lege of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *Circulation*. 1998;98:1949-84.

2. <http://www.ctsnet.org/file/AnticoagulationSurveyFinalResultsSlidesPDF.pdf>.
3. Sundt TM, Zehr KJ, Dearani A, Daly RC, Mul-lany CJ, McGregor CG, et al. Is early anticoagulation with warfarin necessary after bioprosthetic aortic valve replacement? *J Thorac Cardiovasc Surg*. 2005;129:1024-31.

doi:10.1016/j.jtcvs.2005.07.006

Atrial septal defect in infancy: To close or not to close?

To the Editor:

I read with great interest the article by Lammers and associates¹ advocating that closure of an atrial septal defect (ASD) should not be postponed to a later age if clinical problems that can be attributed at least in part to the ASD are present. However, a closer look at the historical cohort of Lammers and associates reveals that it is composed mainly of premature syndromic infants in whom the major issue is bronchopulmonary dysplasia and pulmonary hypertension rather than left-to-right shunt across the ASD.² Hence the suggestion of the authors, in the opinion of this reader, is controversial.

Although ASD is the second most common congenital heart disease in children,³ there are still few unanswered questions related to the appropriate timing of closure. Because patients with even large ASDs are mostly asymptomatic, closure is recommended around 3 to 5 years of age, before the child goes to school. Postponing surgical intervention to this age also allows for spontaneous closure of the ASD in some children.⁴ In fact, there does not appear to be any significant benefit in ASD closure before 3 to 5 years of age in small- to moderate-sized defects.⁵

In the opinion of this reader, in the present era of better ventilator equipment and styles of ventilator management, along with widespread use of corticosteroids prenatally and surfactant, nitric oxide, and pulmonary vasodilator therapy postnatally, surgical ASD closure can be postponed in patients with compromised lung function unless all available means of improving lung function have been tried. Only when pulmonary compromising factors have been corrected will an attempt at surgical ASD closure in infancy be valid because even though mortality for major operations with cardiopulmonary bypass in infants

with low weight has become low, a definite morbidity still persists.

Shahzad G. Raja, MRCS
Department of Cardiac Surgery
Royal Hospital for Sick Children
Yorkhill NHS Trust
Dalnair St
Glasgow G3 8SJ
United Kingdom

References

1. Lammers A, Hager A, Eicken A, Lange R, Hauser M, Hess J. Need for closure of secundum atrial septal defect in infancy. *J Thorac Cardiovasc Surg*. 2005;129:1353-7.
2. Dammann O, Leviton A, Gappa M, Dammann CE. Lung and brain damage in preterm newborns, and their association with gestational age, prematurity subgroup, infection/inflammation and long term outcome. *BJOG*. 2005;112(suppl 1):4-9.
3. Radzik D, Davignon A, van Doesburg N, Fournier A, Marchand T, Ducharme G. Predictive factors for spontaneous closure of atrial septal defects diagnosed in the first 3 months of life. *J Am Coll Cardiol*. 1993;22:851-3.
4. Saxena A, Divekar A, Soni NR. Natural history of secundum atrial septal defect revisited in the era of transcatheter closure. *Indian Heart J*. 2005;57:35-8.
5. McMahon CJ, Feltes TF, Fraley JK, Bricker JT, Grifka RG, Tortoriello TA, et al. Natural history of growth of secundum atrial septal defects and implications for transcatheter closure. *Heart*. 2002;87:256-9.

doi:10.1016/j.jtcvs.2005.06.039

Reply to the Editor:

We appreciate Dr Raja's interest in our recent study.¹

We agree that in asymptomatic children closure of an isolated secundum-type atrial septal defect (ASD II) should be undertaken after 4 to 5 years of age because this might allow for spontaneous closure and facilitate interventional closure in some patients. However, we describe a specific group of patients in whom symptoms have been at least in part related to the presence of an ASD II. In these patients with compromised lungs and rarefied pulmonary vasculature, even a minor left-to-right shunt is poorly tolerated, and early surgical closure could be beneficial.

Our catheter data showed that the majority of the children had a left-to-right shunt that varied in magnitude, as is demonstrated by the Qp/Qs ratio. The actual effect of the left-to-right shunt on the infant's clinical condition is difficult to as-

sess. However, the ASD is an additional factor compromising the child's situation. One cannot treat lung hypoplasia or severe chronic lung disease, but an ASD is amenable to treatment.

There might be a subgroup of patients in whom closure of an ASD is contraindicated. In the presence of progressive pulmonary vascular disease, the existence of an ASD can improve survival.²

Dr Raja suggests that surgical ASD closure in infancy should only be performed after all other compromising factors are corrected. Yet even in the current era of better ventilator management and use of antenatal corticosteroids, nitric oxide, and surfactant leading to improved survival of infants, correction of the lung-compromising factors is not always possible. Moreover, long-term hospitalization and prolonged ventilation of these children is associated with substantial morbidity, including barotrauma, hospital-acquired infections, and immobilization. Therefore we contend that a subgroup of infants can indeed benefit from early ASD closure. Careful patient selection, however, remains a clinical challenge and requires a multidisciplinary approach involving cardiologists, intensivists, and cardiothoracic surgeons to determine the right timing of ASD closure for each individual child.

Astrid Lammers
John Hess, MD, FESC
Klinik für Kinderkardiologie und angeborene Herzfehler
Deutsches Herzzentrum München
Technische Universität München
Munich, Germany

References

1. Lammers A, Hager A, Eicken A, Lange R, Hauser M, Hess J. Need for closure of secundum atrial septal defect in infancy. *J Thorac Cardiovasc Surg*. 2005;129:1353-7.
2. Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. *Br Heart J*. 1986;55:449-58.

doi:10.1016/j.jtcvs.2005.07.020

The evaluation of aortic atherosclerosis and distensibility in aortic valve stenosis—The role of transesophageal echocardiography To the Editor:

We read with great interest and congratulate Weisenberg and associates on their trans-

esophageal echocardiographic (TEE) study entitled "Atherosclerosis of the aorta is common in patients with severe aortic stenosis: An intraoperative transesophageal echocardiographic study."¹ This intriguing study found a strong association between the presence of severe aortic stenosis (AS) and the presence and severity of aortic atheromas, suggesting that AS might be a manifestation of the atherosclerotic process. However, we feel that a few additional comments are necessary.

Evident from previous TEE work, we demonstrated that the average grade of aortic atherosclerosis (AA) using a five-grade scale is significantly increased in AS patients with normal epicardial coronary arteries (1.44 ± 0.64) as compared to control subjects without valvular or coronary heart disease (0.62 ± 0.74). The degree of AA in AS patients is also similar to patients with significant left anterior descending coronary artery (LAD) disease (1.27 ± 0.72).² Furthermore, another TEE study verified that, neither age, gender, high blood pressure, diabetes mellitus, hypercholesterolaemia nor coronary flow velocity reserve were suitable for the prediction of AS patients with significant LAD stenosis from AS subjects with normal epicardial coronary arteries. Only the grade of AA is suitable for the prediction of AS patients with significant LAD stenosis from AS subjects with normal epicardial coronary arteries. With respect to demographic, clinical and echocardiographic data, only the prevalence of grade 2 or 3 AA (aortic plaque) is significantly increased in AS patients with significant stenosis of the LAD.³

Aortic distensibility can also be evaluated during TEE using aortic and blood pressure data. Different elastic properties of the descending aorta can be assessed by TEE as *elastic modulus* and *Young's circumferential static elastic modulus*. Decreased aortic distensibility (increased elastic moduli) and thus, increased stiffness of the descending aorta were demonstrated in AS patients with normal epicardial coronary arteries. This result supports that decreased aortic distensibility in AS patients is an early manifestation of the atherosclerotic process and/or decreased perfusion of the aorta.^{2,5} Our initial results suggest that there are no differences in these values characterizing

aortic distensibility if mitral stenosis is associated with AS.⁴

Overall, these results confirm that TEE is a valuable method for the morphological (grade of aortic atherosclerosis) and functional (elastic properties of the aorta) evaluation of the descending aorta in AS patients. There is a strong relationship between the aortic atherosclerosis/distensibility and AS, suggesting that aortic valve calcification might represent an atherosclerosis-like process. However further investigations are warranted.

Attila Nemes, MD, PhD, FESC

Tamás Forster, MD, PhD, DSc, FESC

Miklós Csanády, MD, PhD, DSc, FESC, FACC

2nd Department of Medicine and

Cardiology Centre

Medical Faculty

Albert Szent-Györgyi Medical and

Pharmaceutical Center

University of Szeged

Szeged, Hungary

References

1. Weisenberg D, Sahar Y, Sahar G, Shapira Y, Iakobishvili Z, Vidne BA, et al. Atherosclerosis of the aorta is common in patients with severe aortic stenosis: An intraoperative transesophageal echocardiographic study. *J Thorac Cardiovasc Surg.* 2005;130:29-32.
2. Nemes A, Forster T, Csanady M. Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. *J Heart Valve Dis.* 2004;13:567-573.
3. Nemes A, Forster T, Thury A, Kovacs Z, Boda K, Csanady M. The comparative value of the aortic atherosclerosis and the coronary flow velocity reserve evaluated by stress transesophageal echocardiography in the prediction of patients with aortic atherosclerosis with coronary artery disease. *Int J Cardiac Imag.* 2003;19:371-376.
4. Nemes A, Forster T, Csanady M. Coronary flow velocity reserve and elastic modulus of the descending aorta in patients with aortic stenosis with or without mitral stenosis. *Eur J Echocardiography Abstracts.* 2003;4 (Suppl 1):S50.
5. Nemes A, Forster T, Csanady M. Aortic distensibility in coronary artery disease and in aortic stenosis. *Acta Cardiol.* 2005;60:55-56.

[Response declined]

doi:10.1016/j.jtcvs.2005.07.032

Association between cyclooxygenase and epidermal growth factor receptor pathways in non-small cell lung cancer

To the Editor:

We read with great interest the article by Sievers and associates.¹ In their orthotopic murine model of lung cancer with adenocarcinoma, they showed inhibition of tumor growth with a low-dose cyclooxygenase-2 (COX-2) inhibitor, celecoxib. In their article, they discussed different mechanisms of association between COX-2 inhibition and attenuation of tumor growth in non-small cell lung cancer (NSCLC), and we want to propose another. COX (or prostaglandin endoperoxide synthase) catalyzes the conversion of arachidonic acid to prostaglandin (PG) H₂. This unstable endoperoxide is then converted into PGE₂, PGI₂, PGD₂, PGF₂, or thromboxane A₂ by each respective PG synthase. Most tumors that express COX have been found to contain high levels of PGE₂ and the microsomal PGE synthase enzyme. Presumably, these bioactive lipid products of COX, such as PGE₂, are responsible for some of the proneoplastic effects mediated by this enzyme.² The epidermal growth factor receptor (EGFR) is a member of the ErbB family of transmembrane tyrosine kinase receptors. The expression of EGFR is common in a number of normal epithelial tissues, and the expression of EGFR is elevated in several solid tumors. In NSCLC, overexpression of EGFR has been reported to be present in more than 50% of cases in several series. Receptor activation leads to recruitment and phosphorylation of several downstream intracellular substrates, leading to mitogenic signaling and other tumor-promoting cellular activities. In addition to this, several retrospective studies have identified the expression of EGFR as a negative prognostic factor in patients with resected early NSCLC.³ Sheng and colleagues⁴ found that PGE₂ initially binds to its cognate receptor, EP4, in LS-174T cells, which in turn activates signals that led to dramatic changes in cell biology. One study demonstrated that the PGE₂-induced migration and invasion occur by rapid transactivation and phosphorylation of EGFR in developing carcinoma cells.⁵ Within minutes after treatment, PGE₂ induces the activation of Akt. This effect is completely abolished by EGFR-specific tyrosine kinase inhibitors, providing evidence for the role of the EGFR in