Influence of arterial wall-stenosis compliance on the coronary diagnostic parameters

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Abstract

Functional diagnostic parameters such as Fractional Flow Reserve (FFR), which is calculated from pressure measurements across stenosed arteries, are often used to determine the functional severity of coronary artery stenosis. This study evaluated the effect of arterial wall-stenosis compliance, with limiting scenarios of stenosis severity, on the diagnostic parameters. The diagnostic parameters considered in this study include an established index, FFR and two recently developed parameters: Pressure Drop Coefficient (CDP) and Lesion Flow Coefficient (LFC).

The parameters were assessed for rigid artery (RR; signifying high plaque elasticity), compliant artery with calcified plaque (CC; intermediate plaque elasticity) and compliant artery with smooth muscle cell proliferation (CS; low plaque elasticity), with varying degrees of epicardial stenosis. A hyperelastic Mooney–Rivlin model was used to model the arterial wall and plaque materials. Blood was modeled as a shear thinning, non-Newtonian fluid using the Carreau model. The arterial wall compliance was evaluated using the finite element method.

The present study found that, with an increase in stenosis severity, FFR decreased whereas CDP and LFC increased. The cutoff value of 0.75 for FFR was observed at 78.7% area stenosis for RR, whereas for CC and CS the cutoff values were obtained at higher stenosis severities of 81.3% and 82.7%, respectively. For a fixed stenosis, CDP value decreased and LFC value increased with a decrease in plaque elasticity (RR to CS).

We conclude that the differences in diagnostic parameters with compliance at intermediate stenosis (78.7–82.7% area blockage) could lead to misinterpretation of the stenosis severity.

1. Introduction

Arterial occlusion resulting from coronary artery disease (CAD) has been known to be one of the main causes of angina and myocardial infarction in humans. Physiological significance of stenosis severity, particularly for intermediate area stenosis (AS), cannot be determined solely on the basis of anatomic endpoints such as angiography. Hence, hemodynamic endpoints such as pressure drop and flow need to be measured across the stenosis (White et al., 1984; Pijs et al., 1993; Kern et al., 2000; Spaan et al., 2006; Tonino et al., 2009, 2010). The functional diagnostic parameters currently employed in clinical settings to measure the ischemic severity of epicardial coronary stenoses are Fractional Flow Reserve (FFR; ratio of average hyperemic pressures distal and proximal to the stenosis) and Coronary Flow Reserve (CFR; the ratio of hyperemic flow to basal flow). Of recently proposed functional parameters, Pressure Drop Coefficient (CDP; ratio of trans-stenotic pressure drop and dynamic pressure) and Hyperemic Stenosis Resistance index (HSRv; ratio of trans-stenotic pressure drop to the average peak velocity) use hemodynamic endpoints, whereas Lesion Flow Coefficient (LFC; ratio of percentage AS and square root of CDP evaluated at the throat) combines both hemodynamic and anatomic endpoints (Meuwissen et al., 2002; Banerjee et al., 2007, 2008, 2009; Sinha Roy et al., 2008).

Clinical Application of Diagnostic Parameters: FFR is a clinically well-established parameter. Based on extensive clinical trials, for single-vessel CAD, a cutoff value of 0.75 for FFR is recommended for coronary intervention (Pijs et al., 1995; Lederman et al., 1997), whereas for multi-vessel CAD, a cutoff value of 0.80 is often used (Silber et al., 2005; Fearon et al., 2007). Thus, for single-vessel CAD as in our case, an FFR < 0.75 suggests coronary intervention whereas an FFR > 0.75 recommends deferment of intervention. Similar cutoff values for CDP and LFC are currently being investigated under clinical settings.

From a clinical perspective, assessing the hemodynamic and geometric factors that can potentially affect the diagnostic parameters is important. FFR values have been shown to be affected by guidewire flow obstruction (Banerjee et al., 2003; Roy et al., 2005), downstream collateral flows (Peelukhana et al., 2009) and by other...
hemodynamic factors such as coronary microvascular resistance, aortic and venous pressures (Siebes et al., 2002).

**Effect of compliance on diagnostic parameters:** Blood flow through compliant, stenosed arteries have been studied in vitro by Siebes et al. (1996) and Gould (1999), in vivo by Siebes et al. (2004) and using computational models by Tang et al. (1999). The in vivo study by Siebes et al. (2004) reported that stenosis compliance could result in angina complaints, especially during periods of low microvascular resistance. However, variations in the values of diagnostic parameters due to arterial wall compliance have not been previously studied. In this study, we hypothesized that arterial wall compliance, together with plaque characteristics (whether caused by calcification or smooth muscle cell proliferation), can alter the hemodynamic endpoints and thereby affect diagnostic parameter (FFR, CDP, LFC and HSRv) values.

2. Methods

2.1. Stenosis geometry

The arterial dimensions (Table 1) were based on single-vessel, single-lesion epicardial CAD obtained from a 32-patient group (Wilson et al., 1988; Rack and Denton, 1992; Roy et al., 2005). The arterial geometry was considered axisymmetric (Fig. 1A). The vessel length proximal and distal to the stenosis was taken to be more than 20 times the vessel diameter for the flow to develop.

### Table 1

<table>
<thead>
<tr>
<th>Area stenosis (%)</th>
<th>$r_e$</th>
<th>$l_e$</th>
<th>$r_m$</th>
<th>$l_m$</th>
<th>$l_r$</th>
<th>$l_m$</th>
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<tbody>
<tr>
<td>70</td>
<td>1.5</td>
<td>1</td>
<td>0.82</td>
<td>6</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>80</td>
<td>1.5</td>
<td>1</td>
<td>0.67</td>
<td>6</td>
<td>1.5</td>
<td>0.1</td>
</tr>
<tr>
<td>90</td>
<td>1.5</td>
<td>1</td>
<td>0.47</td>
<td>6</td>
<td>0.75</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Fig. 1. (A) Schematic diagram showing idealized in vivo lesion geometry (dimensional values are given in Table 1). (B) Time varying physiological pressure and flow profiles applied at the inlet and outlet. The peak velocity, $u_{peak} - u_{rest}$, corresponds to a normalized velocity of 1.0, so that the ratio of mean to peak velocity, $u_{ave}/u_{peak}$, is 0.537.

Three cases of wall model: (1) rigid artery with rigid plaque (RR), (2) compliant artery with rigid (calcified) plaque (CC) and (3) compliant artery with smooth muscle cell proliferation (CS) were considered. It is well-known that arteries tend to become stiffer with age (Alfonso et al., 1994). The RR and CS cases signify physiologically limiting scenarios of stenosed arterial wall properties corresponding to the highest and lowest elasticity, respectively. For each wall model, three cases of AS, 70%, 80% and 90% were investigated (Table 1).

2.2. Blood flow–arterial wall compliance formulation

Blood flow–arterial wall interactions were modeled using the coupled continuity (Eq. (1)) and momentum (Eq. (2)) equations for incompressible, viscous, and laminar blood flow along with the arterial wall stress equilibrium (Eq. (3)) equation. The arbitrary Lagrangian–Eulerian formulation was used to solve Eqs. (1)–(3) with boundary conditions described in the next section. The equations are

$$\nabla \cdot u = 0 \tag{1}\n$$

$$\rho \left( \frac{\partial u}{\partial t} + (u \cdot \nabla)u \right) = -\nabla p + \mu \nabla^2 u \tag{2}\n$$

$$\sigma_{ij}^{W} = 0 \tag{3}\n$$

where $u$ is the blood velocity field (cm/s), $u_{inj}$ the mesh velocity (cm/s), $p$ the pressure field (dynes/cm$^2$), $\mu$ the dynamic viscosity (Poise), $\rho$ the blood density (gm/cm$^3$) and $\sigma_{ij}^{W}$ the stress tensor for the arterial wall (dynes/cm$^2$).

2.3. Boundary conditions

Time varying pressure $p(t)$ (Tang et al., 2009) was applied at the inlet and a transient parabolic velocity, $u(t)$ (Cho et al., 1983) was applied at the outlet of the artery (Fig. 1B). Three mean hyperemic flow rates ($Q$, 175, 165 and 115 ml/min, were used to obtain the velocity profiles for 70%, 80% and 90% AS, respectively (Roy et al., 2005).

Both rigid and compliant cases were solved with the same physiological pressure and flow pulse (Fig. 1B). Before applying the transient pressure and flow, the compliant models were axially stretched by 10% of the initial length (Tang et al., 2009) and pressurized to a mean physiologic pressure of 89.04 mmHg (Fig. 1B) to account for residual stresses (Fung, 1993). No-slip condition was applied at the arterial wall–blood interface.

Following boundary conditions were applied:

$$\sigma_{ij}^{W} n_j = \sigma_{ij}^{S} n_j \text{ at the lumen-wall interface} \tag{4}\n$$

$$d^e = d^f \text{ at the inner wall} \tag{5}\n$$

$$\sigma_{ij}^{S} n_j = 0 \text{ stress-free state assumed at the outer wall} \tag{6}\n$$

where, $d^e, d^f$ are the displacements of the solid and fluid domain, respectively, (cm) and $\sigma_{ij}^{S}$ is the stress tensor for the fluid flow (dynes/cm$^2$).

2.4. Arterial wall and plaque properties

Both arterial wall and plaque were modeled as homogenous, incompressible and hyperelastic materials using a modified Mooney–Rivlin model (Tang et al., 2009). A strain energy density function ($W$) of the form

$$W = W_{isotropic} + W_{orthotropic} \tag{7}\n$$

with

$$W_{isotropic} = C_1(I_1 - 3) + D_1[\exp (D_2(I_1 - 3)) - 1] \tag{8}\n$$

and

$$W_{orthotropic} = \left(K_1/2K_2\right) \exp (K_2(I_2 - 1)^2 - 1) \tag{9}\n$$

was used to model both arterial wall and plaque material properties. The quantities, $I_1$ and $I_2$, are the stress invariants (Holzapfel, 2000) and $C_1, D_1, D_2, K_1$ and $K_2$ are the material constants (Table 2). The calcified plaque region in CC was modeled as an isotropic material ($W_{orthotropic}=0$).

### Table 2

Parameters for material model (Eqs. (8) and (9)) for the arterial wall and plaque material. All values are in dynes/cm$^2$.

<table>
<thead>
<tr>
<th>Model</th>
<th>$C_1$</th>
<th>$D_1$</th>
<th>$D_2$</th>
<th>$K_1$</th>
<th>$K_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial wall</td>
<td>82.917</td>
<td>9072</td>
<td>3.1</td>
<td>68.240</td>
<td>3.7</td>
</tr>
<tr>
<td>Calcified plaque</td>
<td>2,814,430</td>
<td>131,010</td>
<td>11.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smooth muscle cell proliferation</td>
<td>Same as arterial wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.5. Blood model

Blood was modeled as an incompressible (density, ρ = 1.05 g/cm³) non-Newtonian Carreau fluid with shear rate (γ; 1/s) dependent viscosity:

$$\mu = \mu_0 + (\mu_1 - \mu_0)(1 + (\beta \gamma^2)^{1/2})$$

where \(\mu_0 = 0.56 \, \text{Pa}, \mu_1 = 0.0345 \, \text{Pa}, n = 0.3568\) and \(\beta = 3.313 \, \text{s}\) (Cho and Kensey, 1991).

2.6. Numerical method

The arterial wall and the fluid domain were meshed with 4-noded quadrilateral elements. To avoid domain decomposition, the plaque region was meshed with 3-noded triangular elements. The fluid domain was meshed with 7390 elements for each AS case. The arterial wall and plaque were meshed with a total of 6639, 8336 and 8212 elements for 70%, 80% and 90% AS, respectively. Large deformations and large strains were considered for the elements. The finite element code ADINA (ADINA R&D Inc., MA) was used to solve the coupled fluid–structure interaction equations employing the iterative Newton–Raphson scheme. Mesh convergence study was performed to ensure that the solutions in each case differed by no more than 0.5% in velocity values.

2.7. Arterial compliance

The arterial compliance was calculated as the ratio of percentage diameter change and pressure difference between systole and diastole:

$${\text{Compliance}} = \frac{\frac{d_{\text{max}} - d_{\text{min}}}{d_{\text{min}}} \times 100}{P_{\text{min}} - P_{\text{max}}}$$

where \(P_{\text{max}}\) and \(P_{\text{min}}\) are the maximum and minimum pressures (mmHg) at systole and diastole, respectively; \(d_{\text{max}}\) and \(d_{\text{min}}\) are the diameters (cm) at \(P_{\text{max}}\) and \(P_{\text{min}}\) respectively (Boy et al., 2008).

2.7.1. Diagnostic parameters

Fractional Flow Reserve (FFR): FFR, at hyperemia, is given as (Pijls et al., 1995; Lederman et al., 1997).

$$\text{FFR} = \frac{P_{\text{diast}} - P_{\text{venous}}}{P_{\text{diast}} - P_{\text{end}}$$

where \(P_{\text{diast}}\) is the proximal pressure (mmHg), \(P_{\text{venous}}\) is the venous pressure, \(P_{\text{end}}\) is the pressure measured at the end of flow reversal occurring distal to the stenosis (mmHg) and \(P_{\text{diast}}\) is the venous pressure, which is considered to be 0 mmHg.

2.8. Pressure drop coefficient (CDP)

The CDP is a non-dimensional functional index based on fundamental fluid dynamics principles (Banerjee et al., 2007) and takes into account both the trans-stenotic pressure drop as well as velocity proximal to the stenosis at hyperemia. It is defined by

$$\text{CDP} = \frac{\Delta p}{0.5 U_l^2}$$

where \(\Delta p = P_{\text{prox}} - P_{\text{venous}}\) is the trans-stenotic pressure drop (dynes/cm²) and \(U_l\) is the proximal velocity (cm/s). CDP incorporates both viscous loss and loss due to momentum change in a flow through stenosis.

2.9. Lesion flow coefficient (LFC)

LFC is the ratio of percentage AS (1 – k) and square root of CDP evaluated at the throat and thus combines both anatomical and functional endpoints (Banerjee et al., 2007). It is a normalized parameter, ranging from 0 to 1, defined as

$$\text{LFC} = \frac{1 - k}{\sqrt{\Delta p / (0.5 U_l^2)}}$$

where \(k = A_{\text{th}} / A_{\text{th}}\), \(A_{\text{th}}\) is the stenosis area, \(A_{\text{th}}\) is the proximal lumen area (cm²) and \(U_l\) is the velocity at the throat region (cm/s). Banerjee et al. (2007) derived that \((1 - k)^2\) is the net \(\Delta p\) for flows at higher (limiting) Reynolds numbers through a stenotic region.

2.10. Hyperemic stenosis resistance index (HSRv)

HSRv is the ratio of \(\Delta p\) and the average peak distal velocity (APV; cm/s) at hyperemia and is defined as (Meuwissen et al., 2002)

$$\text{HSRv} = \frac{\Delta p}{\text{APV}}$$

Table 3: Percentage diameter change and compliance values at different stenosis severity levels for the compliant models CC and CS. Compliance was computed using the formula, compliance = % diameter change/[(Pmax−Pmin)] where, Pmax and Pmin are the maximum and minimum pressures at the throat. The % diameter change was computed using, % diameter change = ((dmax−dmin)/dmin) × 100 where, dmax and dmin are the diameters at Pmax and Pmin respectively.

<table>
<thead>
<tr>
<th>% Area stenosis</th>
<th>Calculated plaque</th>
<th>Smooth muscle cell proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% diameter change</td>
<td>Compliance ( % diameter change/mmHg)</td>
</tr>
<tr>
<td>70</td>
<td>0.98</td>
<td>0.0283</td>
</tr>
<tr>
<td>80</td>
<td>1.39</td>
<td>0.0279</td>
</tr>
<tr>
<td>90</td>
<td>1.76</td>
<td>0.0276</td>
</tr>
</tbody>
</table>

Fig. 2: Variation of compliance at throat with stenosis severity for CC and CS models.
For CS, Δp increased by 6.7 mmHg from 70% to 80% AS, and further increased by 12.9 mmHg from 80% to 90% AS.

3.1.1. Effect of compliance on coronary diagnostic parameters

3.1.1.1. FFR. For any wall model (RR, CC or CS), FFR values decreased with stenosis severity (Fig. 4). A best fit approximation with linear correlation, \( R^2 = 0.95 \), was plotted to the computed values of FFR. To evaluate a range of uncertainty in FFR values due to the effect of wall compliance was found to be in the range 78.7–82.7% AS.

For CS, \( \Delta p \) increased by 6.7 mmHg from 70% to 80% AS, and further increased by 12.9 mmHg from 80% to 90% AS.

3.1.1.2. CDP. For all wall models, the CDP values exhibit a nonlinearly increasing trend with \( \% \) AS (Fig. 5). For RR, the increase in stenosis severity from 70% to 80% AS resulted in a 2-fold increase in CDP value, from 16.5 to 33.5, whereas a further increase in stenosis severity to 90% AS elevated the CDP value by 4.2 times to 142.6. A similar nonlinear trend was also observed for the compliant models. For CC, a 2-fold increase in CDP value from 15.7 to 30.6 was observed as the stenosis severity changed from 70% to 80% AS; this value further increased to 111.5 with an increase in the stenosis severity to 90% AS. Similarly, for CS, the CDP value increased by 1.8 times from 15.4 to 28.4 with an increase in the stenosis severity from 70% to 80% AS and further increased by 3.6 times to 103.7 at 90% AS.

3.1.1.3. LFC. The LFC values also followed an increasing nonlinear trend with an increase in stenosis severity for each wall model (Fig. 6). The LFC value for RR increased by 19.1% for a change in...
stensosis severity from 70% to 80% AS, but with the subsequent increase to 90% AS, the value increased only by 8.0% to 0.74. Similarly for CC, the increase in stenosis severity from 70% to 80% AS resulted in a 20.3% increase in LFC value from 0.59 to 0.71. A further increase in the value by 7.0% to 0.76 was observed for an increase in stenosis severity to 90% AS. For CS, the LFC value increased from 0.61 to 0.74, a 21.3% increase, as the stenosis severity changed from 70% to 80% AS and further increased by 8.1% to 0.80 at 90% AS.

3.1.1.4. HSRv. For any given wall model, the HSRv values increased with the increase in %AS (Fig. 7). For any given stenosis severity, the HSRv values decreased with the increase in compliance from RR to CS. For 90% AS case, the HSRv value decreased from 1.52 to 1.19 mmHg/cm/s as the compliance increased from RR to CC. The value further decreased to 1.10 mmHg/cm/s from CC to CS.

4. Discussion

Coronary stenoses are partially compliant, and stenosis dimensions then depend on intrastenotic pressure, which could be a contributing factor to angina complaints (Siebes et al., 2004). At intermediate stenosis in a single-vessel lesion, FFR values can vary around the clinically used cutoff value of 0.75 due to variations in hemodynamic conditions (Siebes et al., 2002; Peelukhana et al., 2009) caused by compliance of the arterial wall and plaque. This variability in FFR values can lead to misdiagnosis of intermediate stenosis to decide upon coronary intervention. Hence, the present study quantified the variation in the values of diagnostic parameters (FFR, CDP, LFC and HSRv) with %AS and the arterial wall-stenosis compliance.

Arterial compliance decreases with age (Alfonso et al., 1994) and thus a stiffer artery represented the RR model (no compliance). We compared our results for the compliant models with previous in vivo studies by Jeremias et al. (2000) and Shaw et al. (2002). They reported compliance values based on area change, while the present study used percentage diameter change to compute compliance. Thus, Table 4 adapts our diameter-based results to their area-based calculations. Our compliance result of 1.87 mm²/mmHg was in close agreement with the compliance value of 1.2 ± 0.2 mm²/mmHg (Shaw et al., 2002) obtained from in vivo measurements in patients suffering from unstable and stable CAD. Jeremias et al. (2000) and Shaw et al. (2002) also reported distensibility values from their in vivo studies, which they define as the ratio of percentage area change and variation in pressure. Their distensibility values ranged from 0.8 ± 0.2 to 3.09 ± 2.68 mm Hg⁻¹. The values of 2.81 and 2.97 mm Hg⁻¹ for our compliant models were in close agreement with their range (Table 4). The marginal difference in our results from the referred in vivo studies could be attributed to factors such as difference in arterial diameters, pulse pressures or material properties.

We found that ΔP values decreased with the increase in compliance as expected. Compliant arteries expand more to reduce the momentum change, resulting in a decrease of ΔP. Owing to a larger expansion of both the native artery and the stenosed region in CS, a lower ΔP is observed compared to CC. For RR, the increase in ΔP was due to the increase in momentum change as flow accelerates across the rigid stenosis.

Similar to ΔP, FFR, which is currently the clinical standard for functional diagnosis of CAD, was also affected by the variability in plaque elasticity. For a specific stenosis and flow, RR had a lower FFR value due to lesser Pa compared to CC and CS. Under similar conditions, CS resulted in higher FFR values due to higher compliance, compared to CC. Fig. 4 shows that for AS < 78.7%, the FFR values for compliant wall models were well above the FFR cutoff value of 0.75. Similarly, for AS > 82.7%, the FFR values were below the cutoff value. Thus, FFR values which are either considerably lesser or greater than the cutoff value will not result in misdiagnosis irrespective of the wall model. However, variability in FFR values in the region of uncertainty (78.7–82.7% AS) for different compliant models might lead to the misinterpretation of stenosis severity. For example, at 81.3% AS, the RR had an FFR less than 0.75, suggesting coronary intervention, while CC and CS suggested postponement of intervention as FFR was greater than 0.75. The FFR values obtained in this study were within 2% agreement with values reported by previous in vivo studies (Wilson et al., 1988; Back and Denton, 1992) thus, validating our numerical computations.

Factors that influence the diagnostic parameters such as lesion curvature, vessel bending due to heart motion (Yang et al., 2008; Tang et al., 2009) and wall roughness were not considered in this study. The effect of guidewire obstruction (Back et al., 1996; Banerjee et al., 2008) in conjunction with arterial wall-stenosis compliance on the coronary diagnostic parameters needs future assessment.

5. Conclusion

For a given stenosis geometry, FFR values increased with increase in arterial compliance. In a clinical setting, this variation in diagnostic parameters due to effect of wall compliance might lead to a possible misdiagnosis. Based on the established cutoff value of FFR=0.75 for single-vessel CAD and a linear approximation of the FFR–AS relationship, we identified a range of stenosis severities, between 78.7% and 82.7% AS, in which misinterpretation could occur. We also found that CDP and HSRv values decreased and LFC values increased with decrease in the elasticity of the
plaque material. However, further studies are needed to establish cutoff values for CDP and LFC similar to FFR.

Conflict of interest statement

The authors have no conflict of interest.

Acknowledgment

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Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.jbiomech.2010.12.011.

References


