Coronary Branch Steal
Experimental Validation and Clinical Implications of Interacting Stenosis in Branching Coronary Arteries

K. Lance Gould, MD; Richard Kirkeeide, PhD; Nils P. Johnson, MD

Background—Fluid dynamic analysis predicts a new concept in coronary physiology that we call “branch steal,” whereby stenosis proximal and distal to arterial branching interact with the nonstenotic branch between stenosis that shunts or “steals” flow away from the distal stenotic artery during reactive hyperemia, tested experimentally.

Methods and Results—In 21 large hounds under surgical anesthesia, proximal and distal left circumflex and obtuse marginal coronary arteries were instrumented with electromagnetic flowmeters, proximal and distal machined Teflon screw-down stenoses with round concentric closing and distal silk-in-tubing sleeve occluders. Baseline reactive hyperemia was recorded after 15-second occlusions of both arteries at baseline and for progressive distal stenosis during each step of progressive proximal stenosis. At each combination of stenosis, a coronary arteriogram was obtained using left Judkins catheters and Philips cine calibrated with modulated transfer function to ±0.1 mm accuracy for fluid dynamic analysis of arterial stenosis-branching anatomy. In 324 experiments of parent-child stenosis combinations of the left circumflex artery with an intervening obtuse marginal branch, coronary flow reserve (CFR) calculated by the fluid dynamic model accounting for stenosis-branch interactions and “branch steal” correlated with CFR directly measured by flowmeter (linear regression, CFRartgm=0.18+0.7×CFRflowmtr with Pearson r=0.73). Quantitative arteriography and positron emission tomography perfusion imaging confirmed the concept in clinical examples.

Conclusions—Functional severity of anatomically fixed stenosis is not constant, specific, or independent of other stenosis in branching coronary arteries but requires analysis as an integrated component of the entire branching coronary artery tree to guide revascularizations. (Circ Cardiovasc Imaging. 2010;3:701-709.)

Key Words: coronary steal ■ myocardial perfusion ■ quantitative arteriographic analysis ■ coronary physiology

In randomized and observational trials, selecting patients for revascularization based on physiological severity of coronary artery stenosis is associated with improved survival and fewer adverse outcomes compared with revascularization, based on percent stenosis on arteriography.1–3 Therefore, measuring physiological stenosis severity by fractional flow reserve (FFR) by pressure wire, quantitative maximal myocardial perfusion in milliliters per minute per gram, and/or coronary flow reserve is important to guide clinical management.4–9

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Percent stenosis is inadequate for assessing severity or functional significance as a basis for revascularization procedures due to superposition of diffuse coronary atherosclerosis, multiple stenoses, variable heterogeneous remodeling, heterogeneous endothelial dysfunction, and sympathetic or endothelial mediated vasoconstriction.1–5,9,10 Consequently, there is a poor correlation between percent stenosis and physiological measures of severity such as coronary flow reserve, FFR, or absolute maximal perfusion in milliliters per minute per gram in clinical studies.1–5,9,11 Although FFR is well documented as the current optimal basis for revascularization procedures,1–5 the basic equations for calculating FFR from intracoronary pressures specifically exclude coronary arterial branching between pressure recording sites and stenosis being evaluated.12,13

Pressure flow characteristics of a coronary artery stenosis define its hemodynamic severity in experimental models of localized single stenosis without diffuse disease or other stenosis in the coronary tree.14–19 However, our theoretical fluid dynamic analysis of the entire branching coronary artery tree predicts that a nonstenotic branch between proximal and distal stenosis shunts flow away from the stenotic parallel daughter branch to an extent depending on their relative size and severities of the 2 stenoses.19 This flow shunting into the nonstenotic branch may reduce flow in the stenotic daughter branch to lower than resting values, an effect we call “branch steal.”19 This analysis implies that severity of a coronary

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From The Weatherhead P.E.T. Center for Preventing and Reversing Atherosclerosis and the Department of Medicine, Division of Cardiology, University of Texas Medical School at Houston, and Memorial Hermann Hospital, Houston, Tex.

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Correspondence to K. Lance Gould, MD, University of Texas Medical School, 6431 Fannin St, Room 4.256 MSB, Houston, TX 77030. E-mail k.lance.gould@uth.tmc.edu

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steno

sis cannot be completely characterized in isolation but must be analyzed as an integrated component of the entire coronary artery tree accounting for diffuse narrowing, single, or multiple stenosis and branching patterns.20–25

The current study experimentally tests the hypothesis that “branch steal” occurs with a nonstenotic branch between proximal and distal stenosis as predicted by our integrated fluid dynamic analysis of interacting stenosis in a branching coronary artery. Although this experimental stenosis branching model does not have diffuse disease, it is the basic fluid dynamic “unit” of analysis that can be repeated in iterative application, incorporated with fluid dynamic characteristics of diffuse narrowing and thereby extended to analysis of multiple stenosis an/or diffusely diseased coronary artery trees.

Methods

Experimental Preparation

The Animal Welfare Committee of University of Texas Health Sciences Center at Houston approved the experimental protocol. After overnight fasting, adult healthy hound dogs (n=33) of either sex, 21 to 35 kg, were anesthetized with sodium pentobarbital (Nembutal) 30 mg/kg and underwent endotracheal intubation and mechanical ventilation with adequate anesthesia maintained by small supplemental doses during experiments. Arterial blood gases and core body temperature of 37° were maintained within physiological range by mechanical ventilation with supplemental oxygen and homeothermic blanket on a cradle for coronary arteriograms. Left thoracotomy was performed with instrumentation as previously reported.14–16 A Teflon 20-gauge catheter was placed in the left ventricle (LV) for pressure measurement and arterial blood collection. Left circumflex coronary artery (LCx) was dissected free of surrounding tissues from its origin to a centimeter beyond its first large obtuse marginal branch (OM) that was also dissected free with all small intervening branches ligated. A Zepeda electromagnetic flow probe and a Teflon screw-down mechanical stenoser were placed on the proximal LCx and on the largest part of the obtuse marginal branch or distal left circumflex coronary artery to record coronary flow in both arteries simultaneously. A 1-0 silk in a tubing sleeve occluder was placed around LCx and OM branches distal to the flowmeter and Teflon stenoser.

The Teflon stenoser was precisely machined as 2 sliding, sandwiched plates with semiround half-holes around the artery, such that turning an external Teflon screw progressively narrowed the lumen while maintaining a concentric round lumen. The screw mechanism could be set for no stenosis, 100% diameter stenosis (DS), or any degree of stenosis in between by number of quarter turns of the screw as a guide to severity during experiments but not as the measure of severity that was done from arteriograms.

Arterial access was obtained via the right femoral artery by standard Seldinger technique, using an arterial micropuncture kit (Cook Inc, Bloomington, Ind) with a 6F arterial sheath. All animals received 100 IU/kg of initial heparin bolus with 50 IU/kg every hour for the duration of experiments. A 6F modified Judkins left coronary arteriographic catheter over a guide wire was positioned under fluoroscopy into left main coronary artery ostium. Contrast arteriograms were obtained by hand injection of 2 to 5 mL of Hypaque on a Phillips biplane catheter at 15 frames per second, having a measured resolution of 4 line pairs per millimeter. Coronary flow reserve by flowmeter was the same before as after placing the Judkins catheter for coronary arteriography.

Experimental Procedure

Acute experiments were performed. After surgical preparation, baseline measurements were made: zero baseline of electromagnetic flowmeter (EMF), LV pressure, coronary flows in the LCx and OM coronary arteries, and reactive hyperemia after 15-second occlusion of both arteries using the silk-in-sleeve distal occluders. The Teflon stenoser on the proximal LCx was screwed down to produce a mild stenosis. The distal LCx and OM were occluded with a sleeve occluder for 15 seconds, with baseline zero checked and reactive hyperemia recorded in both arteries. A coronary arteriogram was then obtained. After flow returned to baseline, the OM stenoser was screwed down to produce a mild stenosis, whereas the proximal LCx stenoser remained unchanged. The LCx and OM were again occluded for 15 seconds, reactive hyperemia was recorded, and another arteriogram was obtained. This sequence was repeated as the OM stenoser was closed down to produce a severe stenosis.

The OM stenoser was then backed off to no narrowing, and the proximal LCx stenoser was advanced to a modestly more severe stenosis. The sequence of sleeve occlusion of the LCx and OM, zero-flow baseline check, reactive hyperemia recordings, and coronary arteriogram was repeated for each step of progressive stenosis of the OM. The sequence was repeated for progressive stenosis of proximal LCx stenosis. The sequence of mild to severe LCx and OM stenosis was randomly reversed. Depending on hemodynamic stability, 6 to 22 reactive hyperemia-arteriogram recordings for different stenosis combinations were obtained for each of 21 experiments lasting up to 4.5 hours.

Of the total of 33 animals undergoing thoracotomy, 2 died as the result of developing surgical instrumentation. In 5 animals, branches
from the LCx were too small for instrumentation and too small to have significant effects on the parent artery. Because of the complexity of surgical preparation, prolonged stenosis sequences, and repeated coronary arteriograms, reactive hyperemia in the absence of any stenosis tended to diminish at the end of experiments. Accordingly, some experiments were terminated before a complete sequence of paired LCx-OM stenosis was obtained due to hemodynamic instability as reflected by variability (standard deviation) of an objective index calculated as the product of LV pressure, heart rate, LCx flow without stenosis, and duration of experiment. Based on this objective index, 5 experiments with the highest variability reflecting declining hemodynamic status during the study were excluded. Therefore, from a total of 33 animals, 21 had data that could be analyzed.

After each experiment, animals were euthanized with pentobarbital and potassium. All animals were treated humanely according to Helsinki guidelines and study protocols approved by Animal Welfare Committee of University of Texas Health Science Center.

Data Analysis
Pressure and flow data were recorded in digital format with a PONEMAH physiological digital data acquisition system (Data Sciences International, St Paul, Minn). Absolute coronary flow reserve was measured by flowmeter for the parent LCx and for the largest part of the OM branch or LCx distal to the OM. Flow in the smaller of these branches was then parent flow minus measured flow in the larger of these 2 daughter arteries. Reactive hyperemia measured before and after placement of the left coronary catheter showed no difference in any experiment, thereby documenting no limitation of flow by the arteriographic catheter. For statistical analysis of combined data from separate animals with different baseline coronary flow reserve and to avoid dependency on, and associated variability of absolute coronary flow reserve with changing pressure and heart rate,18 we determined relative coronary flow reserve (normalized CFR [nCFR]) as a fraction of 1.0 as maximum hyperemic flow, with stenosis divided by maximum hyperemic flow without stenosis of the same artery. Therefore, nCFR is equivalent to FFR but nCFR is measured by flowmeter directly, whereas FFR is calculated from pressure measurements.

Coronary arteriograms were analyzed by automated quantitative coronary arteriographic analysis, with a calibrated modulated transfer function for this cine system providing ±0.1 mm resolution.16–18 Fluid dynamic analysis for branching coronary arteries was done for stenosis of parent and child arteries,16–22 as summarized below and detailed in the Online Appendix.

Fluid Dynamic Analysis
As previously described, the model consists of a parent arterial segment, 2 child branch segments, perfusion pressures, resistances of stenoses in each segment, and distal vascular bed resistances and masses that
determine resting flow distribution and their limiting flow resistance at maximal vasodilation.\textsuperscript{5,20–25} Pressure falls across each stenosis according to its severity and flow where pressure distal to the parent stenosis is the input pressure for the child stenosis to determine stenosis flow reserve of each segment based on arterial cross-sectional area, relative percent stenosis, and length in the quadratic equation relating dimensions, pressures, and flow, as previously documented.\textsuperscript{5,20–25}

This arterial parent-child unit of fluid dynamic analysis is experimentally validated in the animal model as reported here. The human arteriographic coronary artery tree is analyzed as a series of these units of fluid dynamic analysis relating anatomic dimensions and pressure-flow characteristics to determine stenosis flow reserve and branch interactions applied sequentially, iteratively to the entire arteriographic coronary artery tree, as previously described.\textsuperscript{19} In tree analysis, the fluid dynamic effects of diffuse narrowing in addition to segmental stenosis are accounted for, based on the coronary arterial length-diameter relations,\textsuperscript{20,21} with details and equations in the online appendix.

**Statistical Analysis**

All statistical analyses were carried out using SPSS v.11.5 (SPSS Inc, Chicago, Ill). Data are reported as mean±1 SD. Linear regression fit the predicted, normalized CFR values as a function of the measured, normalized CFR values. Standard Pearson correlation coefficients were computed for each pairing of predicted and measured, normalized CFR values. Bland-Altman plots were drawn to show average difference and limits of agreement between measured and predicted, normalized CFR.

**Positron Emission Tomography**

For clinical examples to demonstrate concepts and clinical relevance, myocardial perfusion was imaged using positron emission tomography (PET) and rubidium-82 at rest and after dipyridamole stress, as previously described\textsuperscript{22,26,27} in patients undergoing diagnostic rest-dipyridamole PET perfusion imaging for potential coronary artery disease (CAD) after signing standard clinical consent.

**Results**

Figure 1 illustrates the fluid dynamic model of a single branching artery unit with stenosis proximal and distal to the arterial branch. Theoretically predicted CFR is graphed for proximal (parent), distal (child), and branch arteries for each
step of proximal stenosis as distal stenosis is progressively narrowed, as calculated by fluid dynamic model. For example, CFR of proximal, distal, or branch arteries is not reduced by a proximal 40% DS and decreases only distal to the progressively narrowed distal stenosis (dark blue line) as it increases to 50% to 60% DS. However, a proximal 70% DS reduces CFR in proximal, distal, and branch arteries with no distal stenosis. With this fixed 70% DS proximal stenosis, as distal stenosis also reaches 70% DS, CFR of the child artery decreases much more than with a single 70% DS stenosis of proximal or single 70% DS child stenosis and CFR in the nonstenotic branch increases (light blue line). Thus, fluid dynamic theory or model predicts that the nonstenotic branch shunts flow away from or “steals” flow away from the stenotic distal child artery in the presence of a proximal and distal stenosis. Accordingly, we call this phenomenon “branch steal.”

A clinical example helps to understand concept, experimental animal model, and clinical relevance. Figure 2A shows a magnified arteriogram of proximal left anterior descending coronary artery (LAD) with a 57% DS proximal to a second diagonal branch (D2) that has an 80% DS by quantitative coronary arteriographic analysis, without angiographically visible collaterals and with antegrade flow of x-ray contrast media that excludes collaterals below arteriographic resolution. The schematic shows stenosis severity of

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**Figure 4.** A, Predicted nCFR as a function of measured nCFR of the parent artery for all stenosis combinations in the same single experiment shown in Figure 3. Light gray line indicates perfect agreement. B, Linear regression fits of predicted nCFR as a function of measured nCFR of the parent artery for all stenosis combinations in all experiments (light gray indicates each experiment; thick black line, all experiments together). Regression equations and Pearson r values for each experiment are shown in the Table. C, Bland-Altman plot for all data from all experiments comparing agreement between theoretically predicted nCFR and average of predicted and experimentally measured nCFR for parent artery (gray lines: average=0.01; average +1.96 SD=0.34; average −1.96 SD=−0.31).
branching coronary arteries as input to fluid dynamic analysis predicting branch steal, based on branching arteriographic anatomy.

Myocardial perfusion imaging during dipyridamole stress by PET of rubidium-82 confirmed myocardial steal with CFR of 0.6 in the distribution of the diagonal branch on anterior view associated with angina and ST depression. The LAD and its septal perforators show no stress-induced perfusion abnormality. A single 80% DS of the diagonal branch would reduce its CFR but would not make stress flow fall below resting flow\textsuperscript{13,16,17} or cause “steal” seen on dipyridamole PET perfusion imaging.

Figure 2B shows fluid dynamic analysis of this arteriogram. The schematic on the left side shows input to the fluid dynamic model that iteratively solves for maximum flow increase possible in the D2 and LAD. The right-sided graphs show calculated flow increases possible as flow demand increases (upper panel) with associated pressures (mid panel) and resistances (lower panel) of the LAD and D2 branch. For this example of a 57% DS of the LAD and an 80% DS of the D2 branch, the fluid dynamic model predicts coronary steal with a CFR of 0.5 in D2 distribution, comparable to directly measured CFR of 0.6 by PET perfusion imaging. As part of the “shunting” mechanism, distal coronary pressure predicted by the fluid dynamic model is very low, 20 mm Hg, consistent with directly measured coronary pressures distal to stenosis reported during maximal arteriolar vasodilation.\textsuperscript{15–17} This “branch steal” documented by PET perfusion imaging and by quantitative arteriographic analysis is due to the lower-resistance LAD distal to the proximal stenosis shunting off flow from the higher-resistance diagonal with its more severe stenosis.

After angioplasty of the LAD and diagonal branches, the arteriogram and stress PET perfusion image normalized. This relatively simple clinical example is important for demonstrating myocardial steal by arteriographic fluid dynamic analysis and by quantitative PET perfusion imaging without angiographically visible collaterals and with antegrade flow that precludes significant collaterals smaller than angiographic resolution. Thus, integrated anatomic analysis of the entire stenotic branching unit with our fluid dynamic software matches myocardial steal by quantitative PET imaging.

Although clinical examples help us to understand concepts and clinical relevance, the fluid dynamic theory needs validation systematically in an animal model of stenotic coronary artery branches. To relate theoretical model predictions to experimental data, the 3 separate graphs of nCFR for proximal, distal, and branch arteries illustrated in Figure 1 can be combined into a single 3D plot, shown in Figure 3 as a 3D “sheet” display. Theoretically predicted nCFR is on the vertical axis according to the colored scale, with severity of proximal (parent) and distal (child) stenosis severity on horizontal axis. Isocontour colors for CFR show theoretical anatomically predicted nCFR for parent and child stenosis for 1 experiment in which parent and child arteries are progressively stenosed and CFR is calculated from the fluid dynamic model for each anatomic stenosis combination.

In Figure 3, blue circles show measured experimental data by flowmeter fitting theoretical fluid dynamic model (color sheet) in 1 experiment. Figure 3B is an angled view of the same theoretical “sheet display” to better show the fit of experimentally observed data to theoretical model. These examples also indicate that relative masses or bed sizes of branching arteries have major influence on fluid dynamic effects of proximal and distal stenosis, with a corresponding different “sheet display” of progressive parent and child artery stenosis. In the present study, the relative bed size was determined from the absolute resting flows of branch and child arteries before stenosis or hyperemia. Therefore, there is a separate theoretical “sheet display” of nCFR unique for relative bed sizes in each experiment for comparison to the measured nCFR.

Figure 4A illustrates the regression line of directly measured and theoretically predicted nCFR of the parent artery for all stenosis combinations in the same experiment shown in Figure 3. Figure 4B shows regression lines of directly measured and theoretically predicted nCFR of the parent artery for all experiments. Different slopes and intercepts of regression lines for each experiment are due to different relative masses of child and branch arteries. Experimentally measured and theoretically predicted data demonstrate a highly linear relationship (average $R=0.731$ and excellent Bland-Altman agreement (average difference=0.01) in Figure 4C, thereby validating theoretically predicted fluid dynamic interactions of proximal and distal stenosis with intervening arterial branch, or “branch steal.” The Table lists

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Normalized CFR is the predicted $b+m\times\text{nCFR}$, measured. SEE indicates standard error of the regression estimate; $n$, number of points per analysis; $b=y$-axis intercept of the regression line; and $m$, slope of the regression line.
regression equations for each experiment and the overall regression equation of all experiments with probability values. There is modest variability associated with complexity and long duration of surgical preparation and experiments, as described in the Methods section.

For the child artery, experimentally measured and theoretically predicted data also demonstrated a linear relationship (average $R^2=0.6$) and good Bland-Altman agreement (average difference $=0.06$). Fourteen of the severe stenosis combinations (percent DS of parent $=71\pm 7$ and child $=71\pm 14$) showed overt branch steal with flow falling in the child artery to below resting levels during vasodilatory stress, as compared with reduced CFR of the child artery caused by flow shunting into the nonstenotic branch that is a less overt expression of branch steal for less severe stenosis combinations.

An additional clinical example demonstrates relevance to many coronary arteriograms with diffuse CAD. Figure 5 illustrates a clinical example diffuse CAD causing apical myocardial steal in absence of occlusion or collaterals. PET perfusion images of rubidium-82 myocardial uptake at rest and dipyridamole stress are displayed in 4, 90° quadrant views from left lateral to inferior, septal (right), and anterior views, as previously reported.22,26,27 These images of relative radionuclide uptake show severe mid to distal stress induced relative perfusion defects. A generic coronary map based on arteriographic-PET correlations in more than 1000 patients27 is superimposed on relative perfusion images to show arterial distributions.

Figure 5B shows CFR scaled by color bar, based on absolute myocardial perfusion displayed in square quadrants for semiautomated processing into milliliters per minute per gram and coronary flow reserve. “Normal”-appearing proximal areas on standard relative images fail to show profound decreases in absolute coronary flow reserve diffusely throughout the heart with severe myocardial steal in distal regions, particularly anteriorly, apically, and laterally. Absolute CFR of 0.6 indicates that with dipyridamole stress, absolute coronary flow fell to 60% of resting baseline, down 40% below resting levels. In prior literature, this transmural myocardial steal has been associated exclusively with collateralized occluded coronary arteries.19,28

Coronary arteriograms for this patient (Figure 6) showed no occlusion and no visible collaterals, only severe diffuse CAD with several moderate stenosis and antegrade flow that precludes significant collaterals smaller than arteriographic resolution. Schematics in Figure 6 show cumulative cascading units of stenosis with intervening branches and its comparable equivalent of diffuse disease. The fluid dynamic model predicts cumulative, cascading fluid dynamic interactions of multiple stenosis and diffuse disease in the branching coronary artery tree, thereby explaining apical myocardial steal on PET perfusion images as a manifestation of cumulative “branch steal.”

**Discussion**

The present study validates a new concept we call “branch steal,” in the absence of total occlusion that is the typical
substrate for steal phenomenon. Our integrated fluid dynamic analysis demonstrates that physiological characteristics of anatomically fixed stenosis in coronary arteries may not be constant, specific, or independent of stenosis in other coronary arteries in the branching coronary artery tree. Consequently, anatomic or physiological severity of a single coronary stenosis in the presence of other stenosis in other coronary branches may not be completely characterized in isolation but must be analyzed as an integrated component of the entire coronary artery and all its branches.

Each parent-child stenosis branch unit (of several) in a coronary artery may not be sufficiently severe to cause overt “branch steal” by a single branching unit alone but may still cause some shunting of flow into lower resistance branches. However, the cumulative effects of several parent-child stenosis units may cause steal at the LV apex, with angina during dipyridamole stress.

FFR across branch stenosis of bifurcation lesions may overestimate or underestimate severity because of these interactions. For branch stenosis, branch steal may also help explain why an upstream 2-stent strategy for bifurcation lesions provides no benefit over an upstream 1-stent strategy. Stenting the parent and child stenoses may eliminate branch steal, thereby making the fluid dynamic severity of the branch stenosis less severe despite its unchanged anatomic severity. Therefore, stenting the branch stenosis may not add benefit over simply stenting the parent/child stenoses.

Limitations of the Study
Our analysis applies only to arteries with forward flow through measurable anatomic dimensions and not to total occlusion or subtotal occlusion with collateral perfusion replacing forward flow. Under conditions of our experiments, there was forward flow and no visible collaterals. Occluding the artery might have brought out collaterals, but conditions of the artery would not be the same as when we imaged it, with forward flow through a nonoccluding partial stenosis. Occlusion would be a different artery with no forward flow and therefore no branch steal.

In the absence of coronary artery occlusion, flow of invisible preformed collaterals might slightly increase the scatter and reduce the correlation of theory with observed data, but in fact the observed correlation is good. Our measured resting and maximum flows with the most severe stenosis and branch steal were substantially higher than the reported collateral flow of 0.2 to 0.3 of resting flow during total occlusion without increase of reactive hyperemia. Therefore, in the absence of total occlusion, whatever small effect preformed collaterals might have on our measured FFR would be even less than with total occlusion, in which collateral flows are maximal but still far lower than in our experiments with open arteries.

Conclusions
This study validates the concept that functional severity of anatomically fixed stenosis of a coronary artery may not be constant, specific, or independent of other stenosis elsewhere in the branching coronary arteries, cannot be completely characterized in isolation, and must be analyzed as an integrated component of the entire coronary artery tree. Anatomic and functional measures of severity (FFR, CFR) for specific stenosis may be significantly altered by other stenosis proximally, in branches, or by diffuse disease, all of which must be incorporated into analysis of the entire coronary artery tree for guiding revascularization procedures, with outcome trials of procedures based on these concepts and quantitative myocardial perfusion.

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Disclosures
None.

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10. Seiler C, Suter TM, Hess OM. Exercise-induced vasomotion of angio-

**CLINICAL PERSPECTIVE**

The literature indicates a profound disconnection among percent stenosis, coronary flow, patient selection for revascularization, and failure of these procedures to reduce myocardial infarction or mortality in chronic coronary artery disease. It also documents poor correlation between coronary arteriographic severity and coronary flow reserve caused by diffuse disease, arterial remodeling, endothelial dysfunction, and exertional sympathetic vasoconstriction. Failure of revascularization to reduce events or deaths in randomized trials may be due to selecting patients on the basis of percent stenosis, which correlates poorly with coronary flow capacity. In other randomized trials, revascularization based on fractional flow reserve has significantly better outcomes than revascularization based on arteriographic percent stenosis. This study adds insight to this disconnection by elucidating fluid dynamic interactions of multiple stenoses or diffuse disease in the branching coronary artery tree. The experimental model of proximal and distal stenosis separated by a nonstenotic arterial branch used in the study is a typicalatomic-fluid dynamic subunit of coronary artery disease. Cumulative effects of these multiple subunits cause myocardial steal in the absence of occlusions and collaterals, hence the term “branch steal.” The data show that functional severity of anatomically fixed stenosis is not constant or independent of other stenosis or diffuse disease in the branching coronary tree. Given the anatomic complexity of coronary artery disease reiterated in this study, perhaps procedures designed to improve coronary flow should be based on quantitative coronary flow or myocardial perfusion rather than simplistic flawed estimates of percent stenosis on arteriograms.
Coronary Branch Steal: Experimental Validation and Clinical Implications of Interacting Stenosis in Branching Coronary Arteries
K. Lance Gould, Richard Kirkeeide and Nils P. Johnson

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Fluid Dynamic Model. Appendix Figure 1 shows the hemodynamic model used for predicting flows through stenotic coronary artery branches. The model consists of a flow divider with inlet (parent) flow $Q_1$ and outflows through the two child branches $Q_2$ and $Q_3$. Flow is driven by the aortic to venous pressure difference ($P_{ao} - P_v$) and resisted by the stenoses in each branch and the vascular resistance in the vascular bed distal to the child branches. Each lumped vascular bed is characterized by its mass ($M$) that determines resting flow distribution and its limiting flow resistance at maximal vasodilation ($R_m$). Pressure falls across each stenosis according to the severity of and flow through the stenosis. The pressure distal to the stenosis in the parent branch is $P_1$, while pressures distal to stenoses in segments 2 and 3 are labeled $P_2$ and $P_3$.

The coronary system in this model is assumed to have a normal vascular reserve ($CFR_n$) of 5.0 and a normal resting perfusion ($qr,n$) of 80ml/min/100g. Thus, the normal (non-stenotic) maximal perfusion for each bed ($qm,n$) is 400ml/min/100g. Volumetric flow rates ($Q$) in ml/min are calculated for the beds as the product of tissue perfusion times mass of the vascular bed.

Fluid Dynamics Without Stenosis. Appendix Figure 1B shows the assumed normal pressure flow relation at maximal vasodilation, for beds 2 and 3. Without any upstream stenoses, perfusion pressures of the vascular bed is equal to aortic pressure ($P_2 = P_1 = P_{ao}$) and maximal normal flows ($Q_{m,n}$) are achieved with vasodilation of the coronary bed producing minimal bed resistance ($R_m$). When bed perfusion pressure falls, maximal branch and bed flows fall proportionally until flow ceases when perfusion pressure equals venous pressure. Flow demands less than maximal can still be achieved despite the fall in pressure so long as the bed does not become maximally vasodilated. Therefore, in Appendix Figure 1B, the area in each graph above the sloping minimal resistance line and below the horizontal proximal bed pressure line can be attained by varying vascular bed resistance.

Normal (non-stenotic) maximal bed flows are derived from the bed masses by the equations

$$Q_{2m,n} = qr,n \times M_2 \times CFR_n$$  \hspace{1cm} (1a), and

$$Q_{3m,n} = qr,n \times M_3 \times CFR_n$$  \hspace{1cm} (1b).

Minimal bed resistances are then found by the linear relations
\[ R_{2m} = \frac{(P_{ao} - P_v)}{Q_{2m,n}} \quad \text{(2a)}, \]
\[ R_{3m} = \frac{(P_{ao} - P_v)}{Q_{3m,n}} \quad \text{(2b)}. \]

**Fluid Dynamics With Single Stenosis.** The pressure flow dynamics of single coronary artery stenoses are established and experimentally verified\(^{14-19}\). These studies have shown that for single isolated coronary constriction, the pressure loss across the stenoses \((\Delta P)\) is non-linearly related to the flow through the stenosis \((Q)\) according to a quadratic relation as follows:

\[ \Delta P = AQ + BQ^2 \quad \text{(3)}, \]

where \(A\) and \(B\) are coefficients, dependent on blood properties (density and viscosity), normal vessel size, and stenosis geometry\(^{14-19}\). We have previously shown that these coefficients and thus Equation 3 can be determined from coronary arteriograms using quantitative coronary arteriographic methods.

**Fluid Dynamics With Stenotic Branching Coronary Arteries.** In the case of stenotic parent and child vessels of a coronary branch, pressure distal to each stenosis drops with the flow across it. For any given flow through each stenotic branch, it’s distal pressure is described with Equations 3a-c as

\[ P_1 = P_{ao} - \Delta P_1 = P_{ao} - (A_1 Q_1 + B_1 Q_1^2) \quad \text{(4a)}, \]
\[ P_2 = P_1 - \Delta P_2 = P_1 - (A_2 Q_2 + B_2 Q_2^2) \quad \text{(4b), and} \]
\[ P_3 = P_2 - \Delta P_3 = P_2 - (A_3 Q_3 + B_3 Q_3^2) \quad \text{(4c)}. \]

There are however, several constraints on this system of flows through the branches to their distal beds. The volumetric flowrate through the parent of the branch must equal the flows through its child branches i.e,

\[ Q_1 = Q_2 + Q_3 \quad \text{(5)}. \]

When aortic pressure is specified, and the coefficients of stenosis pressure loss determined from angiography, the above 4 equations (4a-c and 5) present 6 unknowns i.e., the distal pressures \(P_1, P_2\) and \(P_3\) and the branch flows \(Q_1, Q_2\) and \(Q_3\). Two more independent relations among the pressures and flow are required to solve the problem.

The particular problem of interest here is to find the maximum flow through each branch for a given set of stenosis geometries, bed sizes, normal vessel size and blood properties. Essentially we want to calculate the maximum flows in each branch as the distal beds progressively dilate until their dilatory reserve
is exhausted and their bed resistance drops to its minimal value (Rm). The analysis requires making the hypothetical "test" assumption that demanded flow attain 50% of its maximum normal flow, whereby Q2 and Q3 would be specified as one-half of the maximum normal bed flow, then compute Q1 using Equation 5, and calculate the distal branch pressures according to Equations 4a-c. If hypothetical “test" flow were fluid dynamically possible, then the vascular bed resistance would have to reach some level of greater than and not less than the minimal vascular bed resistance defined by the predefined constraints or limits of the model. This question is answered by using the pressure-flow relations of the distal bed to solve for the necessary bed resistances i.e.,

\[ R_2 = \frac{(P_2 - P_v)}{Q_2}, \quad \text{where} \quad R_2 \geq R_{2m} \quad \text{(6a)} \]

\[ R_3 = \frac{(P_3 - P_v)}{Q_3}, \quad \text{where} \quad R_3 \geq R_{3m} \quad \text{(6b)} \]

If the resulting inequalities in Equations (6a-b) are true for the assumed “test" flows, then the tested flow demands are possible and additional higher demanded flows could be similarly tested iteratively until reaching minimum vascular bed resistance.

**Application Of The Fluid Dynamic Model To The Experimental Animal Study.** In each experiment 10-20 different combinations of stenoses were placed on the parent and a child branch after branch bifurcation. With each combination, angiograms were made to document the stenosis geometry and normal vessel size. Coronary flow, before and following release of a 15 second distal coronary occlusion, was measured in both stenotic branches to determine their resting and maximal flows. With two simultaneous flow measurements, the difference between the parent and measured child branch was taken to be the flow to the other (non-stenotic) branch and distal bed. Bed masses were determined by dividing the resting volumetric flow rate at the beginning of each experiment by the assumed normal perfusion (80ml/min/100g). The viscous and expansion loss coefficients (A and B) for each stenosis were determined from single plane angiography of the concentric stenosis by off line analysis using our validated quantitative coronary arteriography system (Phillips). Maximal flows through each branch were normalized by the initial (normal) maximum flow for each branch to yield a normalized coronary flow reserve (nCFR*) that was between 0 and 1. Normalized coronary flow reserve was predicted by a numerical model above assuming an aortic and venous pressure of 100 and 10mmHg respectively to avoid variation of CFR due to different pressure separately from stenosis geometry. Normal Coronary flow reserve was taken to be 5.0. For each
experiment event, the derived bed masses along with the angiographically derived stenosis coefficients was provided to the model as input. Model predicted maximal flow was derived by incrementally increasing bed flow demand from 0 to 5 times the resting normal flow (= 80ml/min/100g * bed mass * 5.0). The program derived the pressures distal to the child stenoses (proximal to the distal beds) and checked if they were possible according to the criteria described in Equations 6a and 6b. When the limiting bed resistance was reached in any bed, the demand bed flow was reduced by half of the programs flow increment and another iteration was started. The program continued to adjust distal flow demand until both beds were within 2% of the minimal bed resistance. The final program iteration results were then used for comparison with the experimentally measured values.

**Appendix Figure Legends**

Appendix Figure 1A. Fluid dynamic model of stenotic coronary artery branching.

Appendix Figure 1B. Pressure-flow characteristics of branching stenosis model.
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