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Evaluation of lesion flow coefficient for the detection of coronary artery disease in patient groups from two academic medical centers☆,☆☆

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ABSTRACT

Background: In this study, lesion flow coefficient (LFC: ratio of % area stenosis [%AS] to the square root of the ratio of the pressure drop across the stenosis to the dynamic pressure in the throat region), that combines both the anatomical (%AS) and functional measurements (pressure and flow), was assessed for application in a clinical setting.

Methods and results: Pressure, flow, and anatomical values were obtained from patients in 251 vessels from two different centers. Fractional flow reserve (FFR), Coronary flow reserve (CFR), hyperemic stenosis resistance index (HSR) and hyperemic microvascular index (HMR) were calculated. Anatomical data was corrected for the presence of guidewire and the LFC values were calculated. LFC was correlated with FFR, CFR, HSR, HMR, individually and in combination with %AS. The $p < 0.05$ was used for statistical significance.

LFC correlated significantly when the FFR (pressure-based), CFR (flow-based), and anatomical measure %AS were combined ($r = 0.64$; $p < 0.05$). Similarly, LFC correlated significantly when HSR, HMR, and %AS were combined ($r = 0.72$; $p < 0.05$). LFC was able to significantly ($p < 0.05$) distinguish between the two concordant and the two discordant groups of FFR and CFR, corresponding to the clinically used cut-off values (FFR = 0.80 and CFR = 2.0). The LFC could also significantly ($p < 0.05$) distinguish between the normal and abnormal microvasculature conditions in the presence of non-significant epicardial stenosis, while the comparison was borderline significant ($p = 0.09$) in the presence of significant stenosis.

Conclusion: LFC, a parameter that combines both the anatomical and functional end-points, has the potential for application in a clinical setting for CAD evaluation.

1. Introduction

Ischemic heart disease (IHD) is a multi-level condition that involves the epicardial coronary arteries and the coronary microvasculature, as well as the myocardium. In current clinical practice, the diagnosis of IHD is focused on assessing epicardial stenosis severity as the evaluation of microvascular disease has been a challenge [1–3], particularly in the presence of concomitant epicardial and microvascular disease. Therapeutic decision-making for treatment of IHD is therefore generally based on visual assessment of severity of the stenosis, but visually ambiguous stenoses are often further assessed for their functional severity [4,5]. Currently, the functional significance of such intermediate stenosis is mostly assessed using the coronary pressure-based fractional flow reserve, [6–8] which aims to address the epicardial contribution to IHD, and occasionally using the flow-based coronary flow reserve (CFR), which depicts the combined contribution of the epicardial and microvascular compartments.

However, the hemodynamics of IHD involves a complex interplay between pressure and flow variations due to the presence of microvascular dysfunction and the epicardial stenosis [9]. Therefore, diagnostic

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parameters that combine both coronary pressure and flow [10,11] have been introduced. These include the hyperemic stenosis resistance index (HSR), a stenosis-specific parameter, and the hyperemic microvascular resistance index (HMR), a microcirculation-specific parameter. Although providing additional insight into the origin of IHD, their combined assessment may yield difficulties in clinical decision-making. Hence, a single parameter that can simultaneously account for the presence of epicardial stenosis and microvascular disease could provide important diagnostic advantages.

In view of the above shortcomings, two non-dimensional parameters based on *fundamental fluid dynamics* principles have been introduced. The first one, pressure drop coefficient (CDP), the ratio of trans stenotic pressure drop to distal dynamic pressure, combines both pressure and flow measurements. It has a wider range of 0–1000 and has been extensively validated in pre-clinical trials [12–18]. In a recent study, CDP has been evaluated for clinical application [19] and cut-off values for delineation of epicardial and microvascular impairments have been proposed [20].

The second parameter, the focus of this study, is the *lesion flow coefficient* (*LFC*), the ratio of % area stenosis (%AS) to the square root of CDP at the throat region (CDP_m), that combines both the *anatomical* and *functional* measurements. LFC is a normalized parameter with a range from 0–1, similar to FFR. LFC has also been evaluated *in vitro* [16–18,21] and *in vivo* [12–15,22] for the successful assessment of the functional severity of epicardial stenosis. Further, LFC has also been shown to simultaneously distinguish the presence of epicardial stenosis with concomitant microvascular disease [23] in animal model. In a recent pilot clinical study, LFC was assessed for clinical application in relation to the current diagnostic parameters [24].

Therefore, in this study with a larger sample size, the *patient-level* pressure, flow, and anatomical data from two centers were used to evaluate the LFC in a clinical scenario. The *hypothesis* was that the LFC would prove to be a clinical parameter that could diagnose both the epicardial and microvascular diseases involved in the CAD. To this effect, LFC was correlated with existing parameters. Further, group mean comparisons were performed between: i) the 75% AS groups, ii) the two concordant and the two discordant groups of FFR and CFR, and iii) the normal and abnormal microvasculature groups, in the presence of significant and non-significant epicardial stenosis.

2. Methods

2.1. Patient population

The population consisted of patient-level pressure, flow, anatomical details from 251 vessels. Eighty-four vessel data was obtained from the clinical protocol approved by the Institutional Review Board at the University of Cincinnati and the research and development committee at the Cincinnati Veteran Affairs Medical Center. One hundred and sixty seven data points were obtained from the study by van de Hoef et al. [25], based on a similar protocol approved by the institutional ethics committee at Academic Medical Center-Amsterdam.

Patients of 18 years or above with an abnormal stress test indicating reversible ischemia were considered for enrollment into the study. Patients with by-pass grafts, baseline serum Creatinine >2.5 mg/dl, pregnant women, and significant co-morbid conditions that incapacitated the patients from the consent process were excluded from the study.

2.2. Cardiac catheterization and functional measurements

Patients consented to participate in the study underwent the standard-of-care cardiac catheterization. Unfractionated heparin was administered using a weight-based protocol. Using a 5 or 6 French diagnostic catheter, the coronary arteries were visually assessed for blockages through coronary angiography. According to the standard of care, angiographically moderate to borderline severe lesions [4,5] were further assessed using functional measurements at rest and at adenosine induced maximal arterial dilatation (hyperemia).

The aortic pressure (p_a) and ECG tracings were continuously recorded through Combomap® system (Volcano Therapeutics Inc., CA) or on a personal computer. Pressure and flow readings were obtained using a combination of 0.014″ pressure and flow wires (167 points) or a 0.014″ dual-sensor tipped Combowire (84 points) with a flow sensor at its tip and pressure sensor at 1.5 cm offset. The Combowire (or pressure-wire) was set at zero, calibrated, advanced through the guiding catheter and normalized to aortic pressure (p_a) at the coronary ostium. Following this, the wire was advanced distal to the stenosis and placed at a location downstream to the stenosis and before any side branches to obtain pressure and flow data under baseline conditions. Subsequently, hyperemia was induced using Adenosine, infused intravenously (140 μg/kg/min) or intracoronary (20–140 μg) to obtain pressure and flow data under hyperemic conditions. Anatomical data, the vessel diameter (D_v) and diameter at the stenosis (D_m), was then obtained using quantitative coronary angiography (QCA), as described below.

2.3. Quantitative coronary angiography

The angiographic images taken during the procedure were reviewed. The frames representing the best view of the stenosed artery were selected. Most of the frames were auto calibrated and were ready for analysis. For those needing manual calibration, the size of the guide catheter was used as a reference. Lesion contour was carefully drawn to get the best possible measurements. Using automatic edge-detection techniques available in the GE centricity software, vessel diameter (D_v), stenosis diameter (D_m), and lesion length were obtained. To check for consistency, QCA values were obtained from three different frames using blinded review. The %AS was calculated based on these diameter values. The averaged values were used for the analyses. For some stenoses, the stenosis parameters obtained from a single frame were used.

2.4. Diagnostic parameters

The FFR, CFR, HSR, and HMR were calculated based on their formula provided below.

$$\mathrm{FFR} = \frac{p_d}{p_a}, \text{at hyperemia},$$

$$\mathrm{CFR} = \frac{\mathrm{APV_h}}{\mathrm{APV_b}}, \mathrm{APV} = \text{average peak velocity; subscripts "b" = baseline, "h" = hyperemic},$$

$$\mathrm{HSR} = \frac{\Delta p}{\mathrm{APV_h}}, \Delta p \text{ is the pressure drop across the stenosis},$$

$$\mathrm{HMR} = \frac{p_d}{\mathrm{APV_h}}$$

2.5. LFC calculation

LFC combines the lesion geometry (%AS) and pressure and flow measurements. It is defined as the ratio of the % area obstruction to the square root of CDP_m, In the above equation, the numerator throat region of the stenosis:

$$\mathrm{LFC} = \frac{(1-k)\ \text{or}\%\mathrm{AS}}{\sqrt{\mathrm{CDP_m}}}, k = \left(\frac{A_m - A_g}{A_v - A_g}\right).$$

In the above equation, the numerator $1-k$ is the %AS; in other words, k is the area ratio A_m/A_v, where A_m and A_v are area of the throat

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