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.

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[Response declined]

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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) H_2. This unstable endoperoxide is then converted into PGE_2, PGI_2, PGD_2, PGF_2, or thromboxane A_2 by each respective PG synthase. Most tumors that express COX have been found to contain high levels of PGE_2 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 colleagues[4] found that PGE_2 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 PGE_2-induced migration and invasion occur by rapid transactivation and phosphorylation of EGFR in developing carcinoma cells.[5] Within minutes after treatment, PGE_2 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

this response. The rapid transactivation of EGFR occurs by an intracellular Src-mediated event, but not through the release of an extracellular epidermal growth factor–like ligand. These results suggest that the early effects of COX-2–derived PGE_2 are in part mediated by EGFR, and this transactivation is responsible for subsequent downstream effects, including the stimulation of cell migration and invasion.[5] In the light of this information, we propose that celecoxib may inhibit downstream signaling of EGFR by decreasing the COX-2 protein and PGE_2 levels, resulting in tumor growth inhibition in NSCLC.

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Reply to the Editor:

We thank Ates and colleagues for their thoughtful comments. We agree that there is an interrelationship between the cyclooxygenase-2 (COX-2) enzyme (and prostanoid products) and the epidermal growth factor receptor (EGFR) family. In an important article, Pai and colleagues[1] reported that COX-2/prostaglandin E_2 transactivates the EGFR receptor, with resultant activation of downstream signaling.[1] Similarly it has been proposed that EGFR signaling can increase COX-2 activity. These findings have given cause for initiation of human trials of combination therapy with both EGFR receptor inhibitors and celecoxib in patients with non–small cell cancer, with some exciting initial results. However, the interaction between the two is complex and as yet incompletely understood. Recently, Richardson and colleagues[2] found that COX-2 protein levels are independent of EGFR expression or activation in patients with non–small cell cancer.[2] We have found that combination therapy (EGFR receptor blocker together with COX-2 blockade by celecoxib) are occasionally antagonistic (at least in one cell line) in an animal orthotopic lung cancer model. When understanding the interaction, though, it is important to realize that levels of the COX-2 enzyme (both messenger RNA and protein) are variably affected by celecoxib, but the activity of the enzyme is profoundly blocked even by low doses of the drug. With regard to final sentence of the letter, we would agree that celecoxib decreases PGE_2 levels (but not COX-2 levels) and that interactions with the EGFR cascade probably account for some of the antineoplastic activity of the compound.

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