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An Angiographic Technique for Coronary Fractional Flow Reserve Measurement: In-vivo Validation

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Abstract

Purpose—Fractional flow reserve (FFR) is an important prognostic determinant in a clinical setting. However, its measurement currently requires the use of invasive pressure wire, while an angiographic technique based on first-pass distribution analysis and scaling laws can be used to measure FFR using only image data.

Methods—Eight anesthetized swine were instrumented with flow probe on the proximal segment of the left anterior descending (LAD) coronary arteries. Volumetric blood flow from the flow probe (Q_p), coronary pressure (P_a) and right atrium pressure (P_v) were continuously recorded. Flow probe-based FFR (FFR_q) was measured from the ratio of flow with and without stenosis. To determine the angiography-based FFR (FFR_a), the ratio of blood flow in the presence of a stenosis (Q_s) to theoretically normal blood flow (Q_N) was calculated. A region of interest in the LAD arterial bed was drawn to generate time-density curves using angiographic images. Q_s was measured using a time-density curve and the assumption that blood was momentarily replaced with contrast agent during the injection. Q_N was estimated from the total coronary arterial volume using scaling laws. Pressure-wire measurements of FFR (FFR_p), which was calculated from the ratio of distal coronary pressure (P_d) divided by proximal pressure (P_a), were continuously obtained during the study.

Results—A total of 54 measurements of FFR_a , FFR_p , and FFR_q were taken. FFR_a showed a good correlation with FFR_q ($FFR_a = 0.97 FFR_q + 0.06$, $r^2 = 0.80$, $p < 0.001$), although FFR_p overestimated the FFR_q ($FFR_p = 0.657 FFR_q + 0.313$, $r^2 = 0.710$, $p < 0.0001$). Additionally, the Bland-Altman analysis showed a close agreement between FFR_a and FFR_q .

Conclusions—This angiographic technique to measure FFR can potentially be used to evaluate both anatomical and physiological assessments of a coronary stenosis during routine diagnostic cardiac catheterization that requires no pressure wires.

Keywords

Coronary blood flow; Fractional flow reserve; Coronary angiography; Catheterization

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Introduction

Coronary angiography provides an assessment of stenosis severity by visualizing the opacified arterial lumen. However, angiography alone cannot fully characterize the clinical significance of coronary stenosis. Visual assessment of stenosis correlates poorly with its physiological significance, especially an intermediately severe luminal narrowing cannot be accurately determined.[1,2] While reducing myocardial ischemia by revascularization improves a patient's functional status and outcome, revascularization of nonischemic lesions still remains controversial. [3-6] Recently published results of the FAME (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) study support the evolving strategy to revascularize ischemic lesions and medically treat nonischemic ones. [7] The presence of inducible ischemia related to a coronary artery stenosis is important when deciding whether to revascularize the stenotic lesion. Thus, the rationale for using coronary physiological measurement is to overcome the limitations of coronary angiography and provide the angiographer with an objective indicator of clinically relevant lesion significance.

The most widely accepted method for evaluation of the myocardial ischemia at catheterization laboratory is to measure fractional flow reserve (FFR) with a coronary pressure wire. FFR, as derived from pressure measurements, is a diagnostic tool in the cardiac catheterization laboratory for evaluation of functional stenosis significance. [8] The pressure-derived FFR is based on the assumption that the minimal resistances for the distal microcirculation with and without a stenosis in the supplying artery are nearly the same, or FFR based on pressure measurements will underestimate the FFR from myocardial flow ratio. This is due to the fact that at lower pressures coronary pressure-flow relation is curved towards the pressure axis.[9] Furthermore, several recent studies have shown that the hyperemic microvascular resistance depends on hemodynamic conditions.[10,11] Therefore, a stenosis does not only add resistance to flow in the epicardial arteries, but also impedes myocardial perfusion by increasing microvascular resistance via the passive elastic behavior of the microvascular walls at vasodilation.[12] On the other hand, FFR has its own advantages. Unlike most other physiological indices, FFR has a normal value of 1.0 for every patient and every coronary artery. Moreover, FFR, unlike coronary flow reserve (CFR), is independent of gender and coronary artery disease (CAD) risk factors, such as hypertension and diabetes.[1,13]

Despite extensive evidence regarding the reliability of FFR measurement, some of its limitations are the potential risks associated with advancing a pressure wire across a stenotic lesion, such that the procedure may increase the risks of plaque rupture and vessel wall damage. Additionally, the application of the pressure wire also increases procedure time and cost. To overcome these limitations, we have developed a technique to measure FFR from only angiographic images by using the measured coronary blood flow[14] and arterial lumen volume.[15] Despite providing a less invasive alternative to current clinical protocols, image-based computation may also present new insight into mechanisms of disease progression as evidenced by a recently published paper by Khoo et al.[16] The aim of this study was the in-vivo validation of the FFR measurement technique using only angiographic image data.

Materials and Methods

Protocol

In an open-chest swine model, FFR measurements were made for various severities of epicardial stenosis in the left anterior descending (LAD) arteries at hyperemia. The epicardial stenosis was caused by an external vascular occluder. Coronary angiograms were acquired for each data set. Blood flow from flow probe and coronary pressure from

pressure-wire were continuously measured. The study protocol was approved by the University of California, Irvine Institutional Animal Care and Use Committee.

Animal Preparation

Eight fasted Yorkshire swine (38.9 ± 6.0 kg, S&S Farms, CA) were sedated and pre-medicated with Telazol-Ketamine-Xylazine (TKX, 4.4 mg T/kg, 2.2 mg K/kg, and 2.2 mg X/kg) and Atropine (0.05 mg/kg). Anesthesia was maintained with approximately 1~2% Isoflurane (Highland Medical Equipment Vaporizer; Temecula, CA), and supplemental oxygen was given via endotracheal intubation. Arterial partial pressure of CO₂ was maintained within normal limits (40~45 mmHg). Heart rate and percent of oxygen saturation were continuously monitored (Nellcor N-200 Pulse Oximeter; Hayward, CA). Carotid artery and jugular vein were surgically prepared for sheath placement. Intravenous drip of adenosine (400 µg/kg/min) by a syringe pump was used for maximum hyperemic induction. Electrocardiogram (ECG), arterial blood pressure, x-ray pulse signal, and some relative physiological parameters were continuously measured (Biopac Systems, Inc.; Santa Barbara, CA).

Surgical preparation

Lidocaine (50 µg/kg/min for total 4~5 ml) was administered intravenously to prevent arrhythmia before opening the chest. A lateral thoracotomy was performed by using standard surgical technique. The 4th and 5th ribs were separated and the heart was fully exposed. The pericardium was opened, and the proximal segment of the LAD was dissected free. Transit-time ultrasound flow probes (Transonic Systems, Inc) were placed on the proximal segments of the LAD for blood flow measurement. An extravascular occluder (In Vivo Metric, Healdsburg, CA) was placed around the LAD just distal to the flow probe. It was used to produce variable degrees of epicardial stenosis by injecting saline inside it. The position of the flow probe and the occluder were adjusted to ensure that there were no side branches between them.

Catheterization

Prior to catheterization, Heparin was given (10,000 units bolus followed by additional 4,000~5,000 units per hour). Activating clotting time (ACT) was measured every 30 minutes (Hemochron Model 801, Whole Blood Coagulation System) to monitor coagulation. The left main ostium was cannulated with a 6F hockey-stick catheter through the left carotid artery under fluoroscopic guidance. Another 4F hockey-stick catheter was placed in the right atrium through the right carotid vein to measure the coronary back pressure. Intracoronary measurements of pressure were performed using a pressure wire (Radi Medical System, 0.014"). The coronary pressure wire was advanced into the distal segment of LAD to measure the distal pressure. So aortic pressure (P_a), distal coronary pressure (P_d) and right atrium pressure (P_v) were measured continuously with pressure transducers and the pressure wire, respectively.

Angiographic imaging system

All images were acquired using a conventional x-ray tube with a constant potential x-ray generator (Optimus M200, Philips Medical Systems, Shelton, CT). A cesium-iodide-based flat panel detector (PaxScan 4030A, Varian Medical Inc., Palo Alto, CA) was used for image acquisition. The flat panel detector has a 40×30 cm² field of view and pixel size of 0.194×0.194 mm². The zoom-center mode was used to acquire images with 1024×768 pixels. Gain and flat field corrections were performed prior to image acquisition. The flat panel detector had a dynamic range greater than 8000 and no pincushion distortion. Images were acquired at 30 frames per second. The detector signal in each pixel was digitized with

14-bit precision. All the images were corrected for X-ray scatter before logarithmic transformation. A Pentium V computer and publicly available software (Image J, NIH, Bethesda, MD) were used for image analysis.

Image acquisition and processing

Each swine was positioned on its right side under the flat panel detector. The projection angle was optimized for the separation of the LAD and left circumflex artery perfusion beds. Coronary angiograms were acquired when blood flow reached maximum hyperemia. Prior to coronary angiography, Pancuronium (0.1 mg/kg) was administered intravenously and the ventilator was turned off at the end of full expiration to minimize respiratory motion. Contrast material (Omnipaque-350; Princeton, NJ) was power injected (Leibel-Flarsheim Angiomat 6000; Cincinnati, OH) at 3 ml/sec for 3 seconds. To select a cardiac phase-matched mask image for digital background subtraction, images were acquired for at least one full heart cycle prior to the contrast material injection.

Image calibration

In order to convert the integrated image gray levels to iodine contrast volume, it is necessary to perform a system iodine calibration. The iodine calibration phantom, consisting of different cylindrical cells filled with iodine, was used to convert densitometric integrated gray levels to iodine mass. The calibration phantom was placed on the swine's chest, so that its projection overlapped with the heart. Correction was made for differential magnification of the phantom and the heart. The calibration curve and the known iodine concentration of the contrast material for each study were used to convert the integrated gray levels to contrast volume. [14,17]

Angiographic blood flow measurement

We have previously reported a first pass analysis technique that can be used to measure absolute coronary blood flow by analyzing the propagation of a contrast material signal in the coronary system.[14,15,18] In the first pass analysis technique, the volume of the vascular bed supplied by a major coronary artery is modeled as a reservoir with a single input. The model does not require any assumptions regarding the internal structure of vascular bed or the nature of exit conduits. This technique combines densitometric analysis of spatial and temporal aspects concerning the contrast propagation through the myocardium. The flow measurements are made by summing together pixel values in regions of interest (ROI) with the use of temporal subtraction images (Figure 1).

Coronary blood flow was determined from the change in contrast volume within one cardiac cycle. An ROI for flow measurement was drawn around the LAD vascular bed encompassing the visible arteries, as well as the microcirculatory blush. Power injection of contrast material was assumed to momentarily replace blood with contrast material.[14] The known iodine concentration in the contrast material and a linear regression analysis between measured integrated gray levels and iodine masses in the calibration phantom were used to convert gray level to volume. Therefore, the difference in densitometric signal in the vascular bed can be converted to the volume of contrast bolus entering the vascular bed between successive images using system iodine calibration. The time period of the cardiac cycle was calculated from the image acquisition rate of 30 frames per second. The ratio of the measured volume change to the time period of the cardiac cycle yields volumetric coronary blood flow.

Angiographic FFR

FFR is defined as follows:

$$FFR_q = \frac{Q_s}{Q_N} \quad (1)$$

where Q_s is the hyperemic flow through an artery with a stenosis, and Q_N is the hypothetical normal hyperemic flow through the same artery without disease. As described above, a first-pass distribution analysis technique to measure coronary blood flow using angiographic image data has previously been validated. [18,19] Therefore, coronary blood flow in the stenotic artery (Q_s) can be directly measured using this angiographic technique for coronary blood flow measurement. However, the hypothetical normal hyperemic flow without disease (Q_N) is not known. Therefore, it will have to be estimated using other known parameters such as the arterial lumen volume. Our previous studies have shown that flow through any point in the epicardial coronary arterial tree is related to the sum of the distal coronary arterial lumen volume. [20-25] The relationship between flow (Q) and the distal arterial lumen volume (V) was found to be:

$$Q_N = k \left(\frac{V}{V_{ref}} \right)^{3/4} \quad (2)$$

where k is the scaling coefficient relating crown volume to normal maximum hyperemic flow and V_{ref} is a reference crown volume. The total distal coronary arterial lumen volume, which is used to predict the hypothetical normal hyperemic coronary blood flow, should be in the range of normal or intermediate level of stenosis. By combining equations (1) and (2), angiographic FFR (FFR_a) can then be calculated using:

$$FFR_a = \frac{Q_s}{k \left(\frac{V}{V_{ref}} \right)^{3/4}} \quad (3)$$

This equation shows that FFR can be measured using Q_s , V and k . A technique to measure lumen volume using angiographic image data has previously been validated. [15] Therefore, all of the parameters necessary to calculate coronary FFR can be measured using only angiographic image data. Pressure-derived FFR is based on the assumption that coronary pressure-flow relations are straight at physiological pressures and, when linearly extrapolated, intercept the pressure axis at a value well above venous pressure. [26] At lower pressures, however, they curve toward the pressure axis, intercepting it at a lower pressure (actual zero flow pressure) that is still higher than P_v . Hyperemic microvascular resistance also depends on hemodynamic conditions. Within the linear segment of the relationship between the arterial pressure and the hyperemic flow, the scaling coefficient k in equation 2 can be calculated as a function of pressure:

$$k = m \left(\frac{P_a}{P_{ref}} \right) + b \quad (4)$$

where m and b are the slope and y-intercept of the regression line, respectively. The values of k were calculated from the measured normal coronary flow and volume, and were plotted against P_a . A regression analysis was then performed to determine the values of m and b . The values for the parameters were determined to be $m=0.99$ and $b= 98.07$ [25].

FFR measurement using flow probe

The flow probe data was used as a gold standard for angiographic FFR validation. Flow probe data before and after producing a stenosis was used for FFR measurement. Equation 1 was used to calculate FFR_q based on flow probe data. Flow was measured using the flow probe data over 5 cardiac cycles just prior to coronary angiography.

FFR measurement using pressure wire

Current clinical measurement of FFR is pressure-derived (FFR_p) according to the following expression using aortic pressure (P_a), the coronary pressure distal to the stenosis (P_d) and coronary back pressure (P_v): $FFR_p = (P_d - P_v) / (P_a - P_v)$. This clinically used term can be further described as a measure of myocardial FFR, which takes into account collateral contribution. By using the pressure transducer and pressure wire, P_a , P_d and P_v were continuously measured, respectively. FFR_p was calculated from mean pressure values over 5 cardiac cycles just prior to coronary angiography[27].

Statistical analysis

Linear regression analysis was performed among the angiographic measurement, pressure-wire measurement and the gold standard flow probe data to determine the coefficients in the regression equation. The correlation coefficient (r) and standard error of estimate (SEE) were determined from the linear regression analysis. SEE defines the standard deviation of the measured values from the regression line. The degree of agreement among different methods of measurement was also assessed in the Bland-Altman analysis. $p < 0.05$ was considered to be statistically significant.

Results

A total of 54 imaging measurements were made at hyperemia. The mean heart rate was 91.7 ± 15.6 beats per minute. The mean Q_p and Q_a for LAD were 72.4 ± 37.1 ml/min and 71.6 ± 34.8 ml/min, respectively. The mean LAD coronary arterial volume (V) was 0.92 ± 0.29 ml. The mean FFR_q , FFR_p and FFR_a were 0.74 ± 0.24 , 0.78 ± 0.19 and 0.78 ± 0.26 , respectively. Table 1 showed the hemodynamic data for the eight swine experiments.

Q_a showed a strong correlation with the reference standard Q_p ($r = 0.97$, $SEE = 8.7$). The equation of the regression line was determined as $Q_a = 0.91Q_p + 5.8$ ml/min ($p < 0.0001$) (Figure 2).

FFR_a correlated linearly with FFR_q , as $FFR_a = 0.84 FFR_q + 0.13$ ($p < 0.0001$), with a good correlation coefficient ($r = 0.86$, $SEE = 0.12$). Additionally, in a Bland-Altman plot, the mean differences between FFR_q and FFR_a measurements were 0.01 ± 0.24 . There were no statistically significant differences from zero, implying a lack of bias between these techniques (Figure 3).

Although FFR_p correlated linearly with FFR_q , FFR_p had a tendency to overestimate FFR_q ($FFR_p = 0.657 FFR_q + 0.313$, $r^2 = 0.71$, $p < 0.0001$). This overestimation was improved when FFR_p was defined $P_a - P_v / P_d - P_v$ ($= FFR_p'$) which was considered to be the effect of the curved nature of pressure-flow relations at low values ($FFR_p' = 0.686 FFR_q + 0.271$, $r^2 = 0.748$, $p < 0.0001$) (Figure 4)

Discussion

Currently, FFR measurement by use of pressure wire is widely accepted to evaluate an intermediate coronary lesion or the result of percutaneous coronary intervention, or in the

determination of the culprit lesion in a patient with multivessel disease. However, in order to measure the distal pressure, a pressure wire has to be advanced across the stenosis. Furthermore, it is not practical to re-evaluate FFR data in case of follow-up angiographic study[27]. In the present study, the results of FFR measurements in swine model showed a strong linear correlation between the proposed angiographic FFR and the measurement using gold standard flow-probe FFR (see Figure 3). This correlation is expected, since both angiographic and flow probe FFR were calculated using measured flow ratios (see Equation 1). Our previous report used the clinical pressure-wire method to validate the proposed angiographic FFR measurement technique.[27] In the present study, the angiographic technique was validated by using a flow probe as the gold standard. Therefore, the existing angiographic images without the need to advance a pressure wire distal to a stenotic lesion can be used to simultaneously evaluate both anatomical and physiological assessments of a coronary stenosis. The present study proposes a simple angiographic method to assess the coronary physiology as a potential solution to the well known limitations of the current visual assessment of coronary anatomy. However, given the variability of angiographic anatomically based FFR_a in our ideal controlled experimental model, any angiographic anatomically based estimate of FFR_p may lack the precision of directly pressure derived FFR_p in the critical range of 0.6 to 0.9 necessary for clinical decisions. Therefore, the FFR_a may be potentially used to screen the epicardial stenosis severity for patients.

Coronary pressure-flow relations and microvascular resistance

A direct relation between coronary pressure and flow may be presumed only if coronary resistances remain constant and minimal as theoretically is the case during maximum arteriolar vasodilatation. In that case, pressure measurements alone theoretically can be used to predict flow and thereby functional stenosis severity.[28] In the present study, the FFR measured from pressure ratios overestimated the measurement using gold standard flow-probe FFR, especially at low values (see Figure 4). Our results are in agreement with a previous report that compared coronary FFR, as defined by flow ratio, to myocardial FFR, calculated by a pressure ratio[27]. Pijls et al. [28,29] compared $(P_d - P_v) / (P_a - P_v)$ with the coronary flow ratio Q_S / Q_N . Their results showed that with increasing stenosis severity the coronary flow ratio progressively underestimated the pressure-based index. Siebes and Spaan et al. [12,30] demonstrated the curved nature of pressure-flow relations and how this shape relates to the pressure dependence of minimal coronary microvascular resistance. [31] Therefore, the flow based FFR and pressure derived FFR correlated well in the range of the linear relationship between pressure and flow. The clinical trials that established the guidelines for FFR are based on pressure measurements. Therefore, it will be necessary to perform new clinical trials to establish the guidelines of FFR based on angiographic flow measurements before its clinical introduction.

The frequently used pressure-derived FFR is based on the simplified myocardial FFR model [26,32], which assumed that the hyperemic microvascular resistance is independent of the hemodynamic conditions. Some previous experimental studies supported that the minimal microvascular resistance during distal vasodilation is independent of hemodynamic conditions and epicardial stenosis.[33] However, restoration of coronary driving pressure after percutaneous coronary intervention (PCI) resulted in a reciprocal reduction in minimal microvascular resistance index during distal vasodilation, providing evidence for its pressure dependence in humans. Microvascular remodeling, which is induced by long-term exposure to a low-pressure environment, will also cause the significant increase on microvascular resistance.[34] Additionally, many studies[10,11,35] also lead to a conclusion that a stenosis not only adds resistance to flow in the epicardial arteries, but additionally impedes myocardial perfusion by increasing microvascular resistance via the passive elastic behavior of the microvascular walls at vasodilation.[12]

On the other hand, the results of the present study showed a linear correlation between angiographic FFR and flow probe FFR even at lower ranges. This discrepancy can be explained by the inherent theoretical differences between the pressure ratio P_d/P_a and the flow ratio Q_s/Q_N and the nonlinear relationship between flow and pressure changes[24]. It should be pointed out that in the case of a very severe stenosis, the angiographic FFR can potentially overestimate the actual FFR[24]. This is due to the fact that the theoretically normal flow (Q_N), in the case of angiographic FFR, is estimated based on the measured vascular volume. The vascular volume distal to the stenosis is expected to decrease if the distal pressure drops to very low levels. However, the main clinical interest for FFR measurement is a stenosis with an intermediate level of severity.

Comparing to Pijls's previous results in five individual dogs, the current data showed a bigger scatter between the FFR_p and FFR_q measurements. One probable reason is the differences of the slope and intercept between individual animals' regression line. Additionally, the current study measured FFR in a large range of normal and diseased states and showed a good correlation between the proposed method and the gold standard. However in the clinical settings, FFR values in the critical range of 0.6 to 0.9 with a cut-off value of approximately 0.8 is very important for the therapeutic decision making. The current results (see Figure 3) show a relatively large variability in this clinically important range. Therefore, further optimization of the proposed angiographic technique is necessary before clinical implementation of the technique.

Collateral flow

In this study, an ultrasound flow probe was used as the gold standard for FFR measurement. So the FFR based on the flow probe was the gold standard for coronary FFR but not the myocardial FFR. In 1993, Pijls et al. [28] validated the pressure derived FFR in a dog animal model. The regression lines for pressure derived coronary FFR versus flow derived FFR were through the origin, while for the myocardial FFR versus flow derived FFR had a positive intercept on the y-axis, which is similar to the results from the current study. Previous reports [36-38,32] have documented an increase in microvascular resistance in the presence of an epicardial artery stenosis. However, if collateral flow is accounted for, the minimum achievable microvascular resistance is not significantly affected by increasing epicardial artery stenosis [39,40].

Many physiological studies [5] show that the pressure-flow lines, even in the absence of collateral vessels, are straight at physiological pressures, but follow a convex curve toward the pressure axis at lower pressures. Spaan et al. suggested that collateral flow, which plays a role only at low distal pressures, is not needed to explain the difference between pressure-derived and flow-derived fractional flow reserve. Additionally, collateral flow under an intermediate stenosis is not significant in a swine model.[41] On the other hand, for our current angiographic flow measurement, an ROI large enough to encompass the LAD vascular bed was drawn. This technique ensured that any visible potential collateral flow perfusion would be included in the angiographic FFR measurement. However, in cases of severe stenosis, coronary angiography still has only a limited sensitivity for quantifying collateral circulation capacity. In future studies, it will be necessary to measure the coronary wedge pressure (P_w), end-diastolic pressure and flow to gain a better understanding of the coronary hemodynamics.

Limitations

First, only coronary angiograms without respiratory motion were analyzed for angiographic FFR. However, images without respiratory motion cannot always be expected in a clinical setting. Respiratory motion can introduce misregistration artifacts in phase-matched

subtracted images and increase measurement error in coronary flow and volume. However, motion misregistration artifacts can be minimized through breath-holding during the short time interval required for image acquisition (3-5 seconds), as compared to a previously reported technique that required 15-20 seconds.[29]

Second, this study examined only normal coronary arteries from healthy swine. The experimental model tested only a focal epicardial stenosis. In the case of diffuse coronary artery disease, it will be necessary to calculate relative FFR_a . Relative FFR_a can be calculated by taking the ratio of the measured FFR_a for the arterial tree with the focal epicardial stenosis to the FFR_a of an adjacent arterial tree without the stenosis. Therefore, it will be necessary to also evaluate the FFR_a technique in the presence of diffuse disease in future.

Third, the scaling coefficient k is mainly pressure dependent for each patient. Thus, the clinical application of this methodology will require a reassessment of the scaling coefficient expressed in Equation. 4 as well as a study on the threshold for hemodynamically significant stenoses similar to that validated for FFR_p . The mean differences between FFR_q and FFR_a measurements were minimal. However, the $\pm 1.96\text{SD}$ in the Bland-Altman plot indicated a 95% confidence interval for the index when compared to the gold standard. From the current FFR_a measurements results, ± 0.24 will need to be further optimized before its clinical applications.

Conclusions

This study validated a linear relationship between an angiographic FFR and the gold standard flow probe-derived FFR, although there were still errors between flow-based FFR and pressure-derived FFR, especially at low values. The application of angiographic FFR in humans would provide an alternative method to assess the physiological severity of a coronary stenosis during diagnostic cardiac catheterization without the need to cross a stenosis with a pressure-wire. Therefore, angiographic images may potentially be used for both anatomical and physiological assessments of coronary artery disease.

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$$FFR = \frac{Q_S}{Q_N}$$

Equation (1)

Measured using angiography based on the FPA

Estimated from the crown volume $Q_N = k \left(\frac{V}{V_{ref}} \right)^{3/4}$

Equation (2)

Flow (Q_S)

Volume (V)

$$FFR_a = \frac{Q_S}{k \left(\frac{V}{V_{ref}} \right)^{3/4}}$$

Equation (3)

Figure 1. Region of interest (ROI) for fractional flow reserve (FFR) measurements

Coronary angiograms with an example of a global ROI used for measuring blood flow (a) and an example of an arterial ROI used for determination of arterial lumen volume (b).

Figure 2. A linear regression analysis (a) and the Bland-Altman analysis (b) of Q_a and Q_p measurements

The solid line represents the regression line ($Q_a=0.91 Q_p +5.8$, $r^2=0.939$, $SEE=8.7$, $p<0.0001$).

Figure 3. A linear regression analysis (a) and the Bland-Altman analysis (b) of FFR_a and FFR_q measurements

The solid line represents the regression line ($FFR_a = 0.84 FFR_q + 0.13$, $r^2 = 0.743$, $SEE = 0.12$, $p < 0.0001$).

Figure 4. A linear regression analysis of FFR_p(p') and FFR_q measurements

(a) FFR_p was defined as P_d/P_a ($\text{FFR}_p = 0.657 \text{ FFR}_q + 0.313$, $r^2 = 0.71$, $p < 0.0001$). Standard errors in the slope and y-intercept values are 0.06 and 0.05, respectively.

(b) FFR_p' was defined as $P_d - P_v / P_a - P_v$. ($\text{FFR}_p' = 0.686 \text{ FFR}_q + 0.271$, $r^2 = 0.748$, $p < 0.0001$). Standard errors in the slope and y-intercept values are 0.06 and 0.04, respectively.

Table 1**Hemodynamic data**

The table shows the hemodynamic data for the eight swine experiments. The mean value and standard deviation (σ) of each parameter are given.

	Mean	σ
Body weight (kg)	38.9	6.0
Heart rate (beats/minute)	91.7	15.6
P _a (mmHg)	54.3	10.7
ΔP with adenosine (%)	16.3	7.7
CFR on normal conditions	5.1	1.4
Q _p for LAD (ml/min)	72.4	37.1
Q _a for LAD (ml/min)	71.6	34.8
LAD arterial volume (ml)	0.92	0.29
FFR _q	0.74	0.24
FFR _p	0.78	0.19
FFR _a	0.78	0.26