INTRODUCTION
Coronary circulation is mainly regulated by two serial resistances, namely, epicardial stenosis and microvascular impairments, both causing abnormal coronary blood circulation [1]. Delineation of the true severities of these diseases is important to guide clinical decision-making processes for the selection of appropriate treatment procedures [2]. The presently used diagnostic parameters: FFR (fractional flow reserve defined as the ratio of distal to proximal hyperemic pressure) and CFR (coronary flow reserve defined as ratio of basal to hyperemic flow) [1], for the evaluation of severity of epicardial coronary stenosis are well established in clinical practice. On the other hand, current methods to evaluate the microcirculatory status are limited [3].

Invasive indices, currently used in clinical practice, are also limited by guidewire flow obstruction effect that increases the blood flow resistance in addition to the atherosclerotic lumen constriction during the simultaneous physiological measurements [4]. Such artificial flow restriction changes the physiological milieu and creates diagnostic uncertainty [5].

Simultaneous measurements of FFR and CFR distal to the epicardial coronary stenosis have been proposed for unmasking the severity of epicardial stenosis from that of microvascular impairments [2]. However, clinical indices that can simultaneously evaluate the severity of epicardial stenosis and microvascular impairments in conjunction with each other have not yet been established.

METHODOLOGY
Mathematical Formulation
Recently, the indices Pressure Drop Coefficient (CDPε) and Lesion Flow Coefficient (LFC) were introduced for the delineation of coronary epicardial and microvascular status [4, 6-7]. The CDPε was defined as the ratio of trans-stenotic pressure drop to distal dynamic pressure (½×blood density×APV²); where APV: distal flow velocity and was validated extensively in the in-vitro studies [4]. The LFC was defined as the ratio of % area stenosis to the square root of CDPε evaluated at the site of stenosis. Thus, LFC not only considers the simultaneous pressure and flow measurements but also incorporates the anatomical details. The mathematical formulation of CDPε and LFC is summarized in Fig. 1.

Figure 1. Functional measurements with single guidewire in a left anterior descending (LAD) coronary artery.

Microvasculature offers relatively more flow resistance as compared with epicardial coronary stenosis [8]. Thus, we hypothesize that the diagnostic parameter combining anatomical information of epicardial stenosis and hemodynamic details, with more weight given to APV, can effectively characterize the severity of epicardial stenosis and microvascular impairment simultaneously. We sought to
investigate the CDPe and LFC in these in-vivo studies for characterizing normal and abnormal microcirculation during both mild and severe epicardial stenoses.

**Experimental Method**

The in-vivo study was performed on 14 Yorkshire pigs (46±3 kg) at University of Cincinnati and at Cincinnati Children’s Hospital. In closed-chest pig heart model, standard catheterization procedure was performed by inserting an arterial sheath through carotid artery followed by a 1.98 mm diameter guide-catheter that was placed at the left main coronary ostium. Then the native lumen area of left anterior descending (LAD) artery was measured by a 0.88 mm diameter intravascular ultrasound (IVUS) catheter (In-Vision Gold, Volcano Therapeutics, CA). Seven pigs each were assigned to normal and abnormal microcirculation. The abnormal microcirculation was simulated by disrupting the microvasculature by injecting 12000 polybead microspheres of 90μm diameter (Polyscience Inc, PA) [9]. In all 14 pigs, the severity of epicardial stenosis was varied from mild (area stenosis < 50%) to severe (area stenosis > 50%) by injecting angioplasty-balloon (Voyager, Guidant Corp, CA) that was inserted through guide-catheter. The phasic distal coronary pressure and APV were simultaneously measured by dual sensor-tipped guidewire (Combowire, Volcano Therapeutics, CA) as shown in Fig. 1. These hemodynamic measurements were performed at baseline flow and at maximal hyperemic flow after injecting intracoronary papaverine (10 mg). The in-vivo data was analyzed by two-way ANOVA model on SAS 9.1.3 (SAS Institute Inc, NC) with p < 0.05 as a statistical significance to distinguish between the severity of epicardial stenosis and microvascular dysfunction simultaneously.

**RESULTS**

A total of 316 simultaneous pressure-flow readings were recorded with mean native LAD diameter of 3.01±0.53 mm. The CDPe and LFC were calculated from the above pressure-flow data. The mean % area stenosis varied from 0.37±0.12 to 0.64±0.1 for mild and severe epicardial stenoses, respectively.

The group mean CDPe values are summarized for severities of epicardial coronary stenosis and microvascular diseases in Fig. 2. The vertical error bars in Fig. 2 indicate the confidence interval at the level of α=0.05. The group mean CDPe increased significantly from mild to severe stenosis (180 vs. 289, respectively) at the level of p<0.01. At the same time, an increase in CDPe from normal to abnormal microcirculation was also significant (137 vs. 306, respectively) with p<0.01. However, the increase in group mean CDPe from normal to abnormal microcirculation (i.e. 306-137=169) is more significant than the similar increase from mild to severe stenosis (i.e. 289-180=109) using Bonferroni’s method with p=0.0001. This supports the hypothesis of considering the quadratic velocity term in the expression of CDPe for effectively delineating epicardial and microvascular diseases.

The group mean LFC values are also presented in Fig. 3 in a similar manner. The LFC increased from mild to severe stenosis (i.e. 0.072 vs. 0.117, p<0.01). However, it decreased from normal to abnormal microcirculation (i.e. 0.126 vs. 0.081, p<0.05). The consideration of anatomical details along with CDPe proves the usefulness of LFC for further human clinical trials.

**CONCLUSION**

CDPe and LFC are the diagnostic parameters derived from fundamental hemodynamic endpoints. Both parameters are clinically feasible indices for assessing the severities of epicardial coronary stenosis and microcirculatory resistance simultaneously.

**REFERENCES**