown to cause pulmonic stenosis, cholestasis, and loss of intrahepatic bile ducts, a syndrome similar to arteriohepatic dysplasia.[9,10]

The use of intravenous DSA for the evaluation of patients with congenital heart disease has been described,[11,12] as well as the use of DSA for the evaluation of congenital abnormalities of the aorta and aortic arch,[13] intracardiac masses,[14] anomalies associated with intracardiac left-to-right shunts,[15] and aneurysms of the atrial and ventricular septum.[16] This is the first report detailing the use of intravenous DSA in patients to evaluate the pulmonary artery anatomy in the Alagille syndrome. The techniques for the intravenous administration of contrast material have been previously described.[11–16] Digital and analog systems with single and average multiple masks were used along with two commercially available systems with radiographic or continuous modes. All patients had 1 mL/kg or less of contrast media (Renografin, Squibb) injected intravenously for the study.

The subtraction of unnecessary background information in DSA provides an enhanced spatial resolution allowing identification of structures with low concentrations of intravenously injected iodine. At the same time, the ability to post process images and extract numbers from the images theoretically allows not only a structural analysis, but also a quantitative analysis of the cardiovascular system. Our system can readily discern a 1mm vessel with 1% contrast material. The resolution visualized by the television system is 2.3 line pairs/mm in the 6-in mode. Because of its inherently superior spatial resolution, DSA provides accurate information about the level of left-to-right shunting and the presence of associated cardiac anomalies and provides an opportunity to assess chamber size and contractility. The utility of this technique in patients with congenital heart disease and left-to-right shunts has been recently described.[15] The ability of DSA techniques to define structural, congenital, and acquired cardiac abnormalities with a resolution similar to that obtained from standard cardiac catheterization has been shown.[11–13] One obvious advantage of DSA is that it is less invasive than standard cardiac catheterization techniques. An accurate assessment of pulmonary artery anatomy in which only peripheral intravenous injections were used was possible with two of our three patients. DSA techniques can be performed easily on an outpatient basis, and they allow for long-term assessment of vascular and structural abnormalities. There is significantly decreased x-ray exposure, with radiation approaching 2–3 R.[11] The total radiation dose during DSA is two

to 10 times lower than the radiation received during conventional angiography.[11] A decreased volume of injectant can be used, and our three patients had injections which ranged from 0.3 to 1.0 mL/kg of contrast material. Thus, DSA techniques are ideally suited for pediatric patients with Alagille syndrome in order to assess not only anomalies of the pulmonary arteries, but also intracardiac abnormalities, such as atrial and ventricular septal defects[15] and coarctation of the aorta.[13]

Conclusion

DSA studies appear to be the best method for the noninvasive evaluation of intracardiac and pulmonary artery abnormalities in patients with the Alagille syndrome. These studies can be performed in an outpatient setting to assess the long-term evaluation and progression in pulmonary artery abnormalities, and associated intracardiac anomalies can be readily identified. DSA provides an easy, safe method to study the intracardiac and pulmonary artery abnormalities in patients with the Alagille syndrome.

Douglas S. Moodie, M.D.
Department of Cardiology
The Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland OH 44106

References

1. Watson GH, Miller V. Arteriohepatic dysplasia: familial pulmonary arterial stenosis with neonatal liver disease. Arch Dis Child 1973; **48:**459–466.
2. Alagille D, Odièvre M, Gautier M, Dommergues JP. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. J Pediatrics 1975; **86:**63–71.
3. Riely CA, Cotlier E, Jensen PS, Klatskin G. Arteriohepatic dysplasia: a benign syndrome of intrahepatic cholestasis with multiple organ involvement. Ann Int Med 1979; **91**:520–527.
4. Dahms BB, Petrelli M, Wyllie R, et al. Arteriohepatic dysplasia in infancy and childhood: a longitudinal study of six patients. Hepatology 1982; **2:**350–358.
5. Greenwood RD, Rosenthal A, Crocker AC, Nadas AS. Syndrome of intrahepatic biliary dysgenesis and cardiovascular malformations. Pediatrics 1976; **58:**243–247.
6. Levin SE, Zarvos P, Milner S, Schmaman A. Arteriohepatic dysplasia: association of liver disease with pulmonary arterial stenosis as well as facial and skeletal abnormalities. Pediatrics 1980; **66:**876–883.
7. Kocoshis SA, Cottrill CM, O'Connor WN, Haugh R, Johnson GL, Noonan JA. Congenital heart disease, butterfly vertebrae, and extrahepatic biliary atresia: a variant of arteriohepatic dysplasia? J Pediatrics 1981; **99:**436–439.
8. Riely CA, LaBrecque DR, Ghent C, Horwich A, Klatskin G. A father and son with cholestasis and peripheral pulmonic stenosis: a distinct form of intrahepatic cholestasis. J Pediatrics 1978; **92:**406–411.
9. Strauss L, Bernstein J. Neonatal hepatitis in congenital rubella. A histopathological study. Arch Pathol 1968; **86:**317–327.
10. Esterly JR, Oppenheimer EH. Intrauterine rubella infection. Perspect Pediatr Path 1973; **1:**313–338.
11. Moodie DS, Buonocore E, Yiannikas J, Gill CC, Pavlicek WA. Digital subtraction angiography in congenital heart disease in pediatric patients. Cleve Clin Q 1982; **49:**159–171.
12. Buonocore E, Pavlicek W, Modic MT, et al. Anatomic and functional imaging of congenital heart disease with digital subtraction angiography. Radiology 1983; **147:**647–654.
13. Moodie DS, Yiannikas J, Gill CC, Buonocore E, Pavlicek W. Intravenous digital subtraction angiography in the evaluation of congenital abnormalities of the aorta and aortic arch. Am Heart J 1982; **104:**628–634.
14. Yiannikas J, Zaidi AR, Moodie DS. Digital subtraction angiography: evaluation of intracardiac masses. Case report. Am Heart J (in press).
15. Yiannikas J, Moodie DS, Gill CC, Sterba R, McIntyre R, Buonocore E. Intravenous digital subtraction angiography in the assessment of patients with left to right shunts before and after surgical correction. J Am Coll Cardiol 1984; **3:**1507–1514.
16. Yiannikas J, Moodie DS, Sterba R, Gill CC. Intravenous digital subtraction angiography to assess aneurysms of the ventricular and atrial septum pre- and postoperatively. Am J Cardiol 1984; **53:**383–385