Saline-Induced Coronary Hyperemia
Mechanisms and Effects on Left Ventricular Function

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Background—During thermodilution-based assessment of volumetric coronary blood flow, we observed that intracoronary infusion of saline increased coronary flow. This study aims to quantify the extent and unravel the mechanisms of saline-induced hyperemia.

Methods and Results—Thirty-three patients were studied; in 24 patients, intracoronary Doppler flow velocity measurements were performed at rest, after intracoronary adenosine, and during increasing infusion rates of saline at room temperature through a dedicated catheter with 4 lateral side holes. In 9 patients, global longitudinal strain and flow propagation velocity were assessed by transthoracic echocardiography during a prolonged intracoronary saline infusion. Taking adenosine-induced maximal hyperemia as reference, intracoronary infusion of saline at rates of 5, 10, 15, and 20 mL/min induced 6%, 46%, 111%, and 112% of maximal hyperemia, respectively. There was a close agreement of maximal saline- and adenosine-induced coronary flow reserve (intraclass correlation coefficient, 0.922; \( P < 0.001 \)). The same infusion rates given through 1 end hole \((n=6)\) or in the contralateral artery \((n=6)\) did not induce a significant increase in flow velocity. Intracoronary saline given on top of an intravenous infusion of adenosine did not further increase flow. Intracoronary saline infusion did not affect blood pressure, systolic, or diastolic left ventricular function. Heart rate decreased by 15% during saline infusion \((P=0.021)\).

Conclusions—Intracoronary infusion of saline at room temperature through a dedicated catheter for coronary thermodilution induces steady-state maximal hyperemia at a flow rate \(\geq 15 \text{ mL/min}\). These findings open new possibilities to measure maximal absolute coronary blood flow and minimal microcirculatory resistance. (Circ Cardiovasc Interv. 2017;10:e004719. DOI: 10.1161/CIRCINTERVENTIONS.116.004719.)

Key Words: absolute myocardial flow heart rate ■ adenosine ■ coronary microvasculature ■ hyperemia ■ microvascular resistance

A reliable method to assess volumetric maximal myocardial flow and absolute minimal microvascular resistance has been described almost 10 years ago.\(^1\)\(^2\) The method is based on the principle of coronary thermodilution by continuous infusion of saline at room temperature during steady-state hyperemia. One of the prerequisites of the thermodilution principle is the complete and instantaneous mixing of the indicator, in this case saline at room temperature. Yet, the method was hampered by technical difficulties that precluded routine application. The technique was recently simplified by the development of a dedicated rapid exchange infusion catheter\(^3\) and a dedicated software allowing instantaneous calculation of volumetric flow and resistance.

The present work is based on an incidental observation. While performing measurements of minimal microvascular resistance in patients with mild atherosclerosis, we observed the occurrence or the increase of a pressure gradient between the coronary ostium and the distal part of the coronary artery few seconds after the start of the intracoronary infusion of saline, even before the start of adenosine infusion (Figure 1). This observation suggested that the infusion of saline at room temperature could elicit coronary hyperemia. If infusion of saline would indeed induce maximal steady-state hyperemia, this would further simplify the application of coronary thermodilution-derived quantification of myocardial flow and resistance.

This study was designed to study the effects of intracoronary infusion of saline at room temperature on the coronary circulation and myocardial function in humans and to explore its mechanisms.
WHAT IS KNOWN

• Coronary blood flow can be quantified by using continuous thermodilution.
• These measurements are performed under hyperemic conditions, usually obtained by infusing adenosine.

WHAT THE STUDY ADDS

• The continuous infusion of saline at room temperature through a dedicated catheter with side holes elicits a hyperemic steady state.
• The hyperemia induced by saline infusion at rates ≥15 mL/min is of at least the same magnitude than that obtained with adenosine.

Methods

Study Population

A total of 33 patients were studied. All patients had known coronary atherosclerosis, but all vessels studied were free of stenosis of >20% by visual assessment. In 24 patients, a flow velocity guidewire (FloWire; Volcano Corporation, San Diego, CA) was used, and in 9 patients, a pressure/temperature sensor-tipped guidewire (Ceritus Wire; St Jade Medical, Minneapolis, MI) was used. All of them had chest pain suggestive of angina, warranting further physiological exploration. All patients gave written informed consent, and the protocol was approved by the Institutional Review Board of the OLV Clinic Aalst, Belgium.

Study Protocol

After completion of a regular coronary angiogram, a 6F guiding catheter was advanced in the coronary ostium, a bolus of intracoronary nitrates was given, and the target coronary artery was instrumented with a Doppler (n=24) or pressure/temperature sensor-tipped guidewire. In 8 patients, coronary atherosclerosis, but all vessels studied were free of stenosis of >20% by visual assessment. In 24 patients, a flow velocity guidewire (FloWire; Volcano Corporation, San Diego, CA) was used, and in 9 patients, a pressure/temperature sensor-tipped guidewire (Ceritus Wire; St Jade Medical, Minneapolis, MI) was used. All of them had chest pain suggestive of angina, warranting further physiological exploration. All patients gave written informed consent, and the protocol was approved by the Institutional Review Board of the OLV Clinic Aalst, Belgium.

Flow velocity, aortic pressure, and heart rate were measured at baseline, after a first intracoronary bolus injection of 200 μg of adenosine through the guide catheter, followed by escalating infusion rates of saline at room temperature of 5, 10, 15, 20 mL/min, each time during at least 40 s. The hyperemic value was expressed as a percentage of the baseline flow velocity. Figure 2A shows a representative example of flow velocity tracings obtained at baseline and during increasing infusion rates of saline at room temperature through the RayFlow catheter.

2. In 6 patients (among the aforementioned 24, all LAD), the measurements were repeated, and the exact same stimuli were given through the same infusion catheter after removal of the side holes and of the tapered tip so that the saline exits the catheter only through the distal extremity. Figure 2B shows a representative example of flow velocity tracings obtained at baseline and during increasing infusion rates of saline at room temperature through the infusion catheter from which the tapered tip and the side holes have been removed. The catheter and an in vitro example illustrating the poor mixing of an indicator with blood are shown in Figure 1 (lower) in the Data Supplement.

3. In 6 patients (among the aforementioned 24), the same measurements were performed, and the exact same stimuli were given when the RayFlow infusion catheter was positioned in the proximal left circumflex coronary arteries but the Doppler wire was left in the LAD (Figure 2C).

4. In 6 patients (among the aforementioned 24, all LAD), saline was infused at 20 mL/min on top of a steady-state hyperemia obtained by intravenous administration of adenosine at 140 μg kg⁻¹ min⁻¹.

5. Echocardiography substudy: In another 9 patients, transthoracic echocardiography was performed in the catheterization laboratory before and at the end of a 2-minute intracoronary infusion of saline through the RayFlow catheter advanced over a pressure/flow sensor-tipped wire. In 8 patients, saline was infused in the LAD at a rate of 20 mL/min, and in 1 patient, saline was infused in the dominant right coronary arteries at a rate of 15 mL/min. When needed, the patient was turned into the left lateral decubitus to obtain an optimal echocardiographic image quality in apical 4-chamber view. The patient and transducer position was not changed between the serial echocardiographic examinations. All echocardiographic examinations were performed using a commercially available system (Vivid E9; GE Medical Systems, Horten, Norway). All acquired images were stored and analyzed offline using commercially available software (EchoPac BT 13; GE Healthcare). The mean from at least 3 consecutive beats was taken for each measurement. Left ventricular (LV) systolic function was assessed using the speckle-tracking–derived 2-dimensional global longitudinal strain in apical 4-chamber view. In brief, an optimized apical 4-chamber view was recorded with the frame rate between 60 to 90 fps. Systole was defined from pulse wave Doppler recording of the LV outflow tract velocity. Global longitudinal strain was assessed as an average peak systolic strain in 6 segments using semiautomatic contouring with manual correction. LV diastolic function was assessed using the mitral flow propagation velocity. From the 4-chamber view, the color Doppler flow mapping of the mitral inflow was displayed, and color M-mode recordings were acquired after aligning the cursor in the direction of the inflow jet. The horizontal sweep propagation speed was set at 100 mm/s. The propagation velocity was measured from the recording of color M-mode as the slope of the first aliasing velocity (45 cm/s) from the mitral tips to 4 cm distally into the LV cavity in early diastole.

Statistical Analysis

Categorical variables are presented as counts and percentages. For continuous variables, normality was tested using the Shapiro–Wilks test, and the variables are presented as mean±SD or median (25th, 75th value). One-way repeated-measure ANOVA with the Geisser–Greenhouse correction for sphericity was conducted to compare flow velocities and CFR values according to the hyperemic stimulus that was used. Pairwise comparisons were subsequently performed using the Bonferroni adjustment to account for type I error; the reported $P$
values for these comparisons are accordingly adjusted. The agreement between CFR measurements with adenosine and saline as hyperemic stimuli was assessed with the intraclass correlation coefficient (2-way mixed effects model); Pearson r correlation coefficients were also calculated, and a P value of <0.05 was considered statistically significant. Analyses were performed using SPSS version 21 (SPSS Inc,
Results

Patient characteristics and medications are described in Table 1. The main results of the study protocols are displayed in Table 2 and Figures 3 through 5.

Saline infusion through the RayFlow catheter did not change systolic blood pressure (107 [101–145] mmHg at baseline versus 119 [104–141] during infusion; \( P=0.806 \)) or diastolic blood pressure (65 [56–80] at baseline versus 65 [51–73] during infusion; \( P=0.421 \)). Heart rate decreased (67 [54–76] at baseline versus 57 [50–73]; \( P=0.021 \) during infusion).

Hyperemic Effect of Saline Infusion Through the Side Holes of the Catheter (n=24)

Coronary flow velocities differed according to the use of hyperemic stimuli (\( P<0.0001 \) for the repeated-measure 1-way ANOVA; Figure 3A). Infusion of saline at a rate of 10 mL/min given through the side holes produced a small, yet significant increase in coronary flow velocity compared with baseline (\( P=0.022 \); Table 2). With 15 mL/min and 20 mL/min, all patients, without exception, exhibited a sudden increase in flow velocity followed by a stable steady state as long as the infusion was maintained. The average steady-state flow velocity values during infusion at rates of 15 and 20 mL/min were significantly higher than that reached after intracoronary administration of adenosine (\( P<0.0001 \) and \( P<0.0001 \) for the respective pairwise comparisons). In 3 patients, we did not perform saline infusion at 20 mL/min because of atrioventricular block during the infusion at 15 mL/min. The atrioventricular block occurred only during infusion in the right coronary arteries and resolved without clinical complications after stopping the infusion.

CFR as induced by an intracoronary bolus of adenosine was 2.6±0.8. Equivalent measurements obtained during infusion of saline at rates of 5, 10, 15 and 20 mL/min were, respectively, 1.1±0.1 (\( P<0.0001 \) versus adenosine), 1.8±0.9 (\( P=0.002 \) versus adenosine), 2.8±0.9 (\( P=0.010 \) versus...
adenosine), and 2.9±0.9 (P<0.0001 versus adenosine). The intraclass correlation coefficients for CFR measured with adenosine intracoronary and CFR during saline infusion at rates of 5, 10, 15, and 20 mL/min were, respectively, 0.021 (P=0.348), 0.318 (P=0.012), 0.919 (P<0.001), and 0.922 (P<0.001). The relation between coronary blood flow velocity reserve with an intracoronary bolus of adenosine and during infusion of 20 mL/min of saline is shown in Figure 4.

Hyperemic Effect of Saline Infusion Through the End Hole of the Infusion Catheter (n=6)
Saline infusion rates of 5 mL/min given through the end hole did not elicit any changes in coronary flow velocity compared with baseline (P=0.098; Figure 3B). At higher infusion rates, flow velocities tended to increase above the baseline, but the average values remained far below those reached after intracoronary adenosine and tended to show considerable variations.

Hyperemic Effect of Saline Infusion in the Contralateral Artery (n=5)
When the saline infusion was given in the contralateral artery through the side holes, no effect was noticed on flow velocity in the index artery compared with baseline values (P=1.0, P=0.452, P=1.0, and P=1.0 for saline infusion at rates of 5, 10, 15, and 20 mL/min compared with baseline, respectively; Figure 3C).

Additional Effect of Saline Infusion on Top of Intravenous Adenosine (n=5)
The average steady-state flow velocity during saline infusion given on top of intravenous adenosine was numerically higher than that reached after intravenous administration of adenosine alone, but this difference did not reach statistical significance (61±21 versus 56±21 cm/s; P=0.713; Figure 5).

Effect of Intracoronary Infusion of Saline on LV Function (n=9)
No significant changes in systolic or diastolic function, as evaluated by global longitudinal strain (−18.7±3.9% at baseline versus −17.7±4.7% during infusion; P=0.288) and propagation velocity (52.77±10.30 at baseline versus 52.71±9.84 cm/s during infusion; P=0.820), were observed (Figure II in the Data Supplement).

Discussion

Summary of Results
The present data confirm and further quantify an incidental observation, namely that an intracoronary saline infusion at rates of 15 to 20 mL/min through the lateral holes of a dedicated catheter induces maximal hyperemia, of at least the same magnitude than that obtained with adenosine. Coronary flow increases very soon after the start of the infusion—<10 seconds—and plateaus as long as the infusion is maintained. Intracoronary infusion of saline is not accompanied by any significant changes in systemic hemodynamics nor by signs of systolic or diastolic LV dysfunction. This hyperemic effect occurs only when saline is infused perpendicular to the long axis of the artery and does not occur, or greatly varies, when saline is infused through the distal hole or when it is infused through the side holes in the contralateral coronary artery.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient demographics (n=33)</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±9</td>
<td>Male, n (%)</td>
<td>21 (64)</td>
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<tr>
<td>Body weight, kg</td>
<td>82±15</td>
<td>Body mass index, kg/m²</td>
<td>27.7±4.3</td>
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<tr>
<td>Height, cm</td>
<td>172±8</td>
<td>Hypertension, n (%)</td>
<td>19 (58)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>27.7±4.3</td>
<td>Dyslipidemia, n (%)</td>
<td>24 (73)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (27)</td>
<td>Smoking, n (%)</td>
<td>6 (18)</td>
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<td>Previous percutaneous coronary intervention, n (%)</td>
<td>10 (30)</td>
<td>Previous myocardial infarction, n (%)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>107 (101–145)</td>
<td>Diastolic blood pressure, mmHg</td>
<td>65 (56–80)</td>
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<tr>
<td>Heart rate, bpm</td>
<td>67 (54–76)</td>
<td>Medication (n=33)</td>
<td></td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>23 (68)</td>
<td>Dual antiplatelet therapy, n (%)</td>
<td>13 (38)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>26 (77)</td>
<td>β-blocker, n (%)</td>
<td>14 (41)</td>
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<tr>
<td>Calcium channel blocker, n (%)</td>
<td>7 (21)</td>
<td>Angiotensin-converting enzyme inhibitor, n (%)</td>
<td>12 (35)</td>
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<tr>
<td>Angiotensin II receptor blocker, n (%)</td>
<td>3 (9)</td>
<td>Nitroglycerin, n (%)</td>
<td>2 (6)</td>
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<tr>
<td>Oral antidiabetic drugs, n (%)</td>
<td>6 (18)</td>
<td>Insulin, n (%)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Medication (n=33)
Aspirin, n (%) 23 (68)
Dual antiplatelet therapy, n (%) 13 (38)
Statin, n (%) 26 (77)
β-blocker, n (%) 14 (41)
Calcium channel blocker, n (%) 7 (21)
Angiotensin-converting enzyme inhibitor, n (%) 12 (35)
Angiotensin II receptor blocker, n (%) 3 (9)
Nitroglycerin, n (%) 2 (6)
Oral antidiabetic drugs, n (%) 6 (18)
Insulin, n (%) 3 (9)

Values are expressed as mean±SD in cm/s.

Table 2. Average Peak Velocities During the 4 Protocols of Coronary Flow Velocity Measurements

<table>
<thead>
<tr>
<th>Saline infusion side holes (n=24)</th>
<th>Baseline</th>
<th>Saline 5 mL/min</th>
<th>Saline 10 mL/min</th>
<th>Saline 15 mL/min</th>
<th>Saline 20 mL/min</th>
<th>Adenosine IC</th>
<th>Adenosine IV</th>
</tr>
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<tbody>
<tr>
<td>19±8</td>
<td>21±9</td>
<td>32±17</td>
<td>50±16</td>
<td>50±15</td>
<td>46±15</td>
<td>...</td>
<td></td>
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<tr>
<td>Saline infusion end hole (n=6)</td>
<td>17±9</td>
<td>21±8</td>
<td>23±13</td>
<td>23±14</td>
<td>26±14</td>
<td>54±25</td>
<td>...</td>
</tr>
<tr>
<td>Saline infusion in contralateral vessel (n=6)</td>
<td>21±13</td>
<td>23±13</td>
<td>23±13</td>
<td>22±13</td>
<td>56±23</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Saline infusion on top of adenosine IV (n=6)</td>
<td>24±7</td>
<td>24±8</td>
<td>47±20</td>
<td>55±16</td>
<td>57±5</td>
<td>50±15</td>
<td>56±21</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD in cm/s. IC indicates intracoronary; and IV, intravenous.
Potential Mechanisms of Saline-Induced Hyperemia

The mechanisms by which the administration of saline through the side holes of the catheter in proximal epicardial segments induces vasodilation of downstream resistance arteries remain speculative and are probably multifactorial.

First, the stimulation of the proximal part of the coronary artery by the 4 small jets of saline at ≈34°C hitting the vascular wall appears central to the hyperemic effect. Indeed, this phenomenon was weak and inconsistent when saline was given through the distal opening of an infusion catheter advanced in a contralateral artery. P values refer to pairwise comparisons (after adjustment for multiple comparisons) of absolute flow velocity values. * and ** denote statistically significant differences compared with baseline and adenosine IC values, respectively.

Figure 3. Individual values (left) and average values (right) of coronary flow velocity at baseline, after intracoronary (IC) bolus injection of adenosine, during infusion of saline at room temperature at flow rates of 5, 10, 15, and 20 mL/min. The values are expressed as percentages of the baseline value. A, Saline is infused through the side holes of the catheter advanced over the Doppler wire. B, Saline is infused through the distal hole of the catheter advanced over the Doppler wire. C, Saline is infused through the side holes of an infusion catheter advanced in a contralateral artery.

A

B

C

P

P

P

P

P

P

P

P

P

P

P

P
resulting from shear forces or pulsatile strain caused by blood flow,4,5 and NO-dependent mechanisms contribute in a positive feedforward control to hyperemia during exercise in animals.6,7 Endothelial cells can also release other vasoactive compounds, such as prostanoids, endothelin, and endothelium-derived hyperpolarizing factor.8–10 Yet, their exact role on human microvasculature remains largely unknown, as is their stimulation by mechanical forces or changes in temperature. In this study, we did not test the infusion of saline at 37°C which might have distinguished between these 2 possible stimuli.

Second, the dilution of arterial blood by infused saline decreases the local arterial oxygen content. When they are in a low oxygen tension environment, red blood cells release adenosine triphosphate that is broken down in adenosine diphosphate and adenosine monophosphate. Feigl and coworkers11,12 showed that these adenine nucleotides act on purinergic receptors on the capillary endothelial cells to initiate a retrogradely conducted response via gap junctions connecting endothelial cells. The signal dilates the upstream arterioles, thus increasing flow in a negative feedback control. Some findings of this study plea against this hypothesis. Indeed, the infusion of saline through the end hole of the catheter supposedly induced a similar decrease in arterial oxygen tension, although it was not accompanied by an increase in flow. Moreover, one would expect arterial flow to increase to a level equaling basal coronary blood flow plus saline infusion rate, to restore oxygen delivery to the myocardium back to baseline levels, as was observed with the end-hole infusions. Hence, the maximal coronary vasodilation elicited by side-hole saline cannot be solely explained by the infusion of saline itself nor by the adenosine triphosphate hypothesis.

Third, myocardial ischemia is a potent trigger of resistive vessels vasodilation, partially through the adenine nucleotides mechanism. However, the absence of diastolic and systolic myocardial dysfunction during a 2-minute intracoronary infusion pleas against the hypothesis of ischemia-induced vasodilation.

Fourth, the fact that adding intravenous adenosine infusion to saline infusion through the RayFlow catheter does not increase coronary flow suggests that the pathway to induce coronary hyperemia is similar, or that saline infusion overrides many different pathways through which coronary vasodilation occurs.

Finally, hyperemia seems to be strictly localized to the coronary artery in which saline is infused, as we did not observe any crosstalk between different myocardial beds.

Limitations
Many limitations should be taken into account. First, the small number of patients in whom the various protocols were applied calls for caution in the interpretation of the
results. Underpowered comparisons may have resulted in failure to reach statistical significance, and the extrapolation of results to the 3 coronary arteries should be done with prudence. A vast majority of the arteries were LAD, whereas the left circumflex coronary artery was studied in only 3 instances. More specifically, more data are needed to define the occurrence of atrioventricular blocks, particularly when performing measurements in the right coronary arteries. Second, because the study was conducted in humans, a detailed mechanistic exploration of the hyperemic effect of saline was not possible. For instance, we did not explore the effect of L-nitro-arginine methyl ester or methylene blue on saline-induced hyperemia. Third, coronary pressure and flow velocities were not measured simultaneously. Yet, the main goal of the study was not to propose the replacement of adenosine by saline infusion to perform fractional flow reserve and CFR measurements but rather to detail the dose–response of infusion of saline on coronary flow, thus enabling a marked simplification of continuous coronary thermomodulation methods. Fourth, only flow velocity was measured. Small changes in vessel diameter during saline infusion cannot be formally excluded. Changes in vessel diameter would also induce changes in absolute flow. Yet, in a small series of patients, we did not observe any change in de diameters of the epicardial arteries (Figure III in the Data Supplement). Finally, we did not find a saline infusion rate low enough to avoid hyperemia and high enough to be detectable in the distal part of the artery. Stated another way, continuous thermomodulation cannot measure resting flow nor CFR.

Practical Implications

To calculate absolute maximal myocardial blood flow by thermomodulation, at least 2 conditions are required: (1) to work under conditions of maximal hyperemia and (2) to ensure optimal mixing of the indicator at the very place where it is given and where the actual measurement of flow takes place. The present findings indicate that saline infusion through the RayFlow catheter fulfills both conditions. Accordingly, measuring absolute maximal coronary flow and minimal microvascular resistance only requests a monorail dedicated infusion catheter and a pressure/temperature-tipped guidewire.

The present data greatly contribute to the simplification of the thermomodulation-derived method of coronary flow measurement: not only a monorail catheter has been developed and validated in vitro, but the present findings allow avoiding any specific pharmacological microvascular vasodilator when assessing absolute maximal coronary flow and absolute minimal microvascular resistance.

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Disclosures

Drs De Bruyne and Barbato report that their institution gets consultancy fees on their behalf from St Jude Medical, Boston Scientific, and Opsens. Dr Pijls is a consultant for St Jude Medical and Opsens. The other authors report no conflicts.

References

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