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Effect of heart rate on hemodynamic endpoints under concomitant microvascular disease in a porcine model

S. V. Peelukhana,1 R. K. Banerjee,1 K. K. Kolli,1 M. A. Effat,2 T. A. Helmy,2 M. A. Leesar,2 E. W. Schneeberger,4 P. Succop,3 W. Gottliebson,5† and A. Irif2

1School of Dynamic Systems, Department of Mechanical Engineering, 2Departments of Internal Medicine and Cardiology, and 3Department of Environmental Health, University of Cincinnati; 4Deaconess Hospital; and 5Heart Institute, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

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The coronary circulation is characterized by two major resistances, the epicardial stenosis (ES) resistance and the microvascular (myocardial) resistance (Fig. 1A). Coronary artery disease (CAD), one of the main causes of heart failure, is believed to be caused mainly by ES, and studies (8, 23, 30, 35, 37) have shown that the changes in microvascular resistance also influence the CAD. Functional diagnosis of severity of the ES in cardiac catheterization laboratories utilizes diagnostic parameters calculated from invasive pressure and flow measurements, measured under induced maximal arterial dilatation (hyperemia). The measurements are carried out under the assumption of minimal microvascular resistance during peak hyperemia (15, 16). However, the variation of microvascular resistance in the presence of varying concomitant ES is a complex phenomenon that is the subject of ongoing research (1, 4, 9, 12, 24, 25, 27, 36). In the presence of microvascular disease (MVD), there is an increase in the microvascular resistance resulting in reduced transstenotic pressure drop (DP) and flow values. In view of this, the diagnostic parameters need to have the capability to delineate the variations in the functional measurements (pressure and flow) due to MVD and ES separately. To achieve this, several parameters have been proposed in the past. A brief overview of these diagnostic parameters is given below.

Diagnostic parameters currently being used in catheterization laboratories are the pressure derived myocardial fractional flow reserve (FFR; Refs. 14, 33, 34) and the flow-dependent coronary flow reserve (CFR; Refs. 15, 16). FFR is defined as the ratio of the mean pressures distal and proximal to the stenosis during peak hyperemia. CFR is defined as the ratio of maximal hyperemic flow to the normal resting flow. Another new parameter, the hyperemic stenosis resistance (39, 42) has also been proposed to evaluate the severity of the epicardial stenosis. Hyperemic stenosis resistance is defined as the ratio of hyperemic mean transstenotic DP to the distal average peak velocity (APV). All the three parameters fail to delineate between the ES and the MVD conditions (17, 18, 28, 29, 38, 41). In addition, in the presence of MVD, an increase in microvascular resistance at downstream myocardium leads to reduction of flow and CFR values in the upstream epicardial arteries. This leads to reduced DP and increased FFR at the upstream ES. This, in turn, might result in underestimation of the severity of ES. While CFR might provide additional information about the microcirculation, FFR is dependent on the assumption that the resistance of microvasculature and venous pressure are minimal during hyperemia. Thus the assumption of venous pressure ~0 mmHg may not be appropriate to determine FFR in the scenario of concomitant epicardial and microvascular dysfunction.

To address these shortcomings, parameters like the hyperemic microvascular resistance index (42) and index of myocardial resistance (2, 13, 26, 27) have been proposed. The
hyperemic microvascular resistance index is defined as the ratio of hyperemic mean distal pressure to APV, and index of myocardial resistance is defined as the product of hyperemic mean distal pressure and mean transit time measured using thermodilution technique. These parameters have been tested to assess the variation in minimal microvascular resistance with varying ES (1, 12, 27). However, all the parameters discussed above have atypical units and still need to be validated in the presence of MVD.

In view of all the above limitations in the diagnostic parameters and based on the hypothesis that higher weightage to the distal APV will help in delineating the ES from MVD, we have proposed two nondimensional parameters that are based on fundamental fluid dynamic principles. These parameters are the pressure drop coefficient (CDP; the ratio of transstenotic DP to distal dynamic pressure), and the lesion flow coefficient (LFC; the ratio of percent area stenosis (%AS) to the CDP at the throat region; Ref. 7). These parameters have been validated extensively both in vitro (3, 5, 7, 32) and in vivo (4, 19, 20, 40) and tested for delineating different levels of ES (19, 40). More importantly, these parameters have been shown to delineate between the ES and MVD (4, 20).

As mentioned previously, the diagnostic parameters are calculated from the invasive pressure and flow measurements during the cardiac catheterization. These measurements occur in a dynamic environment, and the measurements can vary with the hemodynamic variables like heart rate (HR; Ref. 11) and contractility. The HR is a hemodynamic variable that can vary from patient to patient. Based on multiple factors, the baseline HR might vary (11) between patients. In addition, during hyperemia further increase in HR values is expected. In a normal heart, the increase in HR is associated with elevated flow and reduced coronary resistance values (43). However, in the presence of ES the increase in flow is relatively low and the reduction in coronary resistance is also comparatively less (43). This effect is further amplified by the presence of MVD. The changes in flow with changing HR can affect the diagnostic parameters. Therefore, for a better diagnosis of the CAD, the functional parameter, CDP, and the combined functional and anatomical parameter, LFC, should be independent of the fluctuations in the HR, particularly in the presence of MVD. In a recent in vivo study (19), our group assessed the effect of HR on CDP and LFC in the presence of ES and found that HR had insignificant effect on CDP while variation of LFC was marginal. Therefore, in this study we further sought to assess the dependence of the CDP, LFC, and FFR on HR for different ES in the presence of MVD. We also reported the effect of varying levels of ES, denoted by the level of percent area occlusion in the vessel, i.e., the %AS, in the presence of MVD. The MVD was simulated by creating a microvascular embolization. An additional analysis was done to compare the three diagnostic parameter values under varying levels of DP calculated based on the widely accepted FFR cutoff value of 0.75 in a single lesion vessel (14).

METHODS

Animal Preparation

The animal protocol was approved by the University of Cincinnati and Cincinnati Children’s hospital Institutional Animal Care and Use Committee. Eleven Yorkshire pigs (mean wt. 50 ± 3 kg) were used in this study. The animals were anesthetized with doses of intramuscular xylazine (2 mg/kg), Telazol (7 mg/kg), and atropine (0.05 mg/kg). During the experiment, anesthesia was maintained with 2% isoflurane and supplemental oxygen was given by endotracheal intubation. Intravenous saline was administered to maintain euvolemia conditions during the course of the experiment.

Catheterization Protocol

An intravenous bolus dose of 300 U/kg of heparin was administered, and three surgical incisions were made to access the right carotid, femoral arteries, and right jugular vein. The 7-French sheaths (Cordis, NJ) were introduced into each of the blood vessels for inserting catheters. Two pacing leads connected to a pacemaker (Medtronics, Fridley, MN), were introduced into the jugular vein access and advanced into the right atrium. The carotid artery access was used to advance a Millar solid-tip catheter into the left ventricle (LV), to measure the LV pressure.

A 6-French, guiding catheter (Cordis, NJ) was introduced through the femoral artery and advanced to the coronary ostium using a 0.035-in. guide wire (Cordis, NJ). Subsequently, a 0.014-in. guide wire was introduced into the left anterior descending artery (LAD) under fluoroscopic guidance. The LAD vessel diameter was then measured by inserting an intravascular ultrasound catheter (IVUS; 2.5-F, 40-MHz; Boston Scientific, Boston, MA) over the 0.014-in. guide wire. Automatic pullback of the IVUS catheter was done, and LAD measurements were obtained. To obtain the functional measurements, a 0.014-in. ComboWire (Volcano Therapeutics, San Diego, CA) was introduced into the correct LAD position (part of LAD without any branches). The 0.014-in. guide wire was then withdrawn. Based on the IVUS measured artery size, an angioplasty balloon of rapid exchange type with appropriate size was introduced over the Combo wire to create the desired blockage. Then, a microvascular embolization simulating
the MVD was created by injecting ~12,000 Polystyrene microspheres of 90-μm diameter (Polysciences) into the LAD.

Data Acquisition Protocol

With all the wires and catheters in place, the animal was allowed to acclimatize for 5 min. To assess the effect of the creation of microvascular embolism, initial pressure and flow readings were taken at the baseline flow and hyperemia before the injection of microspheres. After the creation of MVD, similar pressure and flow readings were obtained to calculate and compare the CFR values.

After these initial readings, we waited 2 min to obtain further readings. Aortic pressure was continuously recorded through the 6-French guiding catheter by an external pressure sensor (Edwards Life Sciences, Irvine, CA) connected to the ComboMap machine (Volcano Therapeutics). LV pressure was recorded using the Sonometrics system. HR, simultaneous pressure, and flow in the LAD (basal and hyperemic) were recorded on the ComboMap machine.

Initial pressure and flow readings were taken at the baseline flow. Hyperemia was induced by an intracoronary injection of papaverine (0.4 ml). Typically, we waited 30 s for the hyperemia to set in and then the aortic, LV pressures, LAD pressure and flow, and HR were recorded. After the initial papaverine injection, we took one set of data and waited until basal conditions were reached. Subsequently, two more papaverine injections were given to obtain two additional sets of hyperemic data for a fixed HR. The balloon was then inflated to the required diameter, and the whole procedure was repeated to obtain data at a different %AS condition. Linear variation of diameter with change in inflation pressure for individual balloon, as per manufacturer’s data sheet, was used to calculate the percentage area intraluminal obstructions (4, 19, 40).

It should be noted that HR was varied only by mechanical pacing. Pacing of the heart using an inotropic intervention (e.g., β-adrenergic stimulation) was avoided to eliminate unknown interactions between such a drug and papaverine, which, in turn, could have an influence on the hyperemic condition of the coronary circulation.

The %AS was varied between 30 and 90%. For each %AS, the HR was varied from 70 beats/min to 200 beats/min (43). At each HR and %AS combination, the above-mentioned data acquisition protocol was followed to get the pressure and flow values. All through the data acquisition protocol the MVD was maintained constant without further injection of the microspheres.

Diagnostic Parameters

The three parameters used in this study, FFR, CDP, and LFC are briefly explained below. The pressure and flow values, recorded according to the above-mentioned experimental protocol, were used for calculation of the diagnostic parameters. The lesion details are explained in Fig. 1B.

FFR. The FFR is defined as the ratio of distal pressure to the proximal pressure in the stenosis at maximum vasodilatation i.e., at hyperemic flow condition (14, 33, 34)

$$\text{FFR} = \frac{P_d - P_a}{P_d} \text{ at hyperemic flow}.$$ where $P_d$ is the pressure proximal to the stenosis and measured at the aortic arch in mmHg; $P_v$ is the venous pressure ~0 mmHg; and $P_a$ is pressure distal to the stenosis in mmHg. The proximal pressure is the aortic pressure obtained using the fluid-filled catheter. $P_d$ is obtained using the ComboWire (Volcano Therapeutics) placed in the LAD.

CDP. The CDP (4, 5, 7, 19, 40) is a nondimensional parameter based on pressure and flow measurements (functional endpoints). It is defined as the ratio of DP across a stenosis to distal dynamic pressure (0.5 &times; p &times; APV^2); as shown in Fig. 1B.

$$\text{CDP} = \frac{\text{DP}}{0.5 \times p \times \text{APV}^2},$$ where DP is $P_a - P_d$ in dyn/cm² (1 dyn/cm² = 7.5028 &times; 10^{-4} mmHg); APV is the velocity distal to the stenosis in cm/s; and p is the density of the blood in gm/cm³. Both the pressure values are known from the experiment. The distal APV is obtained from the ComboWire (Volcano Therapeutics). The density of blood is taken as 1.05 g/cm³.

LFC. The LFC (4, 5, 7, 19, 40) is a normalized parameter with values ranging from 0 to 1 and could also be useful, like CDP, under clinical settings. It combines the lesion geometry (anatomical endpoint) and pressure and flow measurements (functional endpoints) (Fig. 1B). It is defined as the ratio of the %area obstruction to the CDP value calculated using the velocity value in the throat region (Fig. 1B):

$$\text{LFC} = \frac{1 - \kappa}{\sqrt{\text{DP} / (0.5 \times p \times \text{APV}^2)_{m}}}$$

where $A_m$ and $A_e$ are areas at throat and proximal regions, cm²; $\kappa$ is the area ratio, $A_m/A_e$; and $\text{APV}_{m}$ is the velocity in the throat region, cm/sec. The $\kappa$ value is obtained from the vessel diameter measured by the IVUS catheter and the balloon diameter (known from the manufacturer’s data sheet) in the inflated condition (4, 19, 40).

Data Analysis

The baseline and hyperemia APV values before and after the injection of microspheres were measured to confirm the creation of microvascular embolism. Using these flow values, the CFR was calculated. All the three values, basal APV, hyperemic APV, and CFR values, were classified in to no MVD and MVD groups. These values were then analyzed using one-way ANOVA and compared across the groups for statistical significance.

To assess the effect of HR and %AS, a total of 444 pressure and flow values were obtained. The recorded data were sorted into four groups based on the %AS and the HR: %AS <50 (156 points), %AS >50 (288 points), HR <120 beats/min (222 points), and HR >120 beats/min (222 points). While the HR is a continuous variable, the 120 beats/min mark was chosen empirically based on the mean HR value (126 ± 1.2 beats/min) obtained from our experimental data, resulting in two groups of HR <120 and HR >120 beats/min. Similar ranges (60–160 beats/min) were considered in humans to test the effect of higher HR values on CFR and coronary circulation (43).

The FFR, CDP, and LFC values were first analyzed using linear regression analysis for the whole range of HR and %AS. In addition, the regression analysis was also done for groups HR <120 beats/min and HR >120 beats/min. The correlation coefficient ($r$) was used to check the strength of correlation between the diagnostic parameters and the variables HR and %AS.

Further analysis to assess the categorical effect of both the HR and %AS on the diagnostic parameters was performed based on a two-way, repeated-measure, mixed ANOVA model using SAS (v 9.0; Cary, NC). Pig was considered as the random factor, and a compound symmetry covariance structure was assumed between the repeated measures.

A similar analysis was conducted based on the threshold limit of transstenotic DP. With the use of the widely accepted cutoff value (14) for FFR of 0.75 in a single lesion vessel and the measured mean aortic pressure, $P_a$, of 55 ± 0.63 mmHg, the distal mean pressure, $P_d$, was calculated. With the use of these $P_a$ and $P_d$ values, the threshold limit of DP, 14 mmHg, was obtained. The data were then grouped into DP < 14 mmHg (274 points) and DP > 14 mmHg (95 points). The effect of these groups on the three diagnostic parameters FFR, CDP, and LFC was also tested using a two-way repeated-measure mixed model ANOVA.

A value of $P < 0.05$ was considered to be statistically significant. All the values are reported as means ± SE.
RESULTS

Effect of Microspheres on APV and CFR Values

The comparison of APV and CFR values before and after the creation of MVD is shown in Fig. 2. The mean values of baseline APV (Fig. 2A) are significantly different before (15.78 ± 0.79 cm/s) and after (12.71 ± 0.87 cm/s) the injection of microspheres ($P < 0.05$). Similarly, the hyperemic APV (Fig. 2B) decreased significantly from 33.42 ± 0.98 to 19.6 ± 1.16 cm/s after the injection of microspheres ($P < 0.05$). Further, the mean CFR values (Fig. 2C) are also significantly different when compared before (1.95 ± 0.06) and after (1.32 ± 0.04) the injection of microspheres ($P < 0.05$). Based on the above statistical findings, the microsphere injection did create a microvascular embolization.

Effect of HR on Diagnostic Parameters

Regression analysis. The scatter plots of FFR, CDP, and LFC against the HR are shown in the Fig. 3. Based on the $r$ values, there is no dependence of the response variables FFR (Fig. 3A; $r = 0.03$), CDP (Fig. 3B; $r = 0.23$), and LFC (Fig. 3C; $r = 0.04$) for the complete tested range (80–200 beats/min) of HR.

Similarly, the scatter plots for the groups HR < 120 beats/min and HR > 120 beats/min are shown in the Fig. 3. In the HR < 120 beats/min group, there is no strong correlation between the HR and the FFR (Fig. 4A; $r = 0.24$), CDP (Fig. 4B; $r = 0.39$), and LFC (Fig. 4C; $r = 0.24$). A similar trend is observed in the HR > 120 beats/min group, with the FFR (Fig. 4D; $r = 0.2$), CDP (Fig. 4E; $r = 0.1$), and LFC (Fig. 4F; $r = 0.05$) showing a weak correlation with the HR values.

ANOVA analysis. Additional analysis to check the categorical effect of HR groups (<120 beats/min and >120 beats/min) was done using repeated measures ANOVA. To assess this effect, the HR groups were combined over the %AS groups. The bar plots showing these group mean comparisons are shown in Fig. 5.

FFR. The variability in FFR under different HR conditions is shown in Fig. 5A. In the presence of MVD, the mean FFR value for the HR < 120 beats/min group is 0.82 ± 0.02. The mean value of FFR for the HR > 120 beats/min group is 0.82 ± 0.02. Thus variable HR groups tested have an insignificant effect ($P > 0.05$) on the FFR in the presence of MVD.

CDP. The variability in CDP under different HR conditions is shown in Fig. 5B. Under MVD condition, the mean CDP values are not significantly different between the HR < 120 beats/min (83.15 ± 26.19) and HR > 120 beats/min (98.62 ± 26.04) groups ($P > 0.05$). Thus it can be inferred that the CDP values do not change significantly with the variation in the HR.

LFC. The variability in LFC under different HR conditions is shown in Fig. 5C. In the presence of MVD, the mean LFC values are not significantly different between the HR < 120 beats/min (0.16 ± 0.03) and HR > 120 beats/min (0.15 ± 0.03) groups. Thus it can be inferred that the LFC values don’t fluctuate significantly with the variation in the HR.

Effect of %AS on Diagnostic Parameters

Regression analysis. The scatter plots of FFR, CDP, and LFC against the %AS are shown in the Fig. 6. Based on the $r$ values, there is a possible linear correlation between the response variables FFR (Fig. 6A; $r = 0.66$), CDP (Fig. 6B; $r = 0.41$), and LFC (Fig. 6C; $r = 0.75$) and the %AS for the complete tested range of 30–90% AS.
Similar to the HR groups, further ANOVA comparison between the FFR, CDP, and LFC values is made in the presence of MVD for varying levels of %AS (≤50 and >50). To assess the main effects of %AS on the FFR, CDP, and LFC the %AS groups are combined over the HR groups.

**FFR.** The variability in FFR under varying %AS conditions in the presence of MVD is shown in Fig. 7A. The mean FFR values are significantly different between the %AS < 50 (0.89 ± 0.02) and %AS > 50 (0.75 ± 0.02) groups. Thus FFR can distinguish various levels of %AS in the presence of MVD.

**CDP.** The variability in CDP for different %AS groups in the presence of MVD conditions is shown in Fig. 7B. The mean CDP values are significantly different between the %AS < 50 (35.97 ± 25.79) and %AS > 50 (143.80 ± 25.41). Thus CDP can distinguish various levels of %AS groups tested in the presence of MVD.

**LFC.** The variability in LFC for different %AS groups with MVD is shown in Fig. 7C. The mean LFC values are significantly different between the %AS < 50 (0.22 ± 0.03) and %AS > 50 (0.09 ± 0.03) groups. Thus LFC can differentiate between various levels of %AS in the presence of MVD.

**Effect of DP on Diagnostic Parameters**

Based on the DP cutoff of 14 mmHg, the group means of the FFR, CDP, and LFC are compared with assess the effect of varying levels of DP (≤14 mmHg and >14 mmHg) on the diagnostic parameters. This additional analysis is conducted to assess how the DP groups, based on FFR cutoff value of 0.75, would affect the two parameters CDP and LFC. To assess the main effects of DP, the DP groups are combined over the HR groups.

**FFR.** The variability in FFR under varying DP conditions in the presence of ES with MVD is shown in Fig. 8A. The mean FFR values are significantly different between the DP ≤ 14 mmHg (0.85 ± 0.01) and DP > 14 mmHg (0.67 ± 0.02) groups, even in the presence of MVD. This trend is expected as the DP cutoff is chosen based on the FFR cutoff of 0.75.

**CDP.** The variability in CDP for different DP groups, in the presence of MVD is shown in Fig. 8B. The mean CDP values are significantly different between the DP ≤ 14 mmHg (38.87 ± 1.22) and DP > 14 mmHg (157.15 ± 1.25). Thus CDP can distinguish various levels of DP groups tested.

**LFC.** The variability in LFC for different DP groups under MVD condition is shown in Fig. 8C. The mean LFC values are significantly different between the DP ≤ 14 mmHg (0.15 ± 0.03) and DP > 14 mmHg (0.21 ± 0.03) groups. Thus, LFC can differentiate between various levels of DP even in the presence of MVD.

**DISCUSSION**

In this study, we sought to test the effect of hemodynamic parameter, HR, on the parameters FFR, CDP, and LFC, in the presence of MVD. We hypothesize that HR has no effect on CDP and LFC. The group mean values for FFR, CDP, and LFC were evaluated and compared for HR ≤ 120 beats/min and HR > 120 beats/min. The mean values did not change significantly, confirming our hypothesis that the CDP, LFC, and FFR are, indeed, independent of HR. The insignificant effect of HR on FFR was expected and has been reported previously. Interestingly, CDP and LFC, the two new parameters tested, also follow the same trend, with HR showing an insignificant effect on both the parameters.

In addition to the effect of HR, the three diagnostic parameters have also been tested for the effect of various levels of %AS in the presence of MVD. The parameter values were significantly different, which confirms the fact that the CDP, LFC, and FFR can account for the variation in the levels of %AS even when there is MVD.
In a clinical setting, the main application of the diagnostic parameters arises in the case of intermediate stenosis. Therefore, based on the accepted cutoff for FFR (0.75) and a mean aortic pressure of 55 mmHg from our study, we obtained a cutoff of DP (14 mmHg). Similar mean aortic pressure was also reported by Fearon et al. (12). The mean values of the diagnostic parameters were then compared between the DP groups. All three parameters, FFR, CDP, and LFC, could significantly distinguish between the DP groups in the presence of MVD.

In this study, it is known a priori that there is a concomitant MVD. However, in a catheterization laboratory, the cardiologist has no definitive knowledge about the concomitant MVD and thus needs to make a decision based on the value of the functional diagnostic parameter. Therefore, under clinical setting, any diagnostic parameter should possess the ability to distinguish between the two types of coronary impairments, i.e., ES and MVD.

The current study was aimed at elucidating the effect of HR on the diagnostic parameters under MVD condition only.

Fig. 4. Scatter plots showing the linear regression for various HR (beats/min) groups. A: FFR vs. HR < 120. B: CDP vs. HR < 120. C: LFC vs. HR < 120. D: FFR vs. HR > 120. E: CDP vs. HR > 120. F: LFC vs. HR > 120.
Therefore, for these set of pigs, we did not collect data for ES without the MVD. To compare the ability of CDP and LFC to differentiate ES and MVD, the values of diagnostic parameters obtained only under ES without MVD from a previous study done on a different set of pigs by Kolli et al. (19) were used. This comparison between the data sets obtained from two different sets of pigs; one (pigs for ES only) from Kolli et al. and the other (pigs for MVD only) from the current study are presented in the Fig. 9.

A Student’s t-test was used for comparison. From Fig. 9A, it can be seen that FFR cannot delineate between ES and MVD, a conclusion similar to previous studies (17, 18, 20, 28, 29, 38, 41). However, the other two parameters, CDP (Fig. 9B) and LFC (Fig. 9C), can delineate the presence of MVD and ES, similar to previous studies in a porcine model (4, 20, 40). It can be seen that there is an overlap in the error bars. However, the P values were significant. The conclusions were based on the significance of P values, even if there is an overlap in the error bars (10, 31).

Fig. 5. Effect of HR groups on diagnostic parameters. A: FFR. B: CDP. C: LFC.

Fig. 6. Scatter plots showing the linear regression for the complete range of percent area stenosis (%AS) groups on the diagnostic parameters. A: FFR vs. %AS. B: CDP vs. %AS. C: LFC vs. %AS.
Therefore, the capability of CDP and LFC to delineate ES from MVD (4, 20), in conjunction with their independence from HR, causes them to be potential diagnostic parameters for application in the catheterization laboratory. Clinical testing of CDP and LFC is currently underway for assessment in humans.

**Limitations**

This study assumes a single blockage with a focal lesion in the LAD created by an angioplasty balloon. This method is similar to

**Fig. 7.** A: histograms comparing the effect of varying levels of %AS on FFR in the presence of concomitant MVD. B: histograms comparing the effect of varying levels of %AS on CDP in the presence of concomitant MVD. C: histograms comparing the effect of varying levels of %AS on LFC in the presence of concomitant MVD.

**Fig. 8.** A: histograms comparing the effect of varying levels of pressure drop (DP) groups on FFR, in the presence of concomitant MVD. B: histograms comparing the effect of varying levels of DP on CDP in the presence of concomitant MVD. C: histograms comparing the effect of varying levels of DP on LFC in the presence of concomitant MVD.
the one used in our previous studies (4, 19, 40). The degree of epicardial stenosis created by balloon catheter is somewhat hemodynamically different from focal lesions found in humans. The balloon lesion leads to slightly increased DP across the stenosis. This is due to the additional flow resistance and increased viscous losses caused by the balloon shaft. However, the values of diagnostic parameters obtained by internal balloon occlusion are expected to follow a similar trend compared with an external stenotic resistance (as is the case of patients in catheterization laboratory) if the resistances of the balloon shaft and the internal balloon occlusion are combined.

The MVD is simulated by creating a microvascular embolism through the injection of 90-/H9262m polystyrene microspheres to block the capillaries responsible for the microcirculation. The method of creating microvascular disruption using the microspheres has also been tried before (4). This method only accounts for one of the many variants of MVDs that can occur (23, 30). In addition, the level of MVD might vary somewhat depending on the level of the microsphere disruption and variation in the capillary diameter of the animals. These variations are not expected to affect the overall trend of the parameters.

Collateral flow plays a vital role in the reperfusion of the myocardium downstream to the stenosis. Therefore, the effect of collateral flow needs to be taken into account while assessing the microcirculation status independent of the epicardial stenosis. However, the pig heart is not known to have significant collateral channels compared with the human heart. Thus effect of collaterals need to be further evaluated in humans for assessing the CDP and LFC.

Besides HR, there are various other hemodynamic variables such as contractility, blood pressure, and factors like multiple blockages, compliance of the artery (21, 22), geometry of the lesion, and eccentricity of guide wire (3, 6) that need evaluation for accurate diagnosis of the functional severity of the stenosis. Studies accounting for the effect of all the above-mentioned hemodynamic variables need to be checked under clinical settings.

Conclusions

There was neither a significant correlation nor was there a significant difference (P > 0.05) in the group mean values of CDP, LFC, and FFR under variable HR conditions, HR = 120 beats/min, and HR = 120 beats/min. This confirms our hypothesis that HR has insignificant effect on FFR, CDP, and LFC when there is MVD. In contrast, these parameters were able to distinguish various levels of %AS and DP groups, which are based on FFR cutoff values, under MVD. We conclude, therefore, that the CDP and LFC are independent of HR in the presence of MVD and have the potential for improved diagnosis of the CAD in the catheterization laboratories.

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EFFECT OF HEART RATE ON DIAGNOSTIC INDEXES UNDER CONCOMITANT MICROVASCULAR DISEASE

DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


