

# Impact of Coronary Remodeling on Fractional Flow Reserve

In the early stage of coronary atherosclerosis, expansive remodeling compensates for plaque growth without affecting luminal dimensions or even results in a mild luminal enlargement.<sup>1,2</sup> However, the impact of subclinical coronary artery disease progression on physiological parameters remains elusive. Coronary computed tomography angiography has emerged as a noninvasive method to evaluate lumen and plaque dimensions.<sup>3</sup> In addition, vessel conductance can be assessed by the 3-dimensional reconstruction of the coronary lumen geometry and simulation of blood flow.<sup>4</sup> This study aimed to evaluate the impact of coronary arterial remodeling and lumen dimensions on fractional flow reserve derived from coronary computed tomography angiography (FFR<sub>CT</sub>).

Serial coronary computed tomography angiography was performed in 24 patients with known coronary artery disease at baseline and the 54-month follow-up. Coronary vessels  $\geq 2.0$  mm in diameter with at least 10 mm in length were analyzed by an independent core laboratory (Cardialysis BV) using a validated software package (Medis QAngioCT). For the serial analyses, vessels were matched in length between baseline and follow-up. The FFR<sub>CT</sub> (HeartFlow, Inc) results are presented as the area under the virtual pullback curve (AUvPC), calculated by plotting the FFR<sub>CT</sub> value at every 10 mm versus length of the vessel (Figure, A). The association between variables was investigated with the Spearman correlation coefficient. Mixed-effect models with random intercept were used to account for the within-patient correlation of vessels. The definition of disease progression and regression was based on 2 times the SD of the mean difference of the repeated measurement.

The study was approved by the ethics committee of each institution, and all subjects signed informed consent.

Overall, 80 vessels from 24 patients were serially assessed and included in this study. All patients were treated with statins. Quantitative coronary computed tomography angiography analysis was feasible in 54 vessels, whereas FFR<sub>CT</sub> was feasible in 45 of 54 (83%) of vessels. At baseline, the mean plaque burden was  $53 \pm 9\%$  and mean luminal area was  $9.41 \pm 4.4$  mm<sup>2</sup>. Overall, plaque and lumen dimensions remained unchanged ( $\Delta$ plaque area,  $0.19$  mm<sup>2</sup>; 95% confidence interval,  $-0.91$  to  $0.53$ ;  $P=0.60$ ; and  $\Delta$ lumen area,  $0.27$  mm<sup>2</sup>; 95% confidence interval,  $-0.63$  to  $0.09$ ;  $P=0.13$ ). In addition, the FFR<sub>CT</sub> remained stable ( $\Delta$ FFR<sub>CT</sub> AUvPC,  $0.27$ ; 95% confidence interval,  $-0.1$  to  $0.1$ ;  $P=0.966$ ). Nineteen vessels showed expansive remodeling; 16 exhibited negative remodeling; and 19 remained unchanged. The FFR<sub>CT</sub> deteriorated in 15 vessels, improved in 23 vessels, and remained unchanged in 7 vessels.

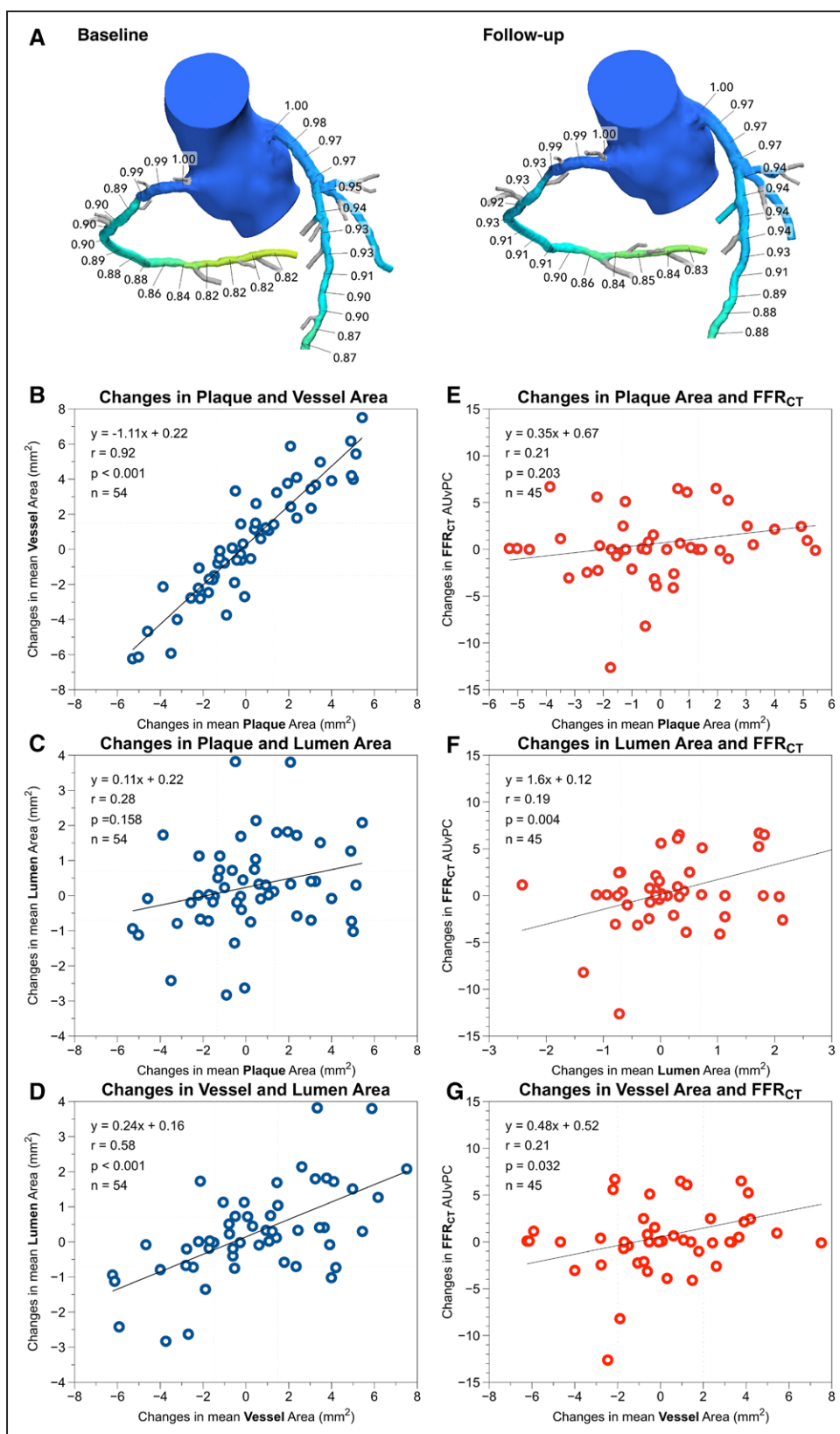
The change in mean plaque area was strongly correlated with the change in mean vessel area (Figure, B), whereas changes in mean plaque area did not correlate with changes in mean lumen area (Figure, C). Expansive remodeling was associated with luminal enlargement; for every 1-mm<sup>2</sup> increase in vessel area, the

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**Figure.** Correlation between changes in vessel, plaque, lumen area, and fractional flow reserve derived from computed tomography angiography (FFR<sub>CT</sub>).

**A**, An example of the serial measurement of FFR<sub>CT</sub>. FFR<sub>CT</sub> was assessed at every 10 mm to calculate the area under the virtual pullback curve (AUVPC). Morphometric relationships are shown on the **left** (blue circles) and the functional (*Continued*)

**Figure Continued.** relationships on the **right** (red circles). **B**, Significant positive correlation between changes in mean plaque area and vessel area. **C**, Significant positive correlation between changes in mean vessel area and lumen area. **D**, Nonsignificant correlation between the changes in mean plaque area and mean lumen area. **E**, Significant positive correlation between the changes in mean vessel area and  $\text{FFR}_{\text{CT}}$  AUvPC. A nonsignificant correlation was found between plaque changes and  $\text{FFR}_{\text{CT}}$  changes (**F**), whereas a significant positive correlation was found between lumen changes and  $\text{FFR}_{\text{CT}}$  changes (**G**). The gray lines indicate the boundaries of the reproducibility of the measurements.

lumen area increased by 0.24 mm<sup>2</sup> (Figure, D). The changes in mean vessel area and mean lumen area were positively correlated with changes in  $\text{FFR}_{\text{CT}}$  AUvPC, whereas plaque changes had no impact on  $\text{FFR}_{\text{CT}}$  (Figure, E through G).

The main findings of this study can be summarized as follows: (1) In patients with nonobstructive coronary artery disease, mean lumen area, plaque area, and vessel area remained unchanged during 4.5 years of observation; (2) the conductance of the vessel, as reflected in the  $\text{FFR}_{\text{CT}}$  AUvPC, did not significantly deteriorate or improve; and (3) vessel area changes were positively correlated with changes in mean lumen area and  $\text{FFR}_{\text{CT}}$  AUvPC.

Studies addressing the impact of statin treatment on coronary plaque have found that atherosclerosis progression can be associated with luminal enlargement.<sup>2</sup> Transcending the anatomic findings, the present study incorporates the functional assessment of the conductance of the coronary vessels. Expansive remodeling was associated with an increase in mean lumen area and improvement in  $\text{FFR}_{\text{CT}}$ . The virtual physiological evaluation allowed us to calculate the  $\text{FFR}_{\text{CT}}$  AUvPC, which showed to be useful in reflecting the physiological changes in subclinical states of coronary artery disease, as an alternative to a topical  $\text{FFR}$  threshold used in clinical practice to detect ischemia (0.75–0.80).

In conclusion, this study shows that in patients with nonobstructive coronary artery disease, expansive remodeling has an impact on  $\text{FFR}_{\text{CT}}$ . Progression of coronary atherosclerosis leading to expansive remodeling can be associated with paradoxical luminal enlargement and improvement in  $\text{FFR}_{\text{CT}}$ .

## ARTICLE INFORMATION

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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## Disclosures

Dr Collet has received research grants from HeartFlow Inc. Drs Rogers, Taylor, and Zarins are employees of HeartFlow Inc. Drs Onuma and Serruys are members of the advisory board of Abbott Vascular. P. Kitslaar is an employee of Medis medical imaging systems. The other authors report no conflicts.

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