Influence of heart rate on fractional flow reserve, pressure drop coefficient, and lesion flow coefficient for epicardial coronary stenosis in a porcine model


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Submitted 27 April 2010; accepted in final form 5 October 2010

Kolli KK, Banerjee RK, Peelukhana SV, Helmy TA, Leesar MA, Arif I, Schneeberger EW, Hand D, Succop P, Gottliebson WM, Effat MA. Influence of heart rate on fractional flow reserve, pressure drop coefficient, and lesion flow coefficient for epicardial coronary stenosis in a porcine model. Am J Physiol Heart Circ Physiol 300: H382–H387, 2011. —A limitation in the use of invasive coronary diagnostic indexes is that fluctuations in hemodynamic factors such as heart rate (HR), blood pressure, and contractility may alter resting or hyperemic flow measurements and may introduce uncertainties in the interpretation of these indexes. In this study, we focused on the effect of fluctuations in HR and area stenosis (AS) on diagnostic indexes. We hypothesized that the pressure drop coefficient (CDP, ratio of transstenotic pressure drop and distal dynamic pressure), lesion flow coefficient (LFC, square root of ratio of limiting value CDP and CDP at site of stenosis) derived from fluid dynamics principles, and fractional flow reserve (FFR, ratio of average distal and proximal pressures) are independent of HR and can significantly differentiate between the severity of stenosis. Cardiac catheterization was performed on 11 Yorkshire pigs. Simultaneous measurements of distal coronary arterial pressure and flow were performed using a dual sensor-tipped guidewire for HR < 120 and HR > 120 beats/min, in the presence of epicardial coronary lesions of ≤50% AS and >50% AS. The mean values of FFR, CDP, and LFC were significantly different (P < 0.05) for lesions of ≤50% AS and >50% AS (0.88 ± 0.04, 0.76 ± 0.04, 0.62 ± 0.08, 151 ± 35, and 0.10 ± 0.02 and 0.16 ± 0.01, respectively). The mean values of FFR and CDP were not significantly different (P > 0.05) for variable HR conditions of HR < 120 and HR > 120 beats/min (FFR, 0.81 ± 0.04 and 0.82 ± 0.04; and CDP, 95 ± 33 and 142 ± 36). The mean values of LFC do somewhat vary with HR (0.14 ± 0.01 and 0.12 ± 0.02). In conclusion, fluctuations in HR have no significant influence on the measured values of CDP, and FFR but have a marginal influence on the measured values of LFC. However, all three parameters can significantly differentiate between stenosis severities. These results suggest that the diagnostic parameters can be potentially used in a better assessment of coronary stenosis severity under a clinical setting.

coronary disease; hemodynamics; catheterization

CORONARY ANGIOGRAPHY is the current gold standard for detecting epicardial coronary artery disease. Augmenting this anatomical data with coronary functional parameters (pressure, flow, and/or velocity) provides unique information that facilitates fully informed therapeutic decision making in the catheterization laboratory. Several invasive functional approaches have been used for the past several years within the cardiovascular laboratory that allow for a determination of the functional significance of epicardial coronary stenoses. These methods include measurement of coronary flow reserve [CFR, the ratio of hyperemic flow to basal flow (10)], fractional flow reserve [FFR, ratio of average distal pressure (pa) to average pressure proximal (pD) to a lesion (22, 23)], and hyperemic stenosis resistance index [hSRv, the ratio of hyperemic pressure drop and distal blood flow velocity (27)]. CFR, FFR, and hSRv are measured under maximum vasodilatation conditions (hyperemia) induced by pharmacological agents like adenosine or papaverine. With the introduction of technologically improved Doppler-tipped flow wires (8) and pressure wires (9), an advanced functional assessment of coronary disease has now become feasible.

Recently, our group introduced two novel functional indexes: 1) the pressure drop coefficient [CDP (4)], defined as the ratio of transstenotic pressure drop (Δp = pD – pa) to distal dynamic pressure (0.5 × blood density × APV2, where APV is average peak flow velocity), measured under hyperemia; and 2) the lesion flow coefficient [LFC (5)], defined as the square root of ratio of theoretical limiting value of CDP (i.e., CDP∞) and CDP at the throat (i.e., CDPm) at hyperemic flow (3). Both these parameters have been derived from fundamental fluid dynamic principles.

The CDP∞ readily obtained during routine cardiac catheterization procedures, has been recently validated for in vitro (4, 21) and in vivo (3, 5, 28) studies. LFC, a novel index that combines both functional and anatomical measurements, has also been validated in preclinical studies for determining the severity of epicardial stenosis under normal microcirculation (28). Recently, our group showed that 1) the LFC and CDP∞ were linearly correlated with FFR, CFR, hSRv, and percent area stenosis (AS, 1 – κ), where κ is the ratio of throat and native artery lumen area, for various epicardial lesions with normal microcirculation (4, 28) and 2) the LFC and CDP∞ can also delineate the significance of epicardial stenosis and status of microcirculation (3). However, these studies did not account for the possible influences of hemodynamic alterations such as heart rate (HR), blood pressure (BP), and contractility on the diagnostic indexes.

A limitation in the use of invasive coronary diagnostic indexes, however, is that fluctuations in hemodynamic factors such as HR (7), BP (20), and contractility (6, 12, 14, 16, 19, 25) may alter resting or hyperemic flow measurements and thus introduce uncertainties in the interpretation of these indexes (13, 16). Ideally, an evaluation of the coronary circulation should rely on methodologies independent of these hemodynamic changes. Hence, extending our in vivo studies, we...
sought here to further investigate CDPe and LFC in animal trials by evaluating the dependence of these parameters along with FFR on HR.

**Glossary**

**Nomenclature**

- A: Vessel lumen area
- APV: Average peak velocity measured distal to the stenosis by Doppler sensor of dual sensor-tipped guidewire
- d: Diameter
- pA: Mean aortic pressure
- pD: Mean pressure measured distal to the stenosis
- Δp: Transstenotic mean pressure drop
- k: Vessel lumen area ratio = A2/A1 (vessel diameters immediately proximal and distal to the stenosis are same)
- μ: Dynamic blood viscosity
- ρ: Blood density (assumed as 1.05 g/cm³)

**Subscripts**

- b: Angioplasty-balloon
- bs: Angioplasty-balloon shaft
- e: Native vessel lumen area
- g: Guidewire
- h: Peak hyperemic flow condition
- m: Minimal vessel area at the stenosis site

**METHODS**

**Animal Preparation**

This study protocol was approved by the Institutional Animal Care and Use Committee at the University of Cincinnati and Cincinnati Children’s Hospital Medical Center. The in vivo study was performed on 11 Yorkshire pigs (44 ± 5 kg), fasted for 24 h and premedicated with intramuscular ketamine (20 mg/kg) or Telazol (2–7 mg/kg), atropine (0.4 mg/kg), xylazine (2 mg/kg), and buprenorphine (0.005 mg/kg). General anesthesia was maintained with 2% of isoflurane and endotracheal oxygen supply as per the surgical procedural standards (1). HR, oxygen saturation, and end-tidal CO2 level were monitored on 11 Yorkshire pigs (44 ± 5 kg), fasted for 24 h and premedicated with intramuscular ketamine (20 mg/kg) or Telazol (2–7 mg/kg), atropine (0.4 mg/kg), xylazine (2 mg/kg), and buprenorphine (0.005 mg/kg). General anesthesia was maintained with 2% of isoflurane and endotracheal oxygen supply as per the surgical procedural standards (1). HR, oxygen saturation, and end-tidal CO2 level were monitored every 15 min, and ventilator changes were made as needed to maintain these values within the normal range.

**Catheterization and Angiography**

An arterial sheath was placed by surgical cut-down in the right carotid, femoral arteries, and right jugular vein. A 7-Fr (2.31 mm) guide catheter was advanced via the femoral artery under fluoroscopic guidance to the left main coronary ostium. An intravenous dose of heparin (300 U/kg) was injected immediately. Angiographic images with FFR on HR.

**Anatomical Measurements**

After we engaged the guide catheter at the coronary ostium, a bolus dose (0.1–1.0 μg·kg⁻¹·min⁻¹) of intracoronary nitroglycerine was injected to prevent coronary spasm. The guide catheter was replaced over a wire by an intravascular ultrasound (IVUS) catheter [2.9-Fr (0.957 mm), In-Vision Gold, Volcano Therapeutics]. The native coronary vessel lumen area was measured by motorized pullback (1 mm/s) of the IVUS catheter.

Based on the IVUS and angiographic images, a portion of the left anterior descending coronary artery was selected for creating epicardial flow obstruction, induced by inflating a coronary angioplasty balloon (Voyager, Guidant). The balloon was mounted on a dual sensor-tipped guidewire that was used for pressure and flow measurements. The configuration of sensor-tipped guidewire in relation to the balloon placement, used to create the percent AS, is shown in Fig. 1. The procedure of inflating a balloon to different pressures for creating intraluminal obstructions of varying severity was similar to our previous studies (3, 4, 28) and that reported by MacCarthy et al. (18).

Linear variation of diameter with a change in inflation pressure, as per the manufacturer’s data sheet (Voyager balloons, Guidant) for an individual balloon, was used to calculate the percent area intraluminal obstructions. Sample balloons were tested for variations of diameter with respect to the recommended inflation pressure within an in vitro flow loop system pressurized to physiological pressure. The influence of the physiological pressure on the balloon diameter was expected to be negligible since the inflation pressure is much higher (at least 3 times the physiological pressure). The inflation pressure for each balloon did not exceed the recommended pressure range and was similar to our previously tested linear variation of pressure versus diameter data (3, 4, 28).

**Functional Measurements**

In all of the 11 Yorkshire pigs, the phasic distal coronary pressure (pD) and APV were measured simultaneously by dual sensor-tipped guidewire (Combowire, Volcano Therapeutics) as shown in Fig. 1. The mean proximal aortic pressure (pA) was continuously recorded by the guide catheter. HR was continuously recorded using the Millar catheter connected to a four-channel transducer amplifier (Sonometric Systems). The hemodynamic measurements were performed at baseline flow and maximal hyperemic flow (induced by injecting 10 mg of intracoronary papaverine). Values of pA, pD, APV, and FFR were recorded in the Combo Map system (Volcano Therapeutics) for two different HR conditions, HR < 120 and HR > 120 beats/min, achieved using atrial pacing. The procedure was repeated for various degrees of epicardial stenosis, obtained by varying the balloon diameter.

After acclimatization, we had the pig rest for about 3 to 5 min until the parameter values of HR, pressure, and velocity returned to normal. We changed the HR only after the parameters returned to normal and then injected papaverine via the intracoronary route to induce hyperemia. Measurements were recorded only after maximal hyperemia was achieved. Typically, we waited 30 s after papaverine injection for three consecutive sets of similar readings for a specific stenotic condition. Once the balloon is deflated, we waited 3–5 min for the

![Fig. 1. Schematic representation of stenosis (balloon obstruction). See main text for definitions.](image-url)
flow, pressure, and HR values to return to normal before the next balloon inflation and data acquisition.

**Stratification of Hemodynamic Conditions**

Studies were performed at two different thresholds: HR and AS. Generally, <60% AS is classified as mild stenosis, whereas intermediate (ischemia threatening) stenosis is defined to be >60% AS (2). We used an angioplasty balloon catheter of relatively higher length (range, 10–18 mm) to create the internal blockage in place of a focal lesion observed in the clinical setting. In addition, it is expected that the 0.79-mm-diameter shaft of the balloon catheter will add extra resistance to the blood flow. Hence, to account for the combined resistances offered by higher balloon length and shaft diameter, we estimated 50% AS to be a better combined resistance (3) for anatomically mild and intermediate stenoses. The HR groups were classified into low HR (<120 beats/min) and high HR (>120 beats/min). The dichotomization of HR into two categories (HR < 120 and HR > 120 beats/min) increases the effect size that is being tested and the power of the study.

**Calculation of FFR**

FFR is defined as the ratio of maximal myocardial blood flow distal to a stenotic artery (Q) to the theoretical maximal flow in the absence of the stenosis (QN). Clinically, maximal flow is achieved by administering intracoronary papaverine or adenosine. Under this maximum flow (hyperemia), the resistance (R) imposed by the myocardial bed is minimal and blood flow is proportional to driving pressure. FFR can thus be expressed as follows:

\[
FFR = \frac{Q}{Q_N} = \frac{\frac{p_a - p_s}{R}}{\frac{p_{a,\text{p}} - p_{s,\text{p}}}{R}} = \frac{p_a - p_s}{p_{a,\text{p}} - p_{s,\text{p}}} \tag{1}
\]

where \(p_a \approx 0\) and \(p_{a,\text{p}}\), \(p_s\), and \(p_{s,\text{p}}\) represent the average values of aortic, distal coronary, and central venous pressures obtained at hyperemia. Generally, central venous pressure is close to zero for normal microvasculature.

**Calculation of CDPe**

CDPe is defined as the ratio of transstenotic pressure drop (\(\Delta p = p_a - p_s\)) to distal dynamic pressure (\(0.5 \times \rho \times APV^2\)), measured at hyperemia, is calculated as the product of blood density (\(\rho\)), square of APV, and a constant value of 0.5. \(\rho\) does not change significantly at hyperemia and thus can be assumed to have a constant value of 1.05 g/cm\(^3\) (3, 5).

\[
CDP_e = \frac{\Delta p}{0.5 \times \rho \times APV^2} \tag{2}
\]

dimensionless parameter, where \(\Delta p = p_a - p_s\), \(p_a\), and \(p_s\) are average pressures measured proximal and distal to the stenosis at hyperemia, respectively.

**Calculation of LFC**

LFC is a more recently introduced index (4, 5) that combines both functional and anatomic measurements. It is defined as the ratio of percent AS (1 – \(\kappa\)) to the square root of CDPe evaluated at the site of stenosis (CDPm) at hyperemia. Here, \(\kappa\) is the ratio of minimum cross-sectional area at the site of stenosis (\(A_e\)) to the native vessel area (\(A_s\)).

\[
LFC = \frac{(1 - \kappa)}{\sqrt{CDP_m}} \tag{3}
\]

The expressions for (1 – \(\kappa\)) and CDPe have been previously described (3, 28).

\[
(1 - \kappa) = \frac{A_b}{A_e - A_{bs}} = \frac{d_b^2}{d_e^2 - d_{bs}^2} \tag{4}
\]

where \(A_b\), \(A_e\), and \(A_{bs}\) are the angioplasty balloon, native vessel lumen, and angioplasty balloon shaft area, respectively, and \(d_b\), \(d_e\), and \(d_{bs}\) are the corresponding diameters (Fig. 1).

Thus CDPe evaluated at the site of stenosis (CDPm) under hyperemia is as follows:

\[
CDP_m = \frac{\Delta p}{0.5 \times \rho \times APV_m^2} \tag{5}
\]

\[
APV_m = APV \left( \frac{A_e - A_{bs}}{A_e} \right) \tag{6}
\]

where \(APV_m\) is the average peak velocity at the throat and APV is the average peak velocity measured distal to stenosis.

**Statistical Analysis**

A two-way random-effects ANOVA model (17) was used to validate the effect of HR and AS on diagnostic indexes with repeated measures on both factors. A compound symmetry correlation structure was assumed between repeated measurements. Data analysis was performed on SAS 9.1.3 (SAS Institute) with \(P < 0.05\) used as the probability level to accept statistical significance. All functional measurements and hemodynamic parameters are represented as means ± SE.

**RESULTS**

A total of 406 simultaneous pressure flow readings were recorded in 11 Yorkshire pigs. In the low HR group, there were 86 readings for lesions < 50% AS and 86 readings for >50% AS. For the high HR group, there were 102 readings for lesions < 50% AS and 132 readings for >50% AS lesions.

**Effect of HR on Diagnostic Parameters**

The main effect of HR on diagnostic parameters (FFR, CDPe, and LFC) is shown in Fig. 2. The main effects are the differences in means over levels of one factor (for, e.g., HR), collapsed over levels of the other factor (for, e.g., AS). Figure 2A shows the bar graph of FFR as a function of HR. The mean values of FFR for the conditions of low HR (0.81 ± 0.04) and high HR (0.82 ± 0.04) remained nearly unchanged \((P > 0.05)\). Hence, there is no statistically significant effect on the mean value of FFR because of changes in HR. Figure 2B shows the bar graph of CDPe as a function of HR. The mean values of CDPe for the conditions of low HR (95 ± 33) and high HR (118 ± 36) remained almost the same \((P > 0.05)\). Hence, there is no statistically significant effect on the mean value of CDPe because of variation in HR. Figure 2C shows the bar graph of LFC as a function of HR. The mean values of LFC for the conditions of low HR (0.14 ± 0.01) and high HR (0.12 ± 0.02) were marginally different. This marginal difference in LFC values showed some statistical significance \((P = 0.013)\), indicating that the mean values of LFC do somewhat vary with HR, unlike FFR and CDPe.

**Effect of AS on Diagnostic Parameters**

The main effect of AS on diagnostic parameters (FFR, CDPe, and LFC) is shown in Fig. 3. The main effects are the differences in means over levels of one factor (for, e.g., AS) collapsed over levels of the other factor (for, e.g., HR). Figure 3A shows the bar graph of FFR as a function of AS. A
significantly lower value of FFR for AS > 50% (0.76 ± 0.04) is observed compared with the value of FFR for AS < 50% (0.88 ± 0.04) (P < 0.05). Thus the mean values of FFR are significantly different for various degrees of epicardial AS.

Figure 3B shows the bar graph of CDPe as a function of AS. A significantly higher value of CDPe for AS > 50% (151 ± 35) is observed compared with the value of CDPe for AS < 50% (62 ± 30) (P < 0.05). Thus the mean values of CDPe are significantly different for various degrees of epicardial AS.
significantly different for various degrees of epicardial stenosis. Figure 3C shows the bar graph of LFC as a function of AS. A statistically significant and higher value of LFC for AS > 50% (0.16 ± 0.01) is observed compared with the value of LFC for AS < 50% (0.10 ± 0.02) (P < 0.05). Thus the mean values of LFC are significantly different for various degrees of epicardial coronary stenosis.

DISCUSSION

In the present study, we further tested the CDPe (3, 4, 28) and LFC (3, 4, 28) for assessment of the severity of epicardial stenosis. Measurements were made for a large range of stenoses severity and HR variation. The major findings of this study are 1) CDPe and FFR are both independent of HR, while LFC is marginally dependent on HR; and 2) CDPe, FFR, and LFC can significantly differentiate between degrees of epicardial stenoses. The marginal dependence of LFC on HR can be attributed to variations due to indirect measurements of AS (native lumen area minus the internal balloon obstruction) obtained in vivo. The direct measurement of stenosis using qualitative coronary angiography as implemented in cardiac catheterization laboratory may improve the area measurement and thus LFC correlation. More importantly, when LFC was correlated for the AS groups, the values were significantly different. Thus we consider that LFC has the appropriate sensitivity to differentiate the subtle hemodynamic changes caused by a change in AS.

Pressure Drop Coefficient

It has been demonstrated in vitro and in vivo that the relationship between stenosis pressure drop and flow (or velocity) is nonlinear and is described by $\Delta p = aV^2 + bV^2$, where $a$ and $b$ are stenosis specific constants and $V$ is the velocity. The term $aV$ refers to viscous losses and $bV^2$ momentum losses associated with the flow due to the presence of a stenosis (obstruction). Hence, the prediction of functional severity of a stenosis depends on pressure drop-flow relationship.

By definition, CDPe is a measure of stenosis resistance as it combines hyperemic pressure drop and velocity measurements (5). It is derived from fundamental fluid dynamic principles. Distal dynamic pressure is used to normalize the pressure drop typically when there is a change in area and has the following advantages: 1) it allows the use of a nondimensional parameter for pressure drop that can be related to a fundamental fluid dynamic parameter: Euler number (3, 28); 2) it includes both the momentum change and viscous related pressure losses; and 3) it has a higher resolving power for separating normal and diseased conditions of epicardial stenosis and microvasculature simultaneously because of square of velocity term in the denominator (3).

Lesion flow coefficient. LFC is defined as the square root of the ratio of theoretical limiting value of CDPe (i.e., $CDP_{\infty}$) and CDPe at the throat (i.e., $CDP_{th}$), where the $CDP_{\infty}$ is the normalization factor. From fluid dynamic fundamentals, it can be shown that the $CDP_{\infty} = (1 - \kappa)^2$ (supplement A of Ref. 5). With increasing flow, losses due to momentum change increase and CDPe has an upper limit when flow or throat mean Reynolds number ($Re_m$) becomes very large, i.e., mathematically tends to infinity. Since $Re_m$ is the ratio of inertial forces to viscous forces, at high $Re_m$ or flow, only losses due to momentum changes are significant. The $CDP_{\infty}$ provides the net pressure drop from stenosis inlet to outlet at high $Re_m$ when losses due to momentum change are significant. Consequently, $CDP_{\infty}$ is greater than $CDP_{\infty}$ since both viscous loss and losses due to momentum change are present in coronary stenoses at physiological flow rates. Also, $CDP_{\infty}$ at basal flow is greater than the $CDP_{\infty}$ at hyperemic flow for a given stenosis because the relative increase in pressure drop (numerator of CDPe) is lower than the increase in dynamic pressure (denominator of CDPe) for hyperemic flow. Furthermore, $CDP_{\infty}$ approaches the CDPe from basal to hyperemic flow. Additionally, LFC is a normalized lesion-specific diagnostic parameter because the nature of nonlinear pressure drop-flow relation of each lesion is distinct. LFC values vary from 0 to ~1. A lower value of LFC represents moderate epicardial stenosis, whereas a higher value indicates intermediate to severe epicardial stenosis.

The normalization parameter of percent AS (1 − $\kappa$) for limiting flows in formulation of LFC (4, 5, 10, 28) has the advantage of combining functional end points, i.e., $\Delta p$ and APV, with the anatomic end point, i.e., percent AS (1 − $\kappa$). Similar to CDPe, LFC can also significantly differentiate between the severity of epicardial stenoses.

Limitations

Hemodynamic conditions. The infusion of cardiac medication (papaverine) can induce an increase in HR and left ventricular contractility (6, 11); thus the hemodynamic variables are interdependent. However, the study protocol was designed to mimic and account for the alterations in these hemodynamic variables during the interventional procedures. These variables were correlated and did not fluctuate randomly.

Flow measurements. The epicardial arterial blockage was introduced internally by inflating the angioplasty balloon. Errors in flow measurement could occur if a downstream placement of the Doppler-flow sensor relative to the angioplasty balloon (28) is inaccurate. While the sensor is placed downstream to the balloon, the arterial branches need to be avoided between the sensor and the balloon. At the same time, sufficient distance between both of them needs to be maintained to avoid instabilities in flow measurement.

Balloons obstruction vs. arterial plaque. The internal balloon obstruction represents different hemodynamic conditions compared with the arterial plaque stenosis (3, 4, 28) in terms of spatial velocity profiles, eccentricity effect, and additional flow resistance (offered by the internal balloon obstruction). The internal balloon obstruction is inaccurate. While the sensor is placed downstream to the balloon, the arterial branches need to be avoided between the sensor and the balloon. At the same time, sufficient distance between both of them needs to be maintained to avoid instabilities in flow measurement.

Collateral flow. In humans, the effect of collateral flow might play an important role in the reperfusion of vascular bed that is originally perfused by the stenosed artery. Porcine hearts are known not to have significant coronary collaterals. Hence, the effect of collateral flow could not be studied in this porcine model study. While the effect of collateral flow on FFR, CDPe, and LFC has been studied in vitro (15, 21, 24, 26), it needs to be further evaluated in an in vivo setting.
Possible influences of contractility and BP on CDPe and LFC have not been investigated in this study. As a future work, further evaluation of CDPe and LFC for the effect of these hemodynamic parameters needs to be performed. An assessment to evaluate the cutoff value for CDPe and LFC that best discriminates the stenosis severity in humans is also needed to establish a prognostic value for their clinical use.

Conclusion

There is a need for methods that can diagnose stenosis severity independent of hemodynamic variables. From this study, we found that CDPe and FFR are independent of fluctuations in HR, whereas LFC is marginally influenced by HR. The diagnostic indexes FFR, CDPe, and LFC are able to significantly differentiate between various degrees of epicardial coronary stenosis. These results suggest that the diagnostic parameters, i.e., CDPe and LFC, can be potentially used in a better assessment of coronary stenosis severity under a clinical setting.

ACKNOWLEDGMENTS

We acknowledge the assistance of Mahesh Krishnamoorthy, Subbhashish Dasgupta from the Fluid Heat and Mass transfer in Biological systems, and MemS devices laboratory at the University of Cincinnati.

GRANTS

This work is supported by American Heart Association of Great Rivers Affiliate Grant-in-Aid 0755236B and National Scientific Development Grant 0335270N.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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