Fractional flow reserve (FFR) is an important physiological index used to assess functional status of coronary artery stenosis severity, particularly in intermediate severity lesions where angiography alone is of limited value. FFR is calculated as the ratio of the mean distal intracoronary artery pressure to aortic pressure at maximal hyperemia and has a normal value of 1.0. A clinical cutoff FFR value of 0.80 has been established as the threshold below which the stenosis is considered clinically significant and necessitates surgical intervention. FFR-guided identification of inducible myocardial ischemia has been reported to have relatively good sensitivity and specificity. Its diagnostic use has been shown to improve patient outcomes when compared with angiography alone in clinical decision making concerning percutaneous coronary intervention (PCI).

Considering that coronary blood flow occurs predominantly during diastole, some researchers have also attempted to measure pressure-based physiological parameters during the diastolic phase of the cardiac cycle. Abe et al have reported sensitivity of 95.8% and specificity of 100% for FFR-based identification of inducible ischemia calculated at the diastolic phase of the cardiac cycle during maximal hyperemia. However, a major limitation of the study was the reliance of the measurement on left-ventricular pressure and manual extraction of the diastolic pressure interval, which added to the complexity of the clinical protocol.

Previous physiological studies during the diastolic phase of the cardiac cycle have also shown promise for instantaneous pressure measurements at end-diastole where both zero-flow pressure (finite back pressure above right atrial or sinus pressure) and capacitance effects on coronary pressure-flow relation have been observed to be minimal. Our present hypothesis was that decreased residual effects of contraction on intracoronary pressure measurement, as well as lower and more constant zero-flow pressure at end-diastole, would result in reduced variability in combined subject data during comparison of pressure-based FFR with actual reductions in coronary blood flow. As such, the goal of this study was to

End-Diastolic Fractional Flow Reserve
Comparison With Conventional Full-Cardiac Cycle Fractional Flow Reserve

David A. Chalyan, MS; Zhang Zhang, PhD; Shigeho Takarada, MD, PhD; Sabee Molloi, PhD

Background—Diastolic fractional flow reserve (dFFR) has been shown to be highly sensitive for detection of inducible myocardial ischemia. However, its reliance on measurement of left-ventricular pressure for zero-flow pressure correction, as well as manual extraction of the diastolic interval, has been its major limitation. Given previous reports of minimal zero-flow pressure at end-diastole, we compared instantaneous ECG-gated end-diastolic FFR with conventional full-cardiac cycle FFR and other diastolic indices in the porcine model.

Methods and Results—Measurements of FFR in the left anterior descending and left circumflex arteries were performed in an open-chest swine model with an external occluder device on the coronary artery used to produce varying degrees of epicardial stenosis. An ultrasound flow-probe that was placed proximal to the occluder measured absolute blood flow in ml/min, and it was used as a gold standard for FFR measurement. A total of 17 measurements at maximal hyperemia were acquired in 5 animals. Correlation coefficient between conventional mean hyperemic FFR with pressure-wire and directly measured FFR with flow-probe was 0.876 (standard error estimate=0.069; P<0.0001). The hyperemic end-diastolic FFR with pressure-wire correlated better with FFR measured directly with flow-probe (r=0.941, standard error estimate=0.050; P<0.0001).

Conclusions—Instantaneous hyperemic ECG-gated FFR acquired at end-diastole, as compared with conventional full-cardiac cycle FFR, has an improved correlation with FFR measured directly with ultrasound flow-probe. (Circ Cardiovasc Interv. 2014;7:28-34.)

Key Words: constriction, pathologic coronary artery disease coronary artery disease fractional flow reserve, myocardial hemodynamics ischemia
WHAT IS KNOWN

- Fractional flow reserve (FFR) acquired during the hyperemic diastolic phase of the cardiac cycle has been shown to have improved sensitivity for presence of inducible myocardial ischemia.
- Instantaneous coronary blood flow and intracoronary pressure measurements acquired at the hyperemic end-diastolic phase of the cardiac cycle have been shown to have excellent correlation, minimal zero-flow pressure, and minimal resistance.

WHAT THE STUDY ADDS

- Three different hyperemic measurements of FFR during the diastolic phase of the cardiac cycle and conventional average full-cardiac cycle FFR were compared with ultrasound flow-probe-based quantification of FFR.
- Instantaneous hyperemic ECG-gated FFR acquired at end-diastole as compared with conventional full-cardiac cycle FFR has an improved correlation with FFR measured directly with ultrasound flow-probe.

compare the relation between FFR acquired at end-diastole with conventional FFR performed at full-cardiac cycle using flow-probe measured FFR as a gold standard.

Methods

Protocol

In an open-chest swine model, FFR measurements were made for various severities of epicardial stenosis in the left anterior descending (LAD) and left circumflex (LCX) arteries at peak hyperemia. The epicardial stenosis was produced by an external vascular occluder. Coronary angiograms were acquired for each data set. Absolute blood flow from the ultrasound flow-probe and coronary pressure from pressure-wire were continuously measured. The study protocol was approved by the Irvine Institutional Animal Care and Use Committee of the University of California.

Animal Preparation

Five fasted Yorkshire swine were sedated and premedicated with telazol-ketamine-xylazine (TKX; 4.4 mg T/kg, 2.2 mg K/kg, and 2.2 mg X/kg) and atropine (0.05 mg/kg). Anesthesia was maintained with 1% to 2% isoflurane (Highland Medical Equipment Vaporizer; Temecula, CA), and supplemental oxygen was given via endotracheal intubation. Arterial partial pressure of CO2 was maintained within normal limits (40–45 mm Hg). Heart rate and percentage of oxygen saturation were continuously monitored (Nellcor N-200 Pulse Oximeter; Hayward, CA). Carotid artery and jugular vein were surgically prepared for shunt placement. Intravenous drip of adenosine (400 μg/kg per min) by a syringe pump was used to produce maximum hyperemic induction. Infusion rates >400 μg/kg per min did not elicit further increase in coronary blood flow, and this was verified for each animal before data acquisition. ECG, arterial blood pressure, x-ray pulse signal, and other physiological parameters were continuously measured (Biopac Systems, Inc, Santa Barbara, CA).

Lidocaine (50 μg/kg per min for a total of 4–5 mL) was administered intravenously to prevent arrhythmia before opening the chest. A lateral thoracotomy was performed by using standard surgical technique. The 4th and 5th ribs were separated, and the heart was fully exposed. The pericardium was opened, and the proximal segment of the LAD or the LCX artery was dissected free. Transit-time ultrasound flow-probes (Transonic Systems, Inc) were placed on the proximal segments of the LAD or LCX artery for blood flow measurement. An extravascular occluder (In Vivo Metric, Healdsburg, CA) was placed around the coronary artery just distal to the flow-probe. It was used to produce variable degrees of epicardial stenosis by injecting saline inside it.

Before catheterization, heparin was administered (10000 U bolus followed by additional 4000–5000 U per hour). Activating clotting time was measured every 30 minutes (Hemochron Model 801, Whole Blood Coagulation System) to monitor coagulation. The left main ostium was cannulated with a 6F hockey-stick catheter through the left carotid artery under fluoroscopic guidance. Intracoronary measurements of pressure were performed using a pressure wire (Radi Medical System, 0.014”). The coronary pressure wire was advanced into the distal segment of the LAD or LCX artery to measure the distal pressure. Measurements of aortic pressure (Pa) and distal coronary artery pressure (Pd) were recorded continuously.

Coronary Pressure and Flow Measurements

Measurements of absolute coronary blood flow and intracoronary pressure in the LAD and in the LCX arteries were recorded at selected phases of the cardiac cycle. Pressure-based FFR was measured as Pd/Pa, where Pd represents distal coronary artery pressure and Pa represents aortic pressure. For conventional mean FFR, this was recorded as an interval value averaged over 3 cardiac cycles. For end-diastolic FFR, the same 3 cardiac cycles were analyzed, respectively, except that instantaneous values at 60 ms before R-wave of the ECG were averaged. This was a slightly modified technique from a large animal study by Pantely et al10 who also sampled the end-diastolic phase 60 ms before onset of the QRS complex of the ECG. We chose the R-wave to simplify and automate ECG-gating.

Diastolic FFR (dFFR), as presented by Abe et al,7 was analyzed at the same corresponding time points with selection of the intracoronary diastolic pressure phase starting from the dicrotic notch of the aortic pressure wave-form and ending with the R-wave of the ECG. Because left-ventricular pressure is not routinely measured during FFR measurements (used by Abe et al7 to correct for zero-flow pressure), we used this method of sampling the full-diastolic pressure phase.

Mid-diastolic FFR was sampled as an instantaneous measurement of Pd/Pa at 25% into the diastolic phase. The diastolic phase was defined as starting from the dicrotic notch and ending with the R-wave of the ECG.

Direct measurement of FFR (Qs/Qn) using ultrasound flow-probe data was averaged over the same 3 full-cardiac cycles as conventional mean pressure–based FFR. The flow reserve ratio was calculated as Qs/Qn where Qs represents hyperemic coronary blood flow through stenosed artery, and Qn represents normal hyperemic blood flow through the same artery before stenosis induction with an external occluder. As such, Qs/Qn calculates an empirical flow ratio that represents a direct reduction in coronary blood flow attributable to epicardial stenosis.

Statistical Analysis

Linear regression analysis was performed among the intravascular pressure-wire measurements and the external flow-probe data to determine the coefficients in the regression equation. The correlation coefficient (r) and standard error of estimate (SEE) were determined from linear regression analysis. SEE defines the standard deviation of the measured values from the regression line. The degree of agreement among different methods of measurement was also assessed in the Bland–Altman analysis. P<0.05 was considered to be statistically significant.

Results

A total of 17 hyperemic FFR measurements were made in 5 different pigs for each of the 4 selected cardiac cycle phases. Of the 17 measurements, 13 were in the LAD and
4 measurements were in the LCX arteries (Table). Mean hyperemic FFR in the presence of an epicardial stenosis was 0.81±0.13 for conventional full-cardiac cycle FFR and 0.72±0.11 for instantaneous end-diastolic FFR, whereas mean Qs/Qn or direct flow reserve ratio was 0.73±0.15. Mean coronary wedge pressure, as measured in 1 animal at 10 different time points during complete occlusion of the LAD artery was 10.12±4.28 mm Hg for full-cardiac cycle and 4.08±2.18 mm Hg at end-diastole. Other physiological parameters at various phases of the cardiac cycle and summary of statistics for linear regression analysis with flow-probe–measured Qs/Qn are listed in the Table.

<table>
<thead>
<tr>
<th>Cardiac Cycle Phase</th>
<th>Condition</th>
<th>n (LAD)</th>
<th>n (LCX)</th>
<th>LAD Resistance</th>
<th>LCX Resistance</th>
<th>LAD Wedge Pressure*</th>
<th>r</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-Diastole</td>
<td>Hyperemia</td>
<td>13</td>
<td>4</td>
<td>0.241 (0.059)</td>
<td>0.503 (0.052)</td>
<td>4.08 (2.18)</td>
<td>0.941</td>
<td>0.050</td>
</tr>
<tr>
<td>Full-Diastole</td>
<td>Hyperemia</td>
<td>13</td>
<td>4</td>
<td>0.253 (0.074)</td>
<td>0.466 (0.067)</td>
<td>7.88 (2.78)</td>
<td>0.943</td>
<td>0.053</td>
</tr>
<tr>
<td>Mid-Diastole</td>
<td>Hyperemia</td>
<td>13</td>
<td>4</td>
<td>0.243 (0.098)</td>
<td>0.440 (0.073)</td>
<td>8.04 (3.03)</td>
<td>0.916</td>
<td>0.069</td>
</tr>
<tr>
<td>Full-Cardiac Cycle</td>
<td>Hyperemia</td>
<td>13</td>
<td>4</td>
<td>0.424 (0.148)</td>
<td>0.642 (0.120)</td>
<td>10.12 (4.28)</td>
<td>0.876</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Values are mean of 3 cardiac cycles (±SD). Intracoronary wedge pressure measured in mm Hg and resistance in mm Hg × min/mL. Comparison of pressure-based FFR with flow-probe–measured Qs/Qn is represented by correlation coefficient (r) and standard error estimate (SEE) around the line of regression for corresponding hyperemic cardiac cycle phase. LAD indicates left anterior descending artery; and LCX, left circumflex artery.

*Wedge pressure measurements were acquired in 1 animal at 10 different time points during hyperemia at corresponding cardiac cycle phase.

Figure 1. Linear regression plot of pressure-based conventional full-cardiac cycle fractional flow reserve (FFR) vs Qs/Qn measured directly with flow-probe (A) during hyperemia (r=0.876, standard error estimate [SEE]=0.069, y=0.705x+0.297; P<0.0001). The corresponding Bland–Altman graph is also shown for comparison (B). Qs represents hyperemic coronary blood flow through stenosed artery, and Qn represents normal hyperemic blood flow through the same artery before stenosis induction with an external occluder.

Figure 2. Linear regression plot of pressure-based ECG-gated end-diastolic fractional flow reserve (FFR) vs Qs/Qn measured directly with flow-probe (A) during hyperemia (r=0.941, standard error estimate [SEE]=0.050, y=0.773x+0.168; P<0.0001). The corresponding Bland–Altman graph is also shown for comparison (B). Qs represents hyperemic coronary blood flow through the same artery before stenosis induction with an external occluder.
Full-cardiac cycle FFR correlated well with directly measured Qs/Qn ($r=0.876$, SEE=0.069, $y=0.705x+0.297$; $P<0.0001$; Figure 1A). End-diastolic FFR had an improved coefficient of correlation with Qs/Qn ($r=0.941$, SEE=0.050, $y=0.773x+0.168$; $P<0.0001$; Figure 2A). Brand–Altman graphs with Qs/Qn for both conventional and end-diastolic FFR were also plotted, as shown in Figures 1B and 2B. These graphs showed a closer agreement between Qs/Qn and FFR at end-diastole. Other hyperemic diastolic parameters including mid-diastolic FFR and full-diastolic phase FFR (dFFR) are shown in Figures 3 and 4, respectively.

Average hyperemic intracoronary resistance in the LAD artery was 0.241 (0.059) mm Hg × minutes/mL at instantaneous end-diastole and 0.424 (0.150) mm Hg × minutes/mL at full-cardiac cycle (Figure 5A). In the LCX artery (Figure 5B), the average measured resistance was 0.503 (0.052) mm Hg × minutes/mL at end-diastole and 0.642 (0.120) mm Hg × minutes/mL at full-cardiac cycle. For comparison, resistance analysis for the remaining diastolic phase parameters is also shown in the Table and Figure 5.

Discussion

Clinical Motivation

The importance of FFR-guided PCI was emphasized in a hallmark study by Tonino et al. who compared the incidence of adverse events in this group with angiography-guided PCI. This prospective study showed a 30% reduction in all types of adverse events with the use of FFR as a diagnostic tool before intervention decisions. One notable detail in this study is the use of 0.80 as the clinical cutoff for PCI treatment despite well-demonstrated correspondence of the 0.75 threshold with presence of inducible myocardial ischemia in previous studies. Given sensitivity of 88% for inducible ischemia in FFR <0.75, the decision to use 0.80 as the clinical cutoff in the study by Tonino et al. was largely motivated by the intention to increase the sensitivity and limit number of untreated lesions despite increased marginal risk of PCI-related complications. In light of these findings and the study by Abe et al., we have examined alternate ways of further improving the sensitivity in an index known for its high specificity and clinical use.
Physiological Basis for End-Diastole

Given previous reports of high sensitivity of hyperemic diastolic FFR for inducible myocardial ischemia in human subjects,7 our goal was to assess the effectiveness of ECG-gated end-diastolic FFR near the clinical cutoff range. The decision to examine end-diastolic FFR was motivated by a large animal study by Pantely et al10,12 who was first to identify the instantaneous hyperemic end-diastolic phase as a dynamic equilibrium state with minimal fluctuations in zero-flow pressure and microvascular resistance along with decreased residual effects of intramyocardial capacitance and ventricular contraction. Subsequent physiological studies also found a good correlation between end-diastolic left-ventricular pressure and zero-flow intracoronary pressure in normal as well as pathological states where increased heart chamber pressure can cause a right shift in the intracoronary pressure-flow curve via increases in physiological back pressure.11 This observation allows for estimation of and subsequent correction for the rightward shift in the pressure-flow relation attributable to increased physiological back pressure (above right atrial pressure) without the need to occlude the coronary artery completely to obtain coronary wedge pressure directly. This may also be relevant in distinguishing the contribution of collateral circulation from the effects of myocardial contraction and increases in left-ventricular chamber pressure on measured coronary wedge pressure.

Comparison With Other Studies

Our findings, as summarized in the Table, corroborate the findings of Pantely et al10,12 relating to the hemodynamic stability of instantaneous hyperemic end-diastolic measurements. This is evident in minimal fluctuations in coronary resistance and wedge pressure despite substantially reduced impedance to coronary blood flow, as opposed to full-cardiac cycle measurements that include the effects of systole. Although fluctuations in LCX resistance were also reduced at end-diastole, as compared with full-cardiac cycle, the absolute values of LCX resistance were not statistically different between the 2 groups (Figure 5B). Because Pantely et al10 did not measure LCX resistance, we are unable to reference our findings. However, it seems plausible that coronary blood flow through the LCX artery is less restricted by the compressing effects of ventricular contraction as compared with the LAD arterial territory.

Other diastolic hyperemic indices, including dFFR and mid-diastolic FFR, performed well compared with full-cardiac cycle, with reduction in both absolute values and fluctuations in resistance and coronary wedge pressure (Table). However, despite a noticeably higher correlation coefficient (r) with Qs/Qn, mid-diastolic FFR was unable to improve the SEE around the line of regression when compared with conventional full-cardiac cycle FFR. We think this may be a cumulative effect of small sample size of our animal study and increased effects of intramyocardial capacitance at mid-diastole.

Diastolic hyperemic FFR (dFFR), as pioneered by Abe et al,7 showed excellent correlation with Qs/Qn (r=0.943, SEE=0.053, y=0.846x+0.104; P<0.0001) and was able to improve on the agreement between flow-probe data and pressure-based full-cardiac cycle FFR (∼0.876, SEE=0.069, y=0.705x+0.297; P<0.0001). Although our study did not assess for presence of inducible myocardial ischemia directly, correlation with external flow-probe was consistent with the improvements in sensitivity found by Abe et al7 with exercise myocardial thallium scintigraphy in patients with intermediate severity lesions. This study showed sensitivity of 95.8% in 46 patients with full-diastolic phase dFFR measurement compared with that of 83.3% for conventional full-cardiac cycle FFR.7

An interesting physiological finding in our study was the presence of an apparent pressure intercept in the linear regression equation, particularly evident during the full-cardiac cycle. This was despite a lack of native collateral circulation in the swine animal model and, of course, lack of changes in collateral circulation between baseline and hyperemic measurements. Additionally, investigation of wedge pressure in the LAD artery found minimal hyperemic physiological back pressure as shown in the Table and was not correlated with the value of the apparent regression line intercepts in hyperemic data. Although Pijs et al also found a finite coronary wedge pressure above right atrial pressure in dogs, he attributed this to well-known collateral circulation in the dog animal model and corrected for this during original validation of FFR. More
recently, Spaan et al.\textsuperscript{13} gave a clear and comprehensive explanation as to the origin of the apparent pressure intercept. This important study\textsuperscript{13} attributed the pressure intercept to compliance in intramyocardial vessel diameter and nonlinearity of the pressure-flow relation attributable to compressive forces of heart contraction (particularly hydraulic conductivity of the inner layers of the myocardial wall).\textsuperscript{14} Pantely et al.\textsuperscript{10,12} also described nonlinearity in the pressure-flow relation and concavity toward the flow axis in the swine animal model with lack of native collateral anastomoses. Because our data were acquired in the linear physiological range, the regression intercept may be an apparent intercept from extrapolation of the linear range to the pressure axis. Hence the distinction between regression line intercept and actually measured wedge pressure is attributed to the range of the data to which the regression line is fitted. The physiological and diagnostic pressure range corresponds with the linear upslope of the inherently nonlinear curved pressure-flow line and produces a high apparent pressure axis intercept, as explained by Spaan et al.\textsuperscript{13,14}

Our findings agree with a report by Spaan et al.\textsuperscript{13} where he explains that full-cardiac cycle zero-flow pressure is $\pm 5$ to $15 \text{ mmHg}$ during maximal hyperemia. The study by De Bruyne et al.\textsuperscript{3} also reported a regression line pressure intercept in investigation of hyperemic FFR in human subjects. The correlation coefficient of 0.87 in the positron emission tomography study by De Bruyne et al.\textsuperscript{15} was also similar to our correlation between conventional full-cardiac cycle FFR and directly measured Qs/Qn ($r=0.876$) shown in Figure 1A. However, the results of De Bruyne et al.\textsuperscript{15} and ours are somewhat different from the reported agreement between FFR and Qs/Qn in the original validation of FFR by Pijs et al.\textsuperscript{3} We think this may be partly explained by the fact that Pijs et al.\textsuperscript{3} presented graphs with individual animal data that are wedge pressure corrected, whereas our study and the study by De Bruyne et al.\textsuperscript{3} present combined subject data that are uncorrected for wedge pressure.

The degree of improvement in sensitivity from conventional FFR observed by Abe et al.\textsuperscript{1} is also observed in our animal study with improvements in the correlation between both full-diastolic FFR and end-diastolic FFR with directly measured Qs/Qn compared with conventional full-cardiac cycle FFR (Table). Although it is not clear from our study whether the method of acquisition reported by Abe et al.\textsuperscript{1} or Pantely et al.\textsuperscript{10} is superior, given the limited sample size, it is clear that FFR is an important index that has the capacity to be further optimized to increase correlation with both coronary blood flow and identification of inducible myocardial ischemia. In the case of instantaneous end-diastolic FFR, the automated acquisition could be robust and completely pressure independent by way of ECG-gating with the R-wave. Furthermore, given a known correlation of end-diastolic left-ventricular pressure with end-diastolic coronary wedge pressure,\textsuperscript{11} comparison of the 2 measurements could distinguish between well-developed collateral circulation and compressive forces attributable to increased heart chamber pressure.

**Resting Diastolic Indices**

One interesting use of the diastolic phase for measurement of intracoronary parameters is the concept of resting wave-free period during which indices like baseline stenosis resistance\textsuperscript{16} and instantaneous wave-free ratio\textsuperscript{2} can be calculated. Although still an evolving field, the prospect of finding a resting diastolic time interval where microvascular resistance approaches hyperemic full-cardiac cycle resistance has been a major driving force behind these new indices. A recent review of current evidence surrounding instantaneous wave-free ratio reports that the index has $\approx 80\%$ diagnostic accuracy for detecting lesions with FFR$<0.80$, with a potential drop in diagnostic accuracy for intermediate and normal severity lesions.\textsuperscript{17} A hybrid instantaneous wave-free ratio/FFR test may be a way of breaches the gap and may achieve a classification match of 95% with FFR.\textsuperscript{17}

The above discussions indicate that further research aimed at increasing the sensitivity rate of FFR by further optimizing this important functional index is essential. Acquisition of intracoronary and aortic pressures at a state of myocardial relaxation, in conjunction with minimal vasomotor tone, may be a simple yet effective way of doing so.

**Study Limitations**

The study was performed in the swine animal model, which limits direct observation of exercise-induced myocardial ischemia measured in the human studies. Transonic flow-probe, instrumented on the LAD or LCX artery, whereas capable of measuring empirical reductions in coronary blood flow, does not provide details concerning oxygen use during periods of exertion. The detection of inducible ischemia in the heart is not only an important diagnostic and prognostic metric but also used to generate the ischemic threshold for FFR.\textsuperscript{4} Therefore, additional studies are necessary to define thresholds for end-diastolic FFR and other diastolic indices. Another important limitation for our study was the manual extraction of the corresponding cardiac cycle phase for analysis.

The fact that our study was performed in a healthy animal model with absence of microvascular disease, compared with studies performed on human subjects, may also be a limiting factor in translating our results into clinical setting. Additionally, the reported sensitivity and specificity rates may not accurately reflect FFR performance in a clinical setting.

Another limitation of the study was the limited sample size, which made it difficult to distinguish between small differences in the diastolic phase indices and anatomic sites on the heart including the LCX coronary artery. Also, the current range of stenosis severities was another limiting factor and may need to be modified in future studies to better target the clinically relevant zone near an FFR of 0.75. Improvements in the SEE in this range would give a more accurate reflection of decreases in FFR threshold ambiguity.

**Conclusions**

Compared with conventional full-cardiac cycle FFR, instantaneous ECG-gated FFR acquired at end-diastole has an improved correlation with Qs/Qn measured directly with flow-probe.

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Disclosures
None.

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