evaluated on a case-by-case basis and could be considered in patients with left-to-right shunt and evidence of progressive right ventricular or atrial enlargement, right-sided chamber dysfunction, or worsening pulmonary hypertension. Closure of iASD in patients with persistent right-to-left shunt with paradoxical embolus or arterial desaturation (hypoxemia) might also be reasonable.

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REFERENCES

REPLY: Iatrogenic Atrial Septal Defect After MitraClip Therapy

We thank Drs. Rogers and Smith for their comments on our paper (1).

Drs. Rogers and Smith state that they were able to publish data from the roll-in phase of the EVEREST II (A Study of the Evalve Cardiovascular Valve Repair [MitraClip] System Endovascular Valve Edge-to-Edge Repair Study EVEREST II High Risk Registry) in 2012 reporting on markedly lower incidence rates of iatrogenic septal defect (iASD) after MitraClip use (27%) (2). This group reported a correlation of detectable iASD with cardiac remodeling (2), which was in part confirmed by our findings (1). Consequently, Drs. Rogers and Smith question the novelty of our data. Before we started our study program, we read their paper with great interest and acknowledge this early work. We want to point out that we did not deem ourselves to be the first group investigating incidence rates of iASD after percutaneous mitral valve repair. To the best of our knowledge we performed the first study in this field “with serial TEE examinations” (1).

Furthermore, several important differences between the 2 studies must be stressed, which makes a head-to-head comparison impossible.

First, Smith et al. (2) reported transthoracic echocardiographic findings, which has important limitations in this setting. Current guidelines define TEE the gold standard for the evaluation of interatrial shunt defects (3), and several studies were able to show significant differences in detectable iASD rates if determined with transthoracic echocardiographic findings or transesophageal echocardiography (TEE) (4). Second, the main focus of our research was to evaluate the correlation of iASD persistence with the treated patients’ clinical outcomes, which was not addressed by Smith et al. (2).

Third, we included nonsurgical, highest-risk patients, including 73% of subjects with functional mitral valve regurgitation, which is in contrast to Smith et al. (2) reporting on degenerative valve disease in patients suitable for MV replacement. The persistence rate of iASD and its clinical consequences might differ relevantly between high-risk heart failure patients and the early EVEREST II population (5). As we discussed in our paper (1), we agree with Smith and Rogers that the “true” significance of iASD after percutaneous mitral valve repair remains unknown. Our results—in context with available data—showed a noticeable correlation of iASD persistence with patients’ functional outcomes and survival. As we clearly stated (1), the underlying pathomechanisms for iASD persistence are not fully understood, and we emphasize the need for prospective trials addressing this topic. Currently, interventional closure of an iASD after percutaneous mitral valve repair must be planned based on a careful, individual case-by-case decision.

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REFERENCES
True Fractional Flow Reserve of Left Main Coronary Artery Stenosis in the Presence of Downstream Coronary Stenoses

With great interest I read the recent paper by Fearon et al. (1) in which they assessed the impact of downstream left anterior descending (LAD) or left circumflex (LCX) coronary stenosis on the assessment of fractional flow reserve (FFR) of an left main coronary artery (LMCA) stenosis. They concluded that if the apparent FFR of the LMCA (FFR_app) is >0.85, the true FFR of the LMCA (FFR_true) is always >0.80. If FFR_app is between 0.81 and 0.85 and the epicardial FFR (FFR_epi) is ≤0.45, then FFR_true is ≤0.80 in some cases.

However, these conclusions are not surprising. These conclusions can be proven mathematically. Bruyne et al. (2) previously described theoretical equations that calculate the true FFR of individual stenosis in a tandem lesion. Based on their study, an equation that calculates FFR_true in a bifurcation lesion can be derived. When the downstream stenosis is located in the LAD, and n is defined as the ratio of microcirculatory resistances of the LCX to the LAD, FFR_true is calculated as per the following Equation 1.

\[
FFR_{true} = \frac{nFFR_{epi} + FFR_{app}}{1 + n(1 - \frac{FFR_{app} - FFR_{epi}}{FFR_{epi}})} \quad (1)
\]

The partial differentiation of FFR_true with respect to FFR_epi is calculated as follows:

\[
\frac{\partial FFR_{true}}{\partial FFR_{epi}} = \frac{n(n + 1)\left(1 - FFR_{app}\right)}{1 + n\left(1 - (FFR_{app} - FFR_{epi})\right)^2} > 0 \quad (2)
\]

The above inequality in Equation 2 indicates that the FFR_true monotonically increases when FFR_epi is larger. Similarly, the partial differentiation of FFR_true with respect to FFR_app and n are calculated as follows:

\[
\frac{\partial FFR_{true}}{\partial FFR_{app}} = \frac{(n + 1)(nFFR_{epi} + 1)}{1 + n\left(1 - (FFR_{app} - FFR_{epi})\right)^2} > 0 \quad (3)
\]

\[
\frac{\partial FFR_{true}}{\partial n} = \left(1 - FFR_{app}\right)\frac{\left(FFR_{epi} - FFR_{app}\right)}{1 + n\left(1 - (FFR_{app} - FFR_{epi})\right)^2} < 0 \quad (4)
\]

The inequalities in Equations 2, 3, and 4 suggest that FFR_true increases with FFR_epi and FFR_app, but that it decreases with an increase in n. n is the ratio of microcirculatory resistances of the LCX to the LAD, which is usually considered approximately 2. Thus, FFR_true > 0.80 is always true when FFR_app is >0.85, FFR_epi is >0.45, and n = 2. Similarly, Equation 1 suggests that when FFR_app is between 0.81 and 0.85 and the epicardial FFR (FFR_epi) is ≤0.45, then FFR_true can be either larger or smaller than 0.80. These calculations are completely in accordance with the study results of Fearon et al. (1). Their study was well designed and the results were reasonable, but it lacked the understandings of the background mechanism. Another important limitation of their study is that they only assessed the LMCA plus 1 downstream stenosis and lacked the assessment of the LMCA plus 2 downstream stenoses both in the LAD and LCX, which is also frequently encountered in clinical practice. In the case of the LMCA plus 2 downstream stenoses, FFR_true is calculated as per Equation 5 when the epicardial FFR of the LAD and LCX are defined as FFR_LAD and FFR_LCX.

\[
FFR_{true} = \frac{nFFR_{LAD} + FFR_{LCX}}{1 - (FFR_{app} - FFR_{LCX})} = \frac{n(FFR_{LAD} + FFR_{LCX})}{1 - (FFR_{app} - FFR_{LCX})} \quad (5)
\]

I hope that the legitimacy of Equation 5 will be assessed in the future clinical study.

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