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DISTINGUISHING EPICARDIAL AND MICROVASCULAR DISEASE USING COMBINED FUNCTIONAL AND ANATOMICAL ENDPOINTS IN A PORCINE MODEL

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ABSTRACT

For a better treatment of coronary artery disease in a catheterization lab, detection of the relative contributions of the epicardial stenosis (ES) and concomitant microvascular disease (MVD) is important. To diagnose ES, fractional flow reserve (FFR), the hyperemic stenosis resistance index (hSRv) and to diagnose MVD, hyperemic microvascular resistance index (hMRv) have been tested in cath labs. However, for concurrent assessment of ES and MVD, functional parameter utilizing flow and pressure values, pressure drop coefficient (CDP) and combined functional and anatomical parameter, lesion flow coefficient (LFC) are defined. To test the ability of CDP and LFC to account for ES and MVD, they were correlated with the hSRv and hMRv. We *hypothesize* that CDP and LFC will have a better combined correlation with hSRv and hMRv.

Simultaneous pressure and flow readings were obtained in 11 Yorkshire swine. Single and multiple linear regression analyses were conducted between the FFR, CDP and LFC vs hSRv and hMRv. The correlation coefficient (r) was used to check the strength of correlation.

The individual correlation between hSRv and hMRV with CDP (r = 0.90; r = 0.78) and LFC (r = 0.89; r = 0.95) was stronger compared to FFR (r = 0.63; r = 0.32). The combined correlation between hSRv and hMRv with CDP (r = 0.95) and LFC (r = 0.95) increased from the individual correlation. Therefore, we conclude that CDP and LFC can diagnose ES and MVD concurrently and might prove to be improved diagnostic parameters than FFR.

INTRODUCTION

Coronary artery disease is mainly characterized by two major resistances, blockages in the large vessels, ES and microvasculature. During catheterization, quantification of the functional significance of the ES is achieved by diagnostic parameters that utilize pressure and flow measurements made during maximal arterial dilation (hyperemia). However, the presence of MVD leads to a lack of flow recovery in the coronary arteries in spite of an angiographically successful intervention. Therefore, the diagnostic parameters need to have the ability to provide an accurate diagnosis of concomitant MVD and ES; more importantly the relative contributions of ES and MVD need distinction to provide a better diagnostic outcome.

Table 1: The diagnostic parameters and their formulae

Parameter		Diagnostic ability	Formulae
FFR	**Only pressure** P_d = Distal pressure P_a = Proximal pressure	ES	P_d/P_a
hSRv	**Pressure and flow** $DP = P_a - P_d$ APV= Average peak velocity	ES	DP/APV
hMRv	**Pressure and flow**	MVD	P_d/APV
CDP	***Pressure and flow*** ρ = *Blood density*	*ES and MVD*	$\frac{DP}{0.5\times\rho\times APV^2}$
LFC	***Pressure, flow and % area stenosis*** $k = \frac{area\ in\ proximal}{area\ in\ throat}$	*ES and MVD*	$\frac{1-\kappa}{\sqrt{DP/\left(0.5\times\ \rho\times APV_m^2\right)}}$ m : at throat region

Diagnostic parameters like FFR [1], hSRv [2] and hMRv [2] (Table 1) are defined for the diagnosis of CAD. However, FFR is defined solely based on pressure measurements and cannot account for the MVD. hSRv is developed to diagnose ES while hMRv is reported

to diagnose MVD. However, parameters that can account for and quantify the individual contributions of the ES and MVD are currently lacking.

Keeping this in view, based on fundamental fluid dynamics, we have developed two parameters, one based on both the *pressure and flow values*, CDP [3], and a unique parameter that combines both *anatomical and functional measurements*, LFC [3,4]. These parameters, CDP and LFC, have been extensively validated *in vitro* and *in vivo* [3, 4].

To further test these parameters, we have correlated the CDP and LFC with the hSRv and hMRv. LFC was correlated with %AS along with hSRv and hMRV, because it combines functional and anatomical information. CDP and LFC have the ability to account for both the ES and MVD, and therefore, in this study, we *hypothesize* that a) CDP will have a better combined correlation with hSRv and hMRv and b) LFC will have better single and multiple correlation values between hSRv, hMRv and %AS combined.

METHODS

The animal protocol for this study was approved by the University of Cincinnati Institutional Animal Care and Use Committee, and the Cincinnati Children's Hospital Medical Research Foundation. Eleven Yorkshire swine (mean wt. 50 ± 3 kg) were premedicated with intramuscular xylazine (2 mg/kg), telazol (7 mg/kg), and atropine (0.05 mg/kg) and anesthesia was maintained with 2% isoflurane and supplemental oxygen. A surgical access was made to the femoral artery. This access was used to engage a 7-F guiding catheter at the coronary ostium. Access to the left anterior descending (LAD) was achieved using a 0.014" guidewire under fluoroscopy guidance. An intravenous bolus dose of 300 Units/Kg. of heparin was administered. An intravascular ultrasound (2.5-F, 40-MHz intravascular ultrasound (IVUS)) catheter was used to measure the lumen cross-sectional area of LAD. Based on the artery size, an appropriate Voyager angioplasty balloon of rapid exchange type (Guidant Inc., IN) was introduced over the Doppler flow wire. The balloon was then inflated to different diameters to create intraluminal epicardial stenosis of varying severity. Polystyrene microspheres of 90µm (Polysciences Inc., NY) were injected to simulate MVD. This procedure is similar to our previous studies.

The distal and proximal pressure, flow and %AS values were used to calculate the diagnostic parameters based on their formulae (Table 1). Single and multiple regression analyses were performed between each of the FFR, CDP, LFC and hSRv and hMRv using SAS software (Cary, NC). The correlation coefficient (r) was used to check the strength of correlation.

RESULTS

The linear regression analysis results between the FFR and hSRv, hMRv are summarized in Table 2.

Table 2: Regression analyses values for the FFR

Parameter	Regression equation	r
FFR vs hSRv	*0.9-0.202×hSRv*; since hSRv is for ES	0.63
FFR vs hMRv	*0.6943+0.03×hMRv*: since hMRv is for MVD	0.32

Table 3: Regression analyses values for the CDP

Parameter	Regression Equation	r
CDP vs hSRv	(-48.07)+263.37×hSRv	0.90
CDP vs hMRv	53.71×hMRv	0.78
CDP vs (hSRv + hMRv)	*-84.15+232.06×hSRv+24.59×hMRV*	*0.95*

FFR is based on only pressure values. Therefore, it can be seen that the correlation between FFR (r= 0.63) and hSRv, which is dependent on flow and pressure, is low. In addition, it is a known fact that FFR cannot account for the MVD, which is apparent from the very weak linear correlation between FFR and hMRv (r = 0.32).

The single and multiple correlation results between the CDP, LFC are summarized in Table 3 and Table 4, respectively. The CDP is defined based on pressure and flow values, similar to the hSRv and hMRv. Therefore, there was a very high linear correlation between the hSRV (r =0.90) and hMRv (r = 0.78). In addition, the ability of the CDP to account for both the ES and MVD is evident from the strong combined linear correlation with the hSRv and hMRv (r = 0.95).

Table 4: Regression analyses values for the LFC

Parameter	Regression equation	r
LFC vs (hSRv + %AS)	-0.197×hSRv+0.622×%AS	0.95
LFC vs (hMRV + %AS)	-0.018×hMRv+ 0.452×%AS	0.89
LFC (hSRV+ hMRv+%AS)	*-0.205×hSRv+0.0037×hMRv+0.62×%AS*	*0.95*

In addition to the pressure and flow values, LFC also considers the anatomical data, the percentage area stenosis. Therefore, it was correlated with the anatomical measurement %AS in addition to the hSRv and hMRV. LFC has very strong linear correlation with %AS and hSRv (r = 0.95). Similarly, LFC has a very strong correlation with %AS and hMRv (r = 0.89). The ability of LFC to account for ES and MVD is evident from the strong correlation with hSRv, hMRv and %AS (r = 0.95).

CONCLUSION

Under MVD, CDP has better correlation strength when both the hSRv and hMRv are combined. In addition, CDP has better correlation with hSRv and hMRv in comparison to FFR. On similar lines, LFC has better correlation strength when hSRv, hMRv and %AS are combined. It also has better correlation with hSRv, hMRv and %AS in comparison to FFR. This leads us to the conclusion that the CDP and LFC can account for the presence of ES and MVD. Therefore, the two parameters, CDP and LFC, might be potential diagnostic parameters that can be used for better detection of CAD in the clinical setting.

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