# Immediate impact of coronary artery bypass graft surgery on regional myocardial perfusion: Results from the Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near-Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity

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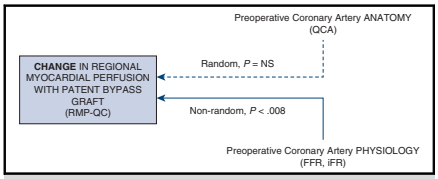
## ABSTRACT

**Objectives:** Coronary artery bypass grafting (CABG) is performed using anatomic guidance. Data connecting the physiologic significance of the coronary vessel stenosis to the acute physiologic response to grafting are lacking. The Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near-Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity study is the first to compare preintervention coronary physiology with the acute regional myocardial perfusion change (RMP-QC) at CABG in a per-graft analysis.

**Methods:** Non-emergent patients undergoing diagnostic catheterization suitable for multivessel CABG were enrolled. Synergy between Percutaneous Coronary Intervention with Taxus score, fractional flow reserve (FFR), instantaneous wave free ratio (iFR), and quantitative coronary angiography was documented in 75 epicardial coronary arteries, with 62 angiographically intermediate and 13 severe stenoses. At CABG, near-infrared fluorescence analysis quantified the relative change (post- vs pregrafting, termed RMP-QC) in the grafted vessel's perfusion territory. Scatter plots were constructed for RMP-QC versus quantitative coronary angiography and RMP-QC versus FFR/iFR. Exact quadrant randomization test for randomness was used.

**Results:** There was no relationship between RMP-QC and quantitative coronary angiography percent diameter stenosis, whether all study vessels were included ($P = .949$) or vessels with core-lab quantitative coronary angiography only ($P = .922$). A significant nonrandom association between RMP-QC and FFR ($P = .025$), as well as between RMP-QC and iFR ($P = .008$), was documented. These associations remained when excluding vessels with assigned FFR and iFR values ($P = .0092$ and $P = .0006$ for FFR and iFR, respectively).

**Conclusions:** The Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near-Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity study demonstrates there is no association between angiographic coronary stenosis severity and the acute perfusion change after grafting; there is an association between functional stenosis severity and absolute increase in regional myocardial perfusion after CABG. (JTCVS Open 2022;12:158-76)




**Anatomic stenosis severity did not predict perfusion response to grafting but FFR/iFR did.**

### CENTRAL MESSAGE

Critical stenoses aside, anatomic stenosis severity is not associated with the acute perfusion change after grafting; preoperative physiology is associated with acute perfusion change after grafting.

### PERSPECTIVE STATEMENT

CABG aims to provide a surfeit of blood at rest with reserve to meet perfusion demand. A better understanding of the physiologic responses to CABG is required if physiology is to be used to optimize CABG. The findings in PERSEUS, a first pilot study of its kind, provide support for further work which could ultimately lead to physiologic techniques to be incorporated into CABG operative strategy.

**Abbreviations and Acronyms**

CABG = coronary artery bypass grafting
FFR = fractional flow reserve
HSR = hyperemic stenosis resistance index
iFR = instantaneous wave free ratio
NIRF = near-infrared fluorescence angiography
PCI = percutaneous coronary intervention
PERSEUS = Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near-Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity
QCA = quantitative coronary angiography
RMP-QC = quantified change in regional myocardial perfusion
SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus

▶ Video clip is available online.

Anatomic coronary stenosis severity has guided graft placement since the early description of coronary artery bypass graft surgery (CABG).[1,2] Experimental data showing reduced reserve flow capacity in coronary arteries with artificially created stenoses ≥70% diameter stenosis further supported this anatomic criterion for CABG.[3] This approach has consistently yielded superior outcomes compared with percutaneous coronary intervention (PCI) in patients with complex coronary artery disease or diabetes.[4,5] In contrast, physiologic guidance of PCI with fractional flow reserve (FFR)-guided coronary intervention has been documented to preserve long-term clinical outcomes of coronary intervention with a substantial reduction in resource utilization compared with angiography-based decision making.[6,7]

Previous studies on physiology-guided CABG have focused on the influence on graft patency rates, yielding conflicting results and has therefore not been employed to guide CABG surgery.[8,9] Data on epicardial stenosis physiology and the influence of bypass grafting on myocardial perfusion may allow a better understanding of the physiological effects of coronary bypass grafting. However, although pre-PCI FFR or instantaneous wave-free ratio (iFR) were shown to identify coronary vessels that will exhibit an immediate improvement in coronary flow after PCI,[10] to date this has not been feasible during CABG.

Near-infrared fluorescence (NIRF) angiography is used in routine clinical care settings in multiple surgical specialties to document graft integrity and tissue perfusion.[11] Changes in regional myocardial fluorescence intensity correlate well with absolute myocardial perfusion changes measured by fluorescent microspheres.[12] NIRF thereby allows periprocedural quantification of myocardial perfusion during CABG surgery. We therefore sought to prospectively evaluate the relationship between preoperative coronary physiology in the cardiac catheterization laboratory using FFR and iFR, and the acute perfusion response to CABG evaluated using NIRF. No a priori assumptions were made about the similarities or otherwise of any potential relationship between FFR/iFR and postgrafting perfusion.

## METHODS

The First-in-Person Correlation Between Preoperative Coronary Physiology and the Acute Perfusion Response to Coronary Artery Bypass Grafting (PERSEUS) (www.ClinicalTrials.gov identifier No. NCT 02138305) was a prospective, nonrandomized pilot study in patients with stable angina or non–ST-segment elevation myocardial infarction referred for diagnostic cardiac catheterization. Patients underwent routine diagnostic cardiac catheterization and were enrolled when a decision to recommend CABG had provisionally been made.

Inclusion criteria were age >21 years, isolated CABG as the preferred revascularization strategy, and no obvious contraindications for CABG based on the coronary angiogram or comorbidities. Exclusion criteria were prior CABG surgery, left ventricular ejection fraction <40%, emergency status or cardiogenic shock, history of active malignant disease, or

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the need for concomitant valvular surgery or other cardiac structural reconstructive surgery.

PERSEUS was approved by East Carolina University and Medical Center Institutional Review Board No. 13-001949; March 14, 2014. All patients provided written informed consent including using their information in this publication.

### Coronary Angiography and Invasive Coronary Physiology Studies

Once a provisional decision for surgical referral was made, all noncritical stenoses (visual assessment 40%-84%) in epicardial coronary arteries suitable for bypass grafting had FFR and iFR measured using standard techniques. Intracoronary nitrates (200 $\mu$g) were administered before coronary pressure-monitoring guidewire (Verrata Plus, Philips-Volcano) insertion. The guidewire sensor was placed $\geq$3 vessel diameters beyond the stenosis. Coronary pressure measurements during non-hyperemic conditions were used to measure iFR and during coronary hyperemia induced by intravenously infusing 140 $\mu$g/kg/min adenosine to calculate FFR. Pressure drift of more than $\pm$0.02 units after retraction of the wire to the vessel ostium prompted repeat measurement after renormalization.

Where feasible, a 0.014-inch dual pressure and Doppler sensor equipped guidewire (ComboWire XT, Philips-Volcano) was used to interrogate the vessel. Baseline flow velocity and pressure were recorded, followed by intravenous infusion of 140 $\mu$g/kg/min adenosine. Pressure drift of more than $\pm$0.02 units prompted repeat measurement. From these data, hyperemic stenosis resistance index (HSR) was calculated as the ratio of the pressure drop across the stenosis and distal coronary flow velocity at maximal hyperemia (Table E1). Vessels with stenoses too severe or unsafe for pressure sensor wire passage (n = 13, diameter stenosis $\geq$85%) were assigned values (FFR = 0.50; iFR = 0.59).[13]

### Angiography and Invasive Physiology Data Analyses

For vessels that underwent pressure wire interrogation, blinded quantitative coronary angiography (QCA) and Synergy Between Percutaneous Coronary Intervention With Taxus (SYNTAX) scoring of angiograms was performed at the Cardiovascular Research Foundation core laboratory. Blinded analysis of anonymized invasive hemodynamic data were performed at Imperial College, London, United Kingdom, to derive iFR, FFR, and flow data using a custom software package written in MatLab (MathWorks) with built-in wave-free period algorithm (Imperial College, London, United Kingdom licensed to Volcano Corp).

### CABG and NIRF

All patients were candidates for multivessel surgical revascularization based on SYNTAX and/or Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial criteria. Conventional on-pump support at moderate hypothermia using cold blood cardioplegic arrest was performed in a standard anatomy-guided manner (50% visual stenosis for left main stenosis grafting, 70% for other vessels). Surgeons were blinded to the preoperative coronary physiology results.

After creation of all grafts and a 10-minute reperfusion period, all accessible grafts had their anastomotic integrity checked using NIRF (Novadaq Luna, Novadaq Technologies).[11] While on partial cardiopulmonary bypass with normosystolic ejection and stable rhythm, defined as 1.25 to 1.5 L/min flow, normal sinus rhythm with a heart rate <90, and with the heart ejecting with the systolic blood pressure >100 mm Hg, 2 imaging sequences were obtained for each graft: first, with the graft closed using a soft-jawed bulldog clamp, and the second with the graft open at 2 to 3 minutes after unclamping. For each sequence, the fluorophobe indocyanine green was injected into the central venous catheter as a bolus; the 3 phases of arterial inflow, microvascular perfusion, and venous outflow were imaged by NIRF. The arterial inflow phase of the NIRF imaging was used, per routine clinical use, to confirm the anatomic integrity of the bypass grafts. Additionally, transit time flowmetry was encouraged and performed according to surgeon preference. We used the setting of partial cardiopulmonary bypass to facilitate NIRF imaging in target areas immediately after revascularization.

Blinded offline NIRF analysis of the video sequences acquired during CABG was performed to assess the arterial inflow phase for graft flow and integrity and the microvascular perfusion phase to determine the relative increase in perfusion after grafting, termed regional myocardial perfusion quantified change (RMP-QC). This was done using proprietary and patented software also used in the 2013 paper (Figures 1 and E1).[14,15] For each imaging sequence pair (with and without antegrade perfusion through the bypass graft), the software matches and normalizes the 2 fields of view and normalizes the fluorescence data to pregrafting intensity. Real-time analyses display any differences in fluorescence intensity in the regional myocardium as dynamic videos, where the software compares the quantified regional myocardial perfusion before and after grafting (see Figure E2 and Videos 1 and 2 for real-time display of image acquisition sequences). Finally, the relative post-CABG increase in regional perfusion is expressed by the ratio of regional myocardial perfusion with and without antegrade flow through the bypass graft, termed RMP-QC. RMP-QC values $\geq$1.10, meaning a 10% increase in fluorescence intensity in the perfusion territory of interest, are considered to reflect relevant increases in regional myocardial perfusion.[14] Definitions and calculations of cath lab and NIRF physiology indices are listed in Table E1.

### Statistical Analysis

The relationship between pre-CABG invasive physiology parameters and the change in perfusion assessed by RMP-QC was visualized using simple scatter plots for FFR/iFR and RMP-QC, using contemporary cutoffs for FFR ($\leq$0.80), iFR ($\leq$0.89), QCA ($\geq$70%) and RMP-QC ($\geq$1.10). The relationship between anatomic stenosis severity and acute change in perfusion was visualized by a RMP-QC versus QCA scatter plot. The exact quadrant randomization test, an extension of the quadrant count measure, was used to determine whether or not there was a nonrandom directional relationship between RMP-QC and QCA, FFR, and iFR, across the 4 respective quadrants. For a nonrandom distribution, cubic spline was used to determine if a linear relationship was present.

Descriptive data were analyzed on per-patient basis for clinical characteristics, and on per-graft basis for the rest of the calculations where each graft was treated as an independent observation. Normally distributed variables are expressed as means $\pm$ SD. Nonnormally distributed variables are expressed as median (quartile 1 [Q1]-quartile 3 [Q3]). Mann Whitney *U* test was used to compare continuous dependent variables with a skewed distribution. Analyses were performed using SAS version 9.4 (SAS Institute).

## RESULTS

### Patient Population

Figure 2 shows the consort diagram for the PERSEUS study. In total, 48 patients were consented. Seven patients became protocol exceptions: comorbidities and ejection fraction <40% at surgical evaluation (n = 2), additional noncoronary surgery performed (n = 2), and operation performed by nonstudy surgeons (n = 3). Thus, 41 patients underwent CABG with a total of 117 grafts placed, of which 81 epicardial coronary arteries with paired invasive physiology and NIRF imaging data. In 6 of these grafted vessels, image quality was inadequate for analysis (poor imaging quality or fluorescence saturation).

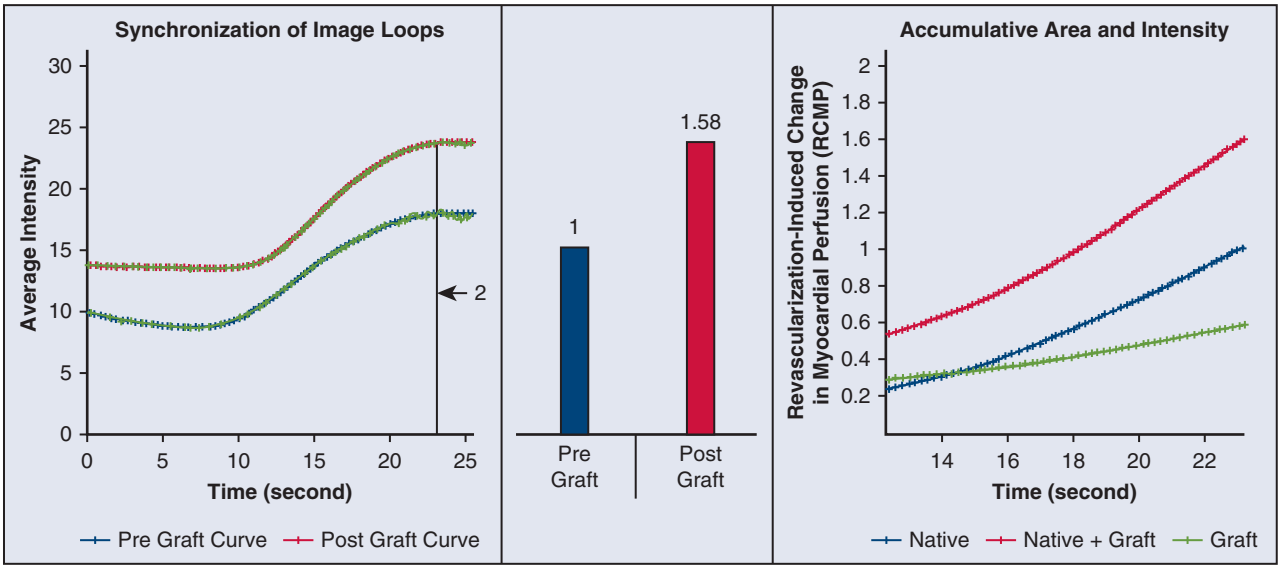
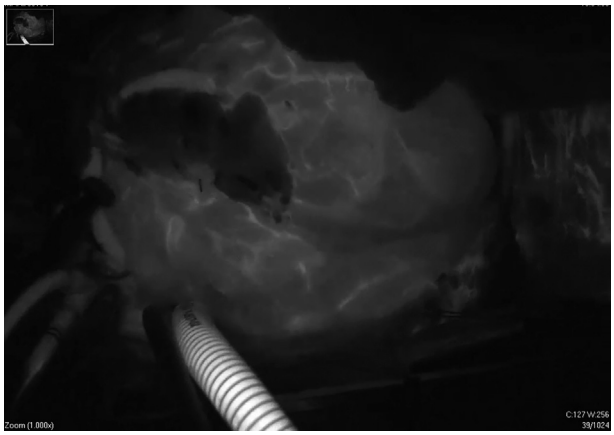



**FIGURE 1.** Regional myocardial perfusion with (*red*) and without (*blue*) antegrade graft flow. Near-infrared fluorescence angiography and quantified change in regional myocardial perfusion (*RMP-QC*) by proprietary software analysis, as a result of diagonal bypass grafting in patient 23. The panel is a still image from the dynamic video as displayed in the software. The software compares post- versus pregrafting regional myocardial perfusion by matching the fields of view and normalizing fluorescence intensities referenced to the color bar (0-255). In this case, pre-grafting is native left anterior descending (*LAD*) + diagonal graft occluded + left internal thoracic artery (*LITA*) occluded versus postgrafting native LAD + diagonal graft open + LITA occluded. The RMP-QC (anterior wall) was 1.58 versus pre-grafting (1.0), shown in the color bars (*center, top*) and the upper right graph (*red indicates combined perfusion*).



**VIDEO 1.** Near-infrared fluorescence angiography indocyanine green injection and circulation through the heart visualizing the native coronary vasculature and graft vasculature, on partial cardiopulmonary bypass at normosystolic ejection and normothermic resting conditions. This video is the pregraft video from Figure E2, Panel *B*. See this panel for landmark labeling. The anterior wall of the heart is displayed. In the video, the aorta is on the left, the apex of the heart is on the right. The left internal thoracic artery pedicle has a bulldog clamp, whereas the diagonal branch graft is open. Note the to-and-fro fluorescence in the left internal thoracic artery vessel; this is due to retrograde flow across the left internal thoracic artery-left anterior descending artery anastomosis when the proximal left internal mammary artery pedicle is clamped. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00349-7/fulltext.

The final study population consisted of 41 patients with paired NIRF and coronary physiology data available in 75 grafted vessels. Anatomical integrity of grafts was confirmed by NIRF angiography in all 75 study grafts, and by transit time flow probe assessment in 80% (60 out of 75). Clinical characteristics in the 41 patients are presented in Table 1. Table 2 and Table E2 depict the surgical procedure data.

### Angiography, Physiology, and NIRF Results

Table 3 presents the invasive angiography and physiology data. In total, 62 out of 75 (83%) of the vessels were evaluated with iFR and FFR, whereas 13 out of 75 (13%) were angiographically critically stenosed, precluding pressure wire study. These vessels were assigned FFR 0.50 and iFR 0.59 values. The mean SYNTAX score was 21 ± 9. In the 62 wire interrogated vessels, median diameter stenosis was 55% (Q1-Q3, 46%-64%), median FFR was 0.72 (Q1-Q3, 0.63-0.82), and median iFR was 0.79 (Q1-Q3, 0.66-0.85). In 38 out of 62 (58%) vessel a ComboXT wire could be passed to measure simultaneous pressure and flow at baseline and hyperemia. The median FFR in these vessels was 0.76 (Q1-Q3, 0.68-0.84) and median iFR 0.81 (Q1-Q3, 0.77-0.86).

### Influence of CABG on Regional Myocardial Perfusion

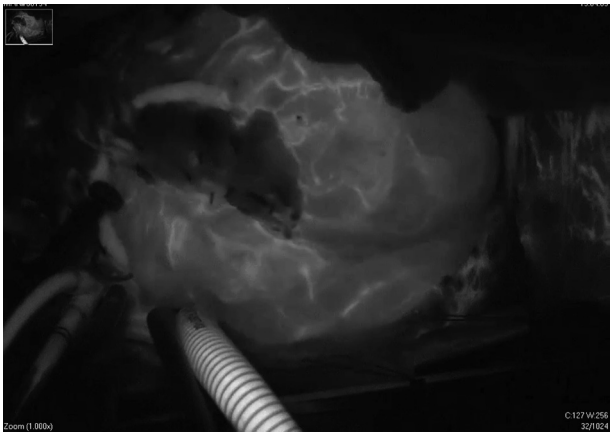
The median RMP-QC for all 75 vessels was 1.5 (Q1-Q3, 1.2-2.2). There was no difference between the RMP-QC for

the 62 pressure wire interrogated vessels (Table 3) compared with the 13 critically stenosed vessels that had assigned FFR and iFR values ($P = .896$). In total, 63 out of 75 (84%) myocardial territories perfused by a study vessel showed an RMP-QC $\geq$1.10 after bypass grafting, which represented 51 out of 62 (82%) of vessels with intermediate stenosis, and 12 out of 13 (92%) critically stenosed vessels.

### Relationship Between Pre-CABG Physiology and Improvement in RMP

Figure 3, *A-C*, show simple scatter plots of RMP-QC versus QCA percent diameter stenosis (Figure 3, *A*), FFR (Figure 3, *B*), and iFR (Figure 3, *C*). There was no relationship between RMP-QC and QCA percent diameter stenosis, whether all study vessels were included ($P = .949$) or vessel with core-lab QCA only ($P = .922$).

A statistically significant nonrandom association between RMP-QC and FFR ($P = .025$), as well as between RMP-QC and iFR ($P = .008$), was documented. These associations remained when excluding vessels with assigned FFR and iFR values ($P = .0092$, and $P = .0006$ for FFR and iFR, respectively). Cubic spline analysis showed no significant linear relationship for FFR or iFR (Figure E3, *A* and *B*).



**VIDEO 2.** Near-infrared fluorescence indocyanine green injection and circulation through the heart visualizing the native coronary vasculature and graft vasculature, on partial cardiopulmonary bypass at normosystolic ejection and normothermic resting conditions. This video is the postgraft video from Figure E2, Panel *B*. See this panel for landmark labeling. The anterior wall of the heart is displayed. In the video, the aorta is on the left, the apex of the heart is on the right. The left internal thoracic artery pedicle is open, and the diagonl graft is open. Note the indocyanine green fluorescence as it circulates through the heart and down the diagonal graft, and the delay in the filling of the left internal thoracic artery vessel with fluorescing dye. The proprietary software analysis demonstrated that both the diagonal graft (1.58) and the left internal thoracic artery graft (1.87) contributed to increased perfusion to the anterior wall as a result of bypass grafting. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00349-7/fulltext.

In PERSEUS, physiologic significance was reached in 58 out of 75 (77%) of vessels using FFR, and 65 out of 75 (87%) of vessels using iFR. For vessels with FFR $\leq$0.80, median RMP-QC was 1.5 (Q1-Q3, 1.3-2.2), and in these vessels, 86% exhibited a relevant increase (RMP-QC $\geq$1.10). In myocardial territories perfused by a vessel with normal FFR, median RMP-QC was similar at 1.7 (Q1-Q3, 1.2-2.1) ($P = .968$ vs FFR $\leq$0.80), and in these vessels, 76% exhibited a relevant increase in RMP-QC. For vessels with iFR $\leq$0.89 median RMP-QC was 1.6 (Q1-Q3, 1.3-2.2), and in these vessels, 86% exhibited a relevant increase in RMP-QC. In myocardial territories perfused by a vessel with normal iFR median RMP-QC was 1.2 (Q1-Q3, 1.0-1.7), and in these vessels, 70% exhibited a relevant increase in RMP-QC ($P = .063$ vs iFR $\leq$0.89).

Simultaneous pressure and flow velocity was measured in 38 vessels (Table E3). Figure E4 plots RMP-QC against HSR. Physiologic significance was reached in 39% (15 out of 38) of vessels using HSR. Median RMP-QC was 1.5 (Q1-Q3, 1.2-2.3) for vessels with an abnormal HSR $\geq$0.80 mm Hg/cm/s, with 87% of these vessels exhibiting a relevant increase in regional myocardial perfusion (RMP-QC $\geq$1.10). Median RMP-QC was 1.4 (Q1-Q3, 1.2-1.9) in myocardial territories perfused by a vessel with normal HSR <0.80 mm Hg/cm/s ($P = .535$ vs HSR $\geq$0.80 mm Hg/cm/s) in these vessels, 78% exhibited a relevant increase in regional myocardial perfusion (RMP-QC $\geq$1.10). Figures 4 and 5 summarize the results in a simple image and graphical abstract respectively, whereas Figure 1 displays a snapshot from the analysis software.

## DISCUSSION

PERSEUS is the first study to document that there is no association between preoperative anatomic epicardial coronary stenosis severity and the postprocedure improvement in regional myocardial perfusion after successful bypass grafting beyond the stenosis. In contrast, there is a complex association between the preoperative functional epicardial coronary stenosis severity and the immediate postprocedure improvement in regional myocardial perfusion after grafting. Because the aims of CABG are to increase myocardial perfusion to the greatest extent, and for this increase to be maintained for as long as possible, this link between preoperative and intraoperative physiology in CABG is novel promising new data.

### Increase in Myocardial Perfusion After CABG

The NIRF technology images the fluorescence intensity in blood traversing the epicardial coronary circulation after an intravenous bolus of indocyanine green. An increase in fluorescence intensity after grafting is a direct indicator of greater delivery of the fluorophobe to the myocardial territory of interest. PERSEUS documents that the change

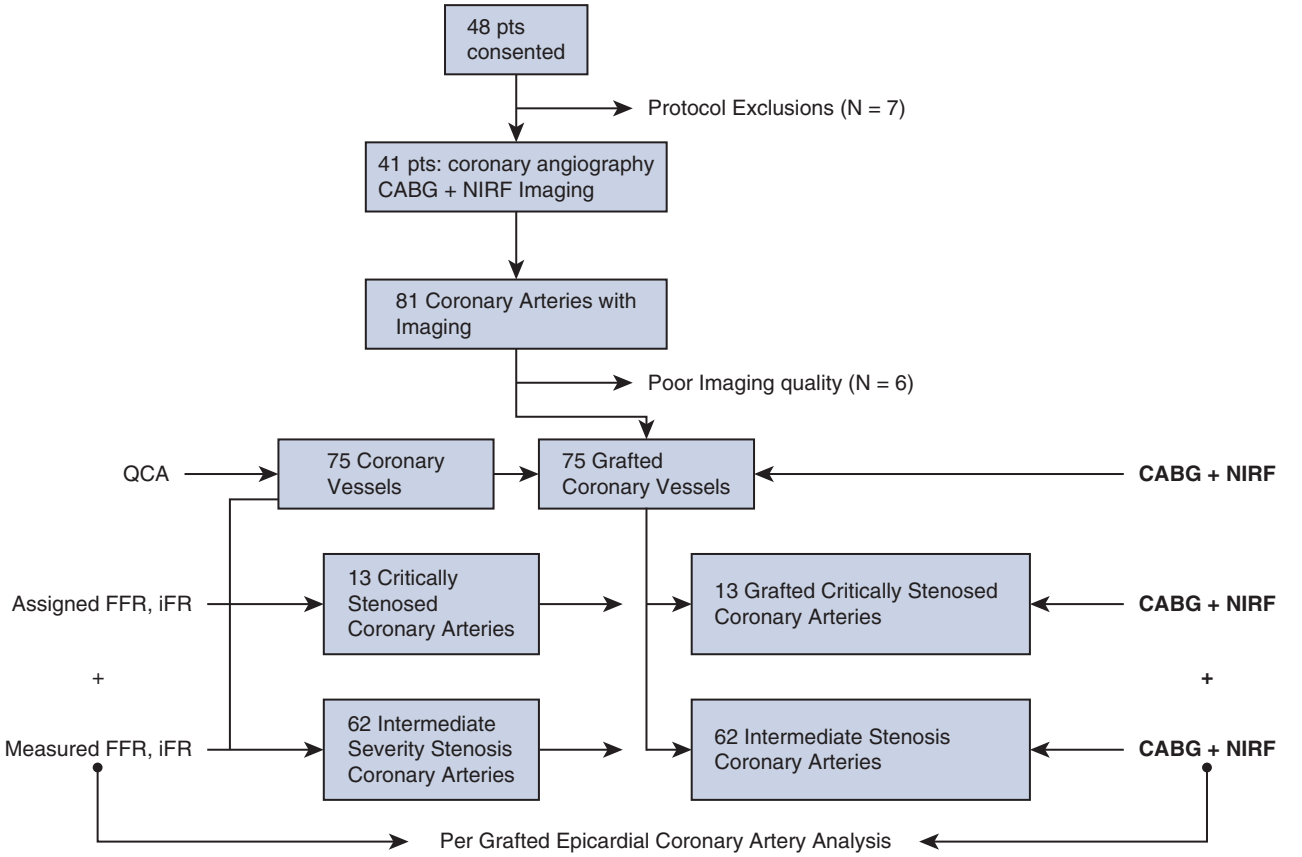



**FIGURE 2.** Study consort diagram for the Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near-Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity. *CABG*, Coronary artery bypass grafting; *QCA*, quantified coronary angiography; *NIRF*, near-infrared fluorescence imaging; *QCA*, quantitative coronary angiography; *FFR*, fractional flow reserve; *iFR*, instantaneous wave-freeratio.

in regional myocardial perfusion from pre- to postgrafting under nonvasodilated conditions is related to the functional stenosis severity documented by iFR and FFR, and not to the quantitative anatomical stenosis severity. These findings mirror those in the setting of pre- and post-percutaneous coronary intervention, where physiological severity and not anatomical severity drives stenosis relevance and identifies stenoses expected to benefit most from alleviation.

These findings in PERSEUS occurred in nonvasodilated conditions. Focus usually goes toward changes in maximal flow after alleviation of epicardial stenosis, but similar findings regarding resting flow have applied to the setting of PCI, where an increase in (diastolic) resting flow post-PCI has been documented to be related to the extent of physiological stenosis severity pre-PCI.[16,17] In these studies, the change in resting flow after alleviation of the stenosis is mirrored by a much larger change in hyperemic coronary flow. Finally, the FFR/iFR thresholds are based on noninvasive stress tests. The finding that some FFR/iFR-negative vessels exhibit an increase in RMP-QC after grafting is not unexpected but consistent with how accurately these indices relate to more sensitive coronary flow measurements before and after PCI.[16] Hence, the findings in PERSEUS with NIRF during CABG surgery document the same phenomenon previously documented using invasive flow measurements in the setting of PCI, strengthening the relevance of the findings. Moreover, although the setting of normotensive ejection with partial cardiopulmonary support is not an exact resting state, the observations in PERSEUS mirror those noted in the prior off pump observational study where hearts were in an exact normal and stable resting state[14] before, during, and after the imaging sequences, further strengthening the robustness of our findings.

### Relationship to FFR-Guided CABG

The objective of PERSEUS was different from prior studies of FFR guided CABG. PERSEUS was designed to better understand the CABG procedure in terms of physiology. In these FFR-guided studies, the preoperative FFR/iFR data were used to select epicardial coronary arteries for bypass, and the outcomes focused on reduction in graft occlusion. In Botman's study[8] of 164 patients, bypasses to

**TABLE 1. Patient demographic and clinical characteristics**

| Characteristic | Result |
|---|---|
| Demographic (n = 41) | |
| Mean age (y) | 59 ± 10 |
| Male gender (%) | 29 (71) |
| Race | |
| Caucasian | 30 (73) |
| African American | 10 (24) |
| Other | 1 (2) |
| Weight (kg) | 91 ± 19 |
| Risk factor | |
| Smoker | |
| Never | 9 (22) |
| Former | 20 (49) |
| Current | 12 (29) |
| Diabetes | 26 (63) |
| Diet controlled | 4 (10) |
| Tablet controlled | 11 (27) |
| Insulin treated | 11 (27) |
| Hypertension (%) | 40 (98) |
| Hyperlipidemia (%) | 39 (95) |
| Family history of coronary artery disease (%) | 9 (22) |
| Previous myocardial infarction (%) | 27 (66) |
| Previous stroke (%) | 7 (17) |
| Prior percutaneous coronary intervention (%) | 17 (41) |
| Peripheral vascular disease (%) | 6 (15) |
| Dialysis dependent renal failure (%) | 2 (5) |
| Presentation | |
| Stable angina (%) | 5 (12) |
| Unstable angina (%) | 24 (59) |
| Non-ST elevation myocardial infarction (%) | 12 (29) |
| Angina classification | |
| I | 0 |
| II | 4 (10) |
| III | 20 (49) |
| IV | 17 (41) |
| Left ventricular ejection fraction (%) | 57 ± 7 |

Values presented as n (%) or mean ± SD. Some totals/subtotals percentages may not add up exactly due to rounding.

**TABLE 2. Cardiac surgical data**

| Data point | Result |
|---|---|
| Total no. of bypass grafts in 41 patients | 117 |
| Mean graft/patient | 2.9 ± 0.7 |
| Bypass time (min) | 129 (100-159) |
| Crossclamp time (min) | 82 (70-104) |
| Overall graft type | |
| Arterial (n = 117) | 41 (35) |
| Venous (n = 117) | 76 (65) |
| 75 vessels with NIRF imaging and physiology data | |
| Arterial grafts | 36 (48) |
| Venous grafts | 39 (52) |

Values are presented as n, n (%), mean ± SD, median (quartile 1-quartile 3). *NIRF*, Near-infrared fluorescence angiography.

functionally insignificant vessels were more likely to be occluded than to functionally significant vessels (21.4% vs 8.9%) with no adverse clinical outcomes. Despite these initial encouraging findings, most subsequent studies have failed to show a significant influence of preoperative FFR use on graft patency.[8,9,18] A propensity score matched retrospective 6-year follow up of patients with ≥1 vessel with FFR >0.80 showed the FFR-guided CABG group had a lower rate of death and myocardial infarction than the angiography-guided group and no difference in angina severity.[18] The 100-patient Fractional Flow Reserve Versus Angiography Randomization for Graft Optimization (FARGO) trial showed no difference in rates of graft failure or clinical outcomes but an apparent fall in FFR in the 24 vessels that had follow-up FFR.[9] More recently, the double blind prospective The Impact of Preoperative FFR on Arterial Bypass Graft Function (IMPAG) trial enrolled 67 patients, 199 coronary lesions, assessed visually and with FFR, all treated with arterial grafts.[19] An FFR ≤0.78 was associated with an anastomotic occlusion rate of 3% at 6 months, whereas diameter stenosis was not predictive of a nonfunctional anastomosis. In the single-blind, multicenter, randomized prospective Graft Patency After FFR-guided Versus Angiography-guided CABG (GRAFFITI) trial of angiographic versus FFR-guided graft placement in 172 patients using FFR ≤0.80 showed no difference in 1-year graft patency or clinical outcomes yet with fewer grafts used in the FFR-guided group.[20] Although Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 3 trial did not have a third arm of FFR-guided CABG, these results confirm the preference for the anatomy-guided strategy for CABG in surgical revascularization.[21] In aggregate, these conflicting trial results support the need to better understand the physiology of CABG. The PERSEUS study showed anatomic stenosis severity did not predict physiologic improvement in perfusion after grafting (Figure 3, *A*), whereas FFR/iFR did (Figure 3, *B* and *C*), but this is complex and reflected in the previous observations that 23% of widely patent grafts by angiography did not result in a physiologic improvement in perfusion. Further work is needed.

### Implications for CABG Strategies

An appropriate conduit, anatomically perfect, grafted to a flow limiting vessel should invariably increase myocardial perfusion. However, this study and our earlier study demonstrate that this is not always the case. This perfusion response behavior is likely due to the increased complexity of CABG physiology (Table E4). For example, after left internal thoracic artery grafting to a left anterior descending artery, the diagonal branch territory may receive significant flow via angiographically invisible collaterals, implying a diagonal graft may not be required.

**TABLE 3. Cardiac catheterization, coronary physiology, and intraoperative perfusion data**

| Data point | | Result |
|---|---|---|
| Core lab data: Angiography (n = 41 patients) | | |
| SYNTAX score | | 21 ± 9 |
| Interrogated vessels (n = 62) | | |
| LMS | | 1 (2) |
| LAD | | 29 (47) |
| Diagonal | | 6 (10) |
| LCX, includes ramus intermedius | | 17 (27) |
| RCA | | 9 (14) |
| Core lab data: QCA | | |
| Vessel and lesion characteristics | | |
| Reference vessel diameter (mm) | | 2.43 (2.10-2.81) |
| Minimal lumen diameter (mm) | | 1.12 (0.84-1.38) |
| Diameter stenosis (%) | | 55 (46-64) |
| Hemodynamic measurements | | |
| Baseline | | |
| Heart rate (bpm) | | 73 ± 11 |
| Mean aortic pressure (mm Hg) | | 95 ± 15 |
| Hyperemia | | |
| Heart rate (bpm) | | 82 ± 14 |
| Mean aortic pressure (mm Hg) | | 88 ± 17 |
| **Pressure wire data** | **Intermediate vessels (n = 62)** | **Severe vessels (n = 13)** |
| Mean distal coronary pressure/mean aortic pressure | 0.88 (0.82-0.92) | N/A |
| FFR | 0.72 (0.63-0.82) | 0.50* |
| iFR | 0.79 (0.66-0.85) | 0.59* |
| FFR (n = 75 vessels) | 0.69 (0.53-0.79) | |
| iFR (n = 75 vessels) | 0.77 (0.59-0.85) | |
| **Intraoperative NIRF RMP-QC data (n = 75 vessels)** | | |
| | **Intermediate vessels (n = 62)** | **Severe vessels (n = 13)** |
| | 1.5 (1.2-2.3) | 1.6 (1.3-1.9) |
| RMP-QC (n = 75 vessels) | 1.5 (1.2-2.2) | |

Values presented as n (%), mean ± SD, or median (quartile 1-quartile 3). *SYNTAX score*, Synergy Between Percutaneous Coronary Intervention with Taxus aggregate for score for all vessels/patient. *LMS*, left main stem; *LAD*, left anterior descending artery; *Diagonal*, main diagonal branch of LAD; *LCX*, left circumflex artery includes ramus intermediate artery; *RCA*, right coronary artery; *QCA*, quantified coronary angiography; *FFR*, fractional flow reserve; *iFR*, instantaneous wave-free ratio; *NIRF*, near-infrared fluorescence; *RMP-QC*, regional myocardial perfusion quantified change. *All 13 severe vessels had FFR/iFR values of 0.50/0.59 assigned.

Thus this intraoperative physiologic perfusion evaluation on a per-graft basis provides data to better understand surgical revascularization techniques and outcomes from a new perspective. This is also suggested by comparative coronary revascularization trials that suggest a contribution by physiologic factors may influence better clinical outcomes with CABG. For example, the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial follow-up data revealed that the superior clinical outcomes in patients with diabetes treated with CABG is independent of SYNTAX score.[22]

These PERSEUS findings suggest a reconsideration of the role of preoperative physiology data, and its connectivity to critically important intraoperative perfusion physiology, as potential avenues of continued investigation in improving the techniques, decision making, and outcomes with CABG. These improvements could augment the use of additional prognostically beneficial arterial grafts,[23-25] and reasonable incomplete revascularization strategies.[26] Finally, as PERSEUS demonstrates, there are multiple preprocedure and intraprocedure parallels that are physiology-based across both PCI and CABG, highlighting an important collaborative opportunity for both interventional

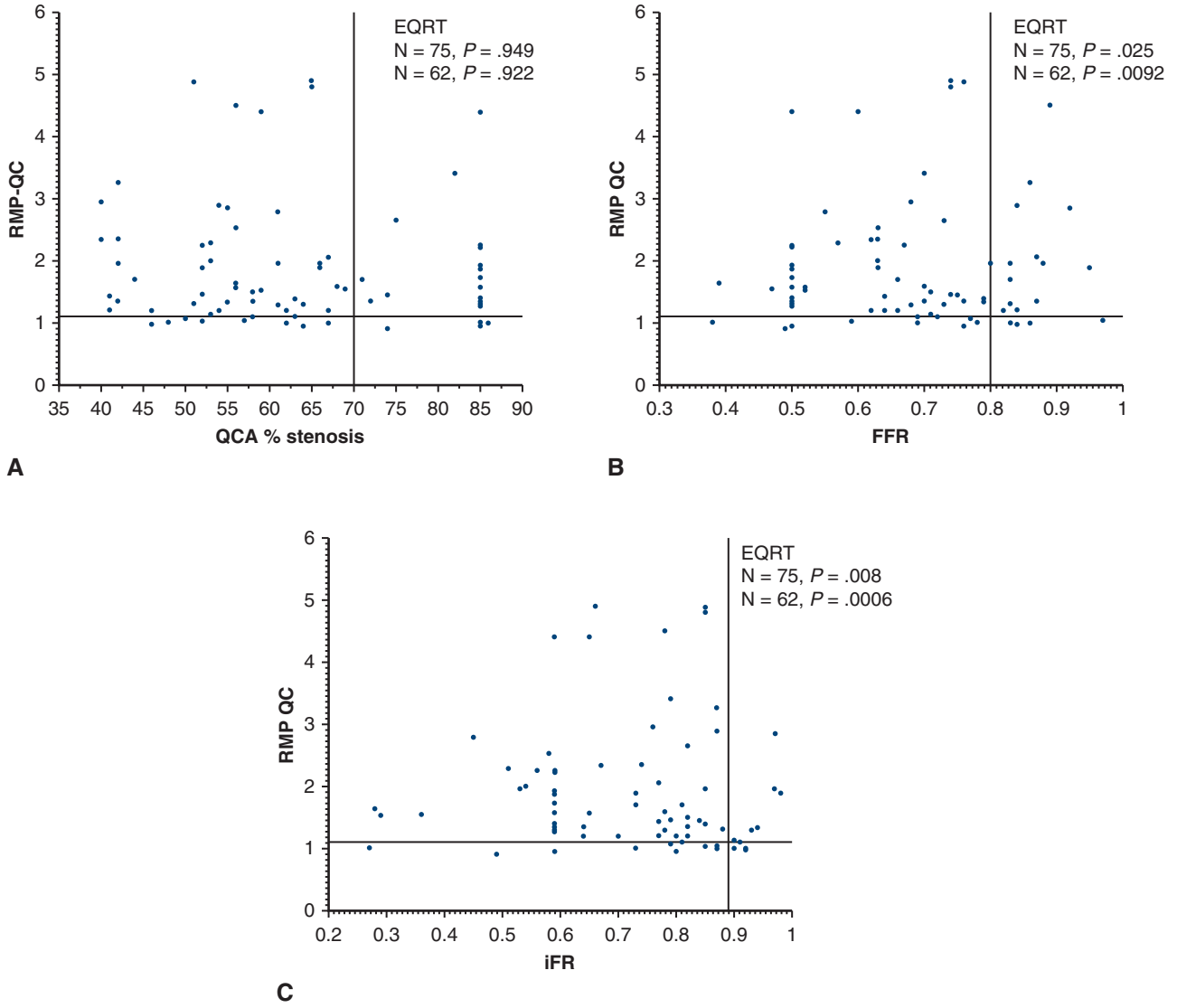



**FIGURE 3.** *A*, Scatter plot of individual paired quantitative coronary angiography (*QCA*) and regional myocardial perfusion quantified change (*RMP-QC*) observations. *B*, Scatter plot of individual paired fractional flow reserve (*FFR*) and RMP-QC observations. C, Scatter plot of individual paired instantaneous wave-free ratio (*iFR*), RMP-QC observations. *EQRT*, exact quadrant randomization test vertical/horizontal quadrant plot reference lines at QCA 70%, FFR 0.80, or iFR 0.89/RMP-QC 1.10.

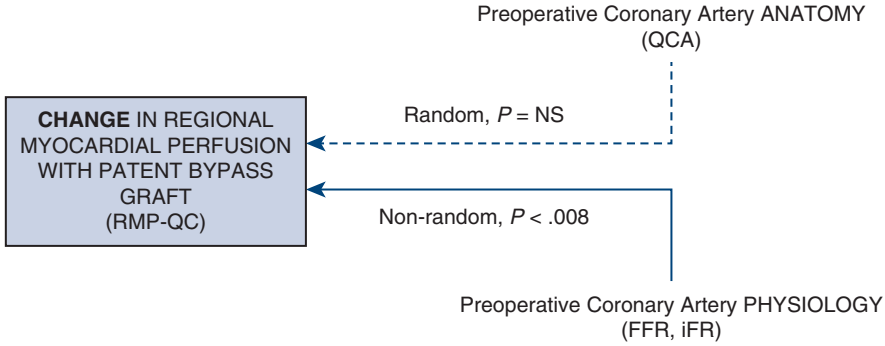



**FIGURE 4.** Anatomic stenosis severity did not predict perfusion response to grafting, but fractional flow reserve (*FFR*)/instantaneous wave free ratio (*iFR*) does. *QCA*, Qquantitative coronary angiography; *NS*, not significant; *RMP-QC*, Regional myocardial perfusion quantified change.

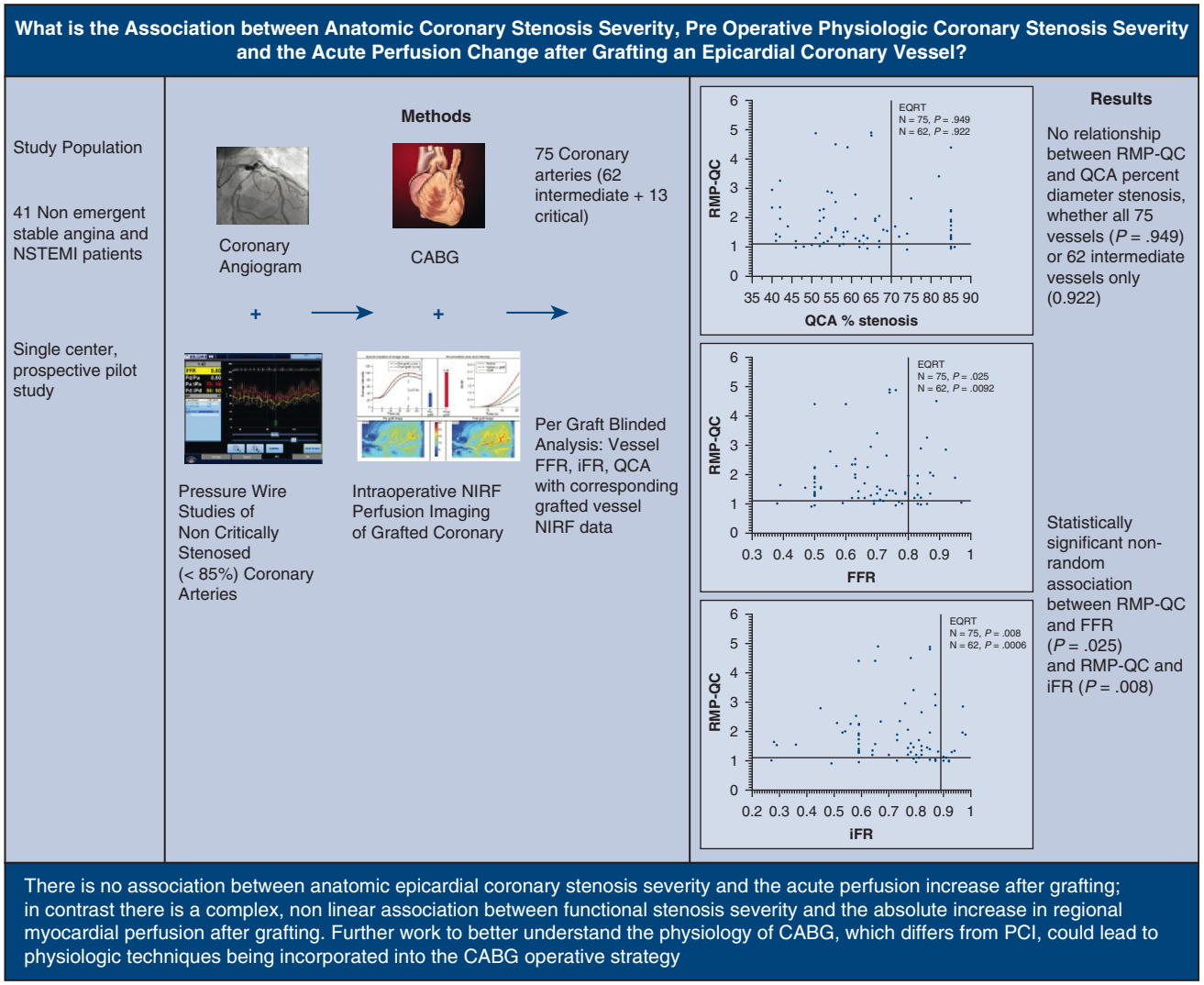



**FIGURE 5.** Immediate impact of coronary artery bypass graft surgery on regional myocardial perfusion: Results from the Collaborative Pilot Study to Determine the Correlation between Intra-Operative Observations Using SPY Near Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity. *NSTEMI*, Non–ST-segment elevation myocardial infarction; *CABG*, coronary artery bypass grafting; *FFR*, fractional flow reserve; *iFR*, instantaneous wave-free ratio; *QCA*, quantitative coronary angiography; *NIRF*, near-infrared fluorescence imaging; *RMP-QC*, regional myocardial perfusion quantified change; *PCI*, percutaneous coronary intervention.

strategies in addressing the same clinical condition of ischemic heart disease.

## Limitations

The sample size of PERSEUS is relatively small, but typical for a pilot study. Our data show most vessels with FFR/iFR $\leq$0.80/0.89 were associated with an increase in RMP-QC $\geq$10% over baseline but the relationship between FFR/iFR and RMP-QC is complex. Studies with intraoperative hyperemic NIRF data would have allowed a direct comparison with preoperative catheterization lab coronary physiology flow and pressure indices. Such work may yield a mathematically simpler relationship between preoperative physiology and intraoperative perfusion findings.

Our results are preliminary and further work is needed to verify. The RMP-QC threshold value of 1.10, corresponding to approximately 10% increase in fluorescence intensity and thus perfusion, was based on our prior work but is nevertheless arbitrary. Future studies may result in a change to this cutoff value. NIRF data were not available in all coronary artery territories, based on the surgeon's decision to perform NIRF imaging on a particular graft. Different perfusion territories could interact in the absence of visible collaterals on an angiogram. The final magnitude of increase in myocardial perfusion after CABG is likely to be greater several months after the surgery. Thus, the acute increase in perfusion after grafting may underestimate this. The study had few right coronary artery vessels and

therefore more data are needed to determine whether or not these observations extend to this coronary vessel's territory. Finally, microvascular disease influences RMP-QC differently from pre-CABG FFR or iFR, further modifying the per-graft RMP-QC relationship with pre-CABG physiology.

## CONCLUSIONS

The PERSEUS pilot study is the first to demonstrate that there is no association between angiographic coronary artery stenosis severity and acute perfusion change after grafting. There is a complex nonlinear association between functional stenosis severity and absolute increase in regional myocardial perfusion after CABG on a per-graft basis.

These findings endorse further investigations to better understand this per graft and global relationship between anatomy, preoperative, and intraoperative physiology to optimize coronary artery bypass grafting in the future.

### Conflict of Interest Statement

Drs Buch and Davies have received research grant funding from Philips-Volcano and paid for the quantitative coronary angiography analysis. Dr Davies holds patents relating to the iFR technology. Drs Buch, Cook, and Petraco have received speakers' honoraria from Philips-Volcano. Dr Buch is a medical advisor and holds stock in Perfusio Corp. Dr Ferguson is cofounder and chief medical office of Perfusio Corp. Dr van de Hoef has received speakers' honoraria from Philips-Volcano and Abbott. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The Collaborative Pilot Study to Determine the Correlation Between Intraoperative Observations Using Spy Near Infrared Imaging and Cardiac Catheterization Laboratory Physiological Assessment of Lesion Severity was an investigator-initiated study. The authors thank the staff of the cardiac catheterization laboratories and the cardiovascular operating rooms at Vidant Medical Center, Greenville, NC, for their help in the study. Dr Wiley L. Nifong, MD, of the Cardiothoracic Division, Greenville, NC, contributed to this study. Finally, the authors thank Linda Kindell for extracting and collating the data from the Society of Thoracic Surgeons database.

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**Key Words:** myocardial perfusion, coronary physiology, bypass grafting

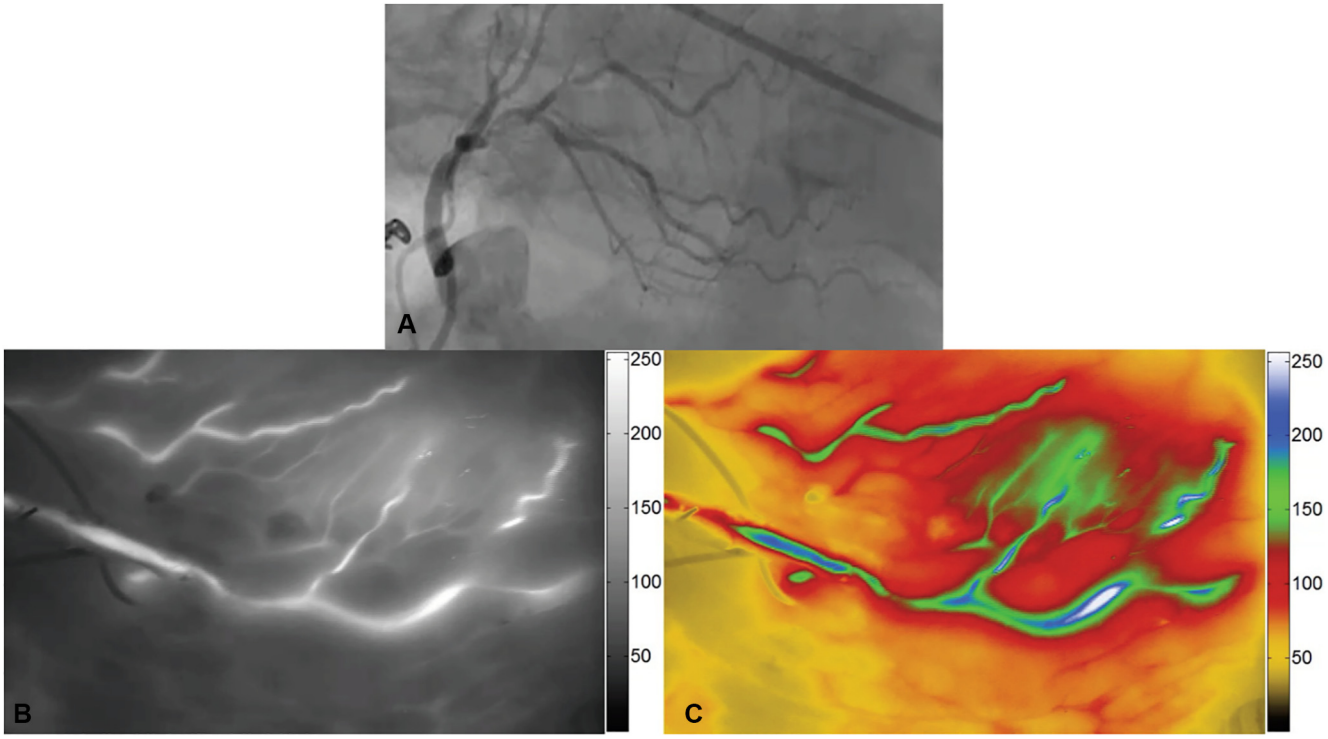
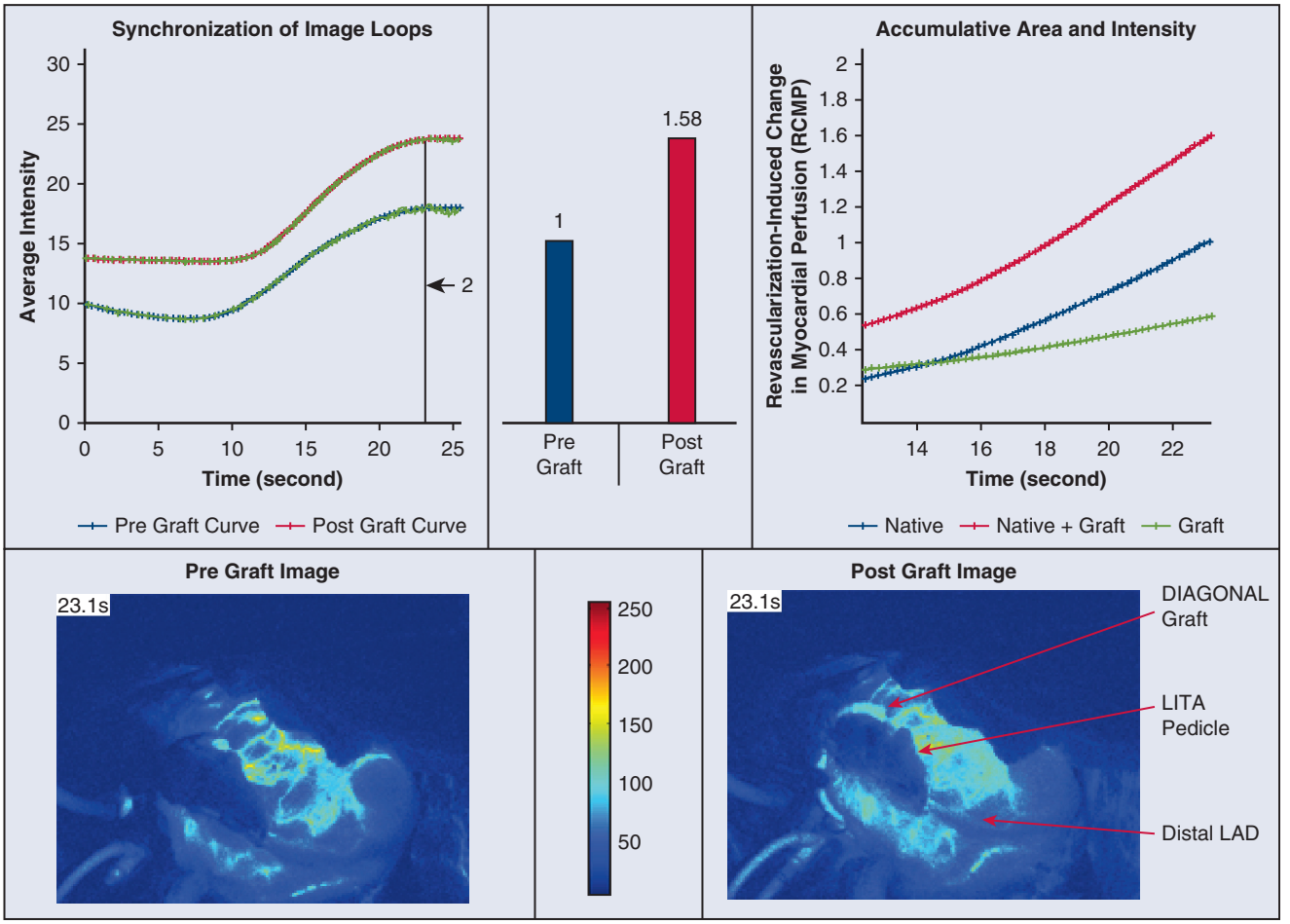
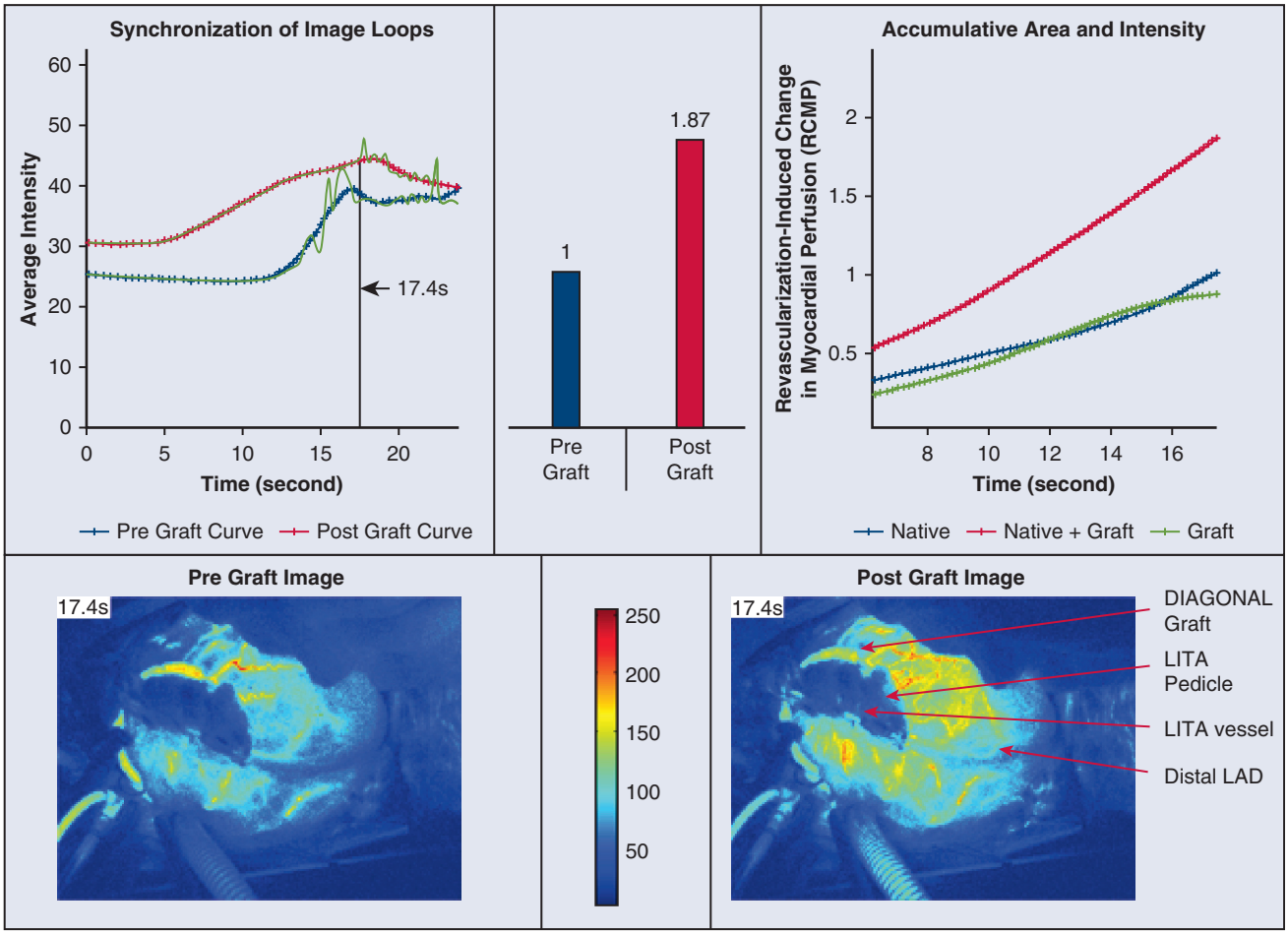



**FIGURE E1.** Corresponding still images of coronary angiogram, intraoperative image and offline analysis, A through C. A, Still image of the coronary angiogram associated with panels B and C. B, Still image from a video sequence a surgeon would see on the near-infrared fluorescence angiography console monitor while performing assessment of a graft during coronary artery bypass grafting (here *left* internal thoracic artery-*left* anterior descending artery). C, Offline proprietary software analysis view of panel B depicting a color-coded fluorescence and thus perfusion intensity map.




**A**

**FIGURE E2.** Regional myocardial perfusion quantified change (*RMP-QC*) in grafted epicardial coronary arteries. Panel A, Diagonal (*DIAG*) graft, and Panel B, *left* anterior descending (*LAD*) bypass grafting in patient 23. Each panel is a still image from the dynamic video as displayed in the software used for post operative offline perfusion analysis (See Videos 1 and 2). The software compares post- versus pregrafting regional myocardial perfusion by matching the fields of view and normalizing fluorescence intensities referenced to the color bar (0-255). The left anterior descending and diagonal are patent, stenosed, but not chronically occluded. By NIRF angiography during CABG both grafts are widely patent, and the subsequent off line analysis showed both grafts contributed to an increase in RMP-QC to the anterior wall. DIAG graft, Panel A: Pre-grafting (lower *left*) = *left* internal thoracic artery (LITA) occluded, DIAG graft occluded = native regional LAD + DIAG perfusion. Postgrafting (lower *right*) = DIAG graft open, LITA occluded. The RMP-QC (anterior wall) was 1.58 versus pre-grafting (1.0), shown in the color bars (*center, top*) and the upper *right* graph (*red indicates combined perfusion*). Perfusion in the images is matched, referenced to the color bar (0-255). LITA Graft, Panel B, Pre-grafting (*lower left*) = LITA graft occluded, DIAG graft open = native regional LAD perfusion + contribution from DIAG Graft. Postgrafting (*lower right*) = DIAG graft open, LITA graft open. The RMP-QC (anterior wall) is increased by 1.87 over perfusion with the DIAG graft alone (1.0), shown in the color bars (*center, top*) and the upper right graph (*red indicates combined perfusion*).




B

**FIGURE E2.** (*continued*).

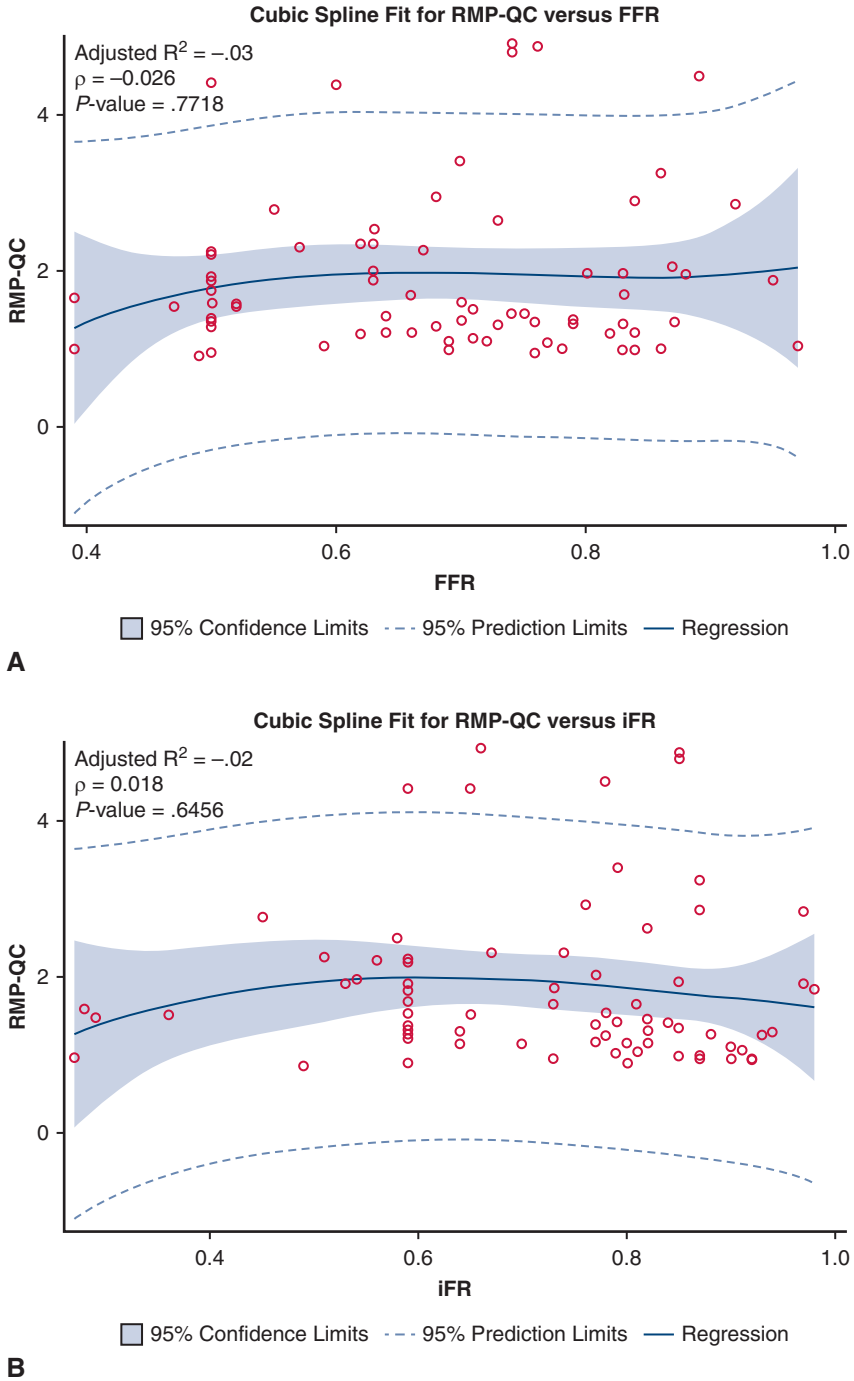



**FIGURE E3.** A, Cubic spline graphs generated by SAS (SAS Institute Inc) for regional myocardial perfusion quantified change (*RMP-QC*) versus fractional flow reserve (*FFR*). B, Cubic spline graphs generated by SAS for RMP-QC versus instantaneous wave-free ratio (*iFR*).

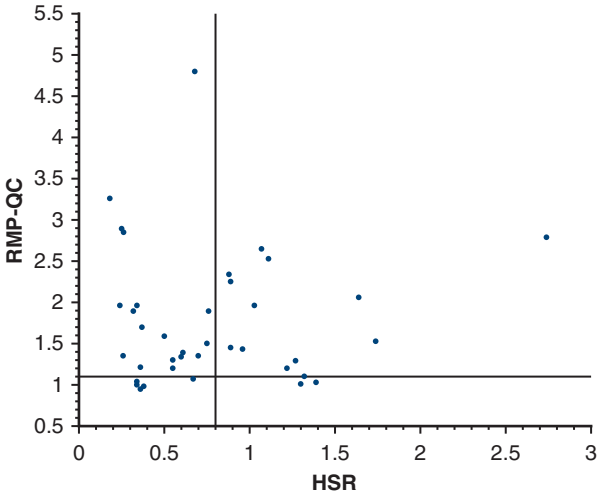



**FIGURE E4.** Scatter plot of individual paired regional myocardial perfusion quantified change (*RMP-QC*). Ratio of the pressure drop across the stenosis and distal average peak coronary flow velocity at maximal hyperemia (*HSR*) observations in 38 vessels interrogated with a ComboXT wire (Philips-Volcano) to obtain simultaneous pressure and coronary flow velocity measurements.

**TABLE E1. Additional definitions of cardiac catheterization laboratory and intraoperative imaging parameters and indices**

| | |
|---|---|
| b-APV or h-APV | Baseline (b) or hyperemic (h) average peak coronary flow velocity, cm/s |
| HSR (hyperemic stenosis resistance) | Mean mean aortic pressure-mean distal coronary pressure/h-APV, mm Hg cm/s |
| HMR (hyperemic microvascular resistance) | mean distal coronary pressure/h-APV, mm Hg/cm per s |
| NIRF (near-infrared fluorescence) angiography imaging | Injection of a fluorophobe excited by near infrared illumination to fluoresce as it passes as a bolus through the vasculature and tissues of interest; a surrogate for angiography and blood flow in each epicardial coronary artery and its corresponding graft and perfusion in the epicardial myocardium |
| Proprietary NIRF quantification software | Sequential NIRF imaging sequences (34 seconds) can be compared for fluorescence intensity at the pixel level in a matched field of view. Postgrafting (graft + vessel flow) vs Pregrafting (graft temporarily occluded + vessel flow) is relatively quantified as regional myocardial perfusion—quantitative comparison (RMP-QC) |
| RMP (regional myocardial perfusion) | Perfusion to epicardial myocardium in the distribution distal to the anastomosis of the grafted epicardial coronary artery |
| RMP-QC (regional myocardial perfusion-quantified comparison) | Relative change in RMP as a result of coronary artery bypass graft flow, added to the native vessel flow. Determined by sequential NIRF imaging and analysis using proprietary patented software, postgrafting vs pregrafting. An increase in fluorescence intensity = an increase in tissue perfusion. RMP-QC is post/pre ratio, range 1.00 to 12.00; a value $\geq$1.10 is the threshold for physiological significance |

**TABLE E2. Intraoperative transit time flow probe data and associated regional myocardial perfusion quantified change (RMP-QC) values**

| | Grafts (N = 60) | Arterial grafts (n = 29) | Venous grafts (n = 31) | *P* value |
|---|---|---|---|---|
| Flow (cm/s) | 45 (29-66.7, 37.7)<br>48 ± 24 | 48 (34-58, 24)<br>49 ± 21 | 39 (28.5-72.5, 44)<br>47 ± 26.7 | .596 |
| Pulsatility index | 1.7 (1.3-2.1, 0.8)<br>1.8 ± 1.2 | 1.7 (1.2-2.3, 1.1)<br>1.6 ± 0.9 | 1.6 (1.3-2.1, 0.8)<br>2.0 ± 1.4 | .653 |
| Diastolic phase | 72 (66-76,10)<br>70 ± 10.6 | 70 (66-76, 10)<br>71 ± 5.7 | 72 (66.5-76.5, 11)<br>69 ± 13.8 | .904 |
| RMP-QC data for grafts assessed with transit time flow probe<br>RMP-QC | 1.6 (1.2-2.3)<br>1.96 ± 1.04 | 1.5 (1.1-2.2)<br>1.8 ± 0.9 | 1.7 (1.3-2.8)<br>2.1 ± 1.2 | .222 |

Values are presented as median (quartile 1-quartile 3) and mean ± SD.

**TABLE E3. Simultaneous coronary flow and pressure and regional myocardial perfusion quantified change (RMP-QC) data for 38 vessels interrogated with Combo-XT wire (Philips-Volcano)**

| Coronary flow data (N = 38 vessels) | |
|---|---|
| Baseline average peak coronary flow velocity (cm/s) | 21 (16-30)<br>24 ± 15 |
| Hyperemic average peak coronary flow velocity (cm/s) | 29 (22-35)<br>32 ± 15 |
| Coronary flow reserve | 1.6 (1.2-1.9)<br>1.6 ± 0.6 |
| Hyperemic microvascular resistance (mm Hg/cm) per second | 2.01 (1.74-2.85)<br>2.77 ± 2.21 |
| Hyperemic stenosis resistance, mean aortic pressure–mean distal coronary pressure/hyperemic average coronary flow velocity (mm Hg cm/s) | 0.67 (0.36-1.1)<br>0.78 ± 0.53 |
| RMP-QC: lesions assessed by ComboXT wire | 1.5 (1.2-2.0)<br>1.77 ± 0.80 |

Values presented as median (quartile 1-quartile 3) and mean ± SD.

**TABLE E4. Potential differences between epicardial coronary artery effect on regional myocardial perfusion (RMP) (cath lab and pregrafting) and epicardial coronary artery + graft effect on RMP (postgrafting) units**

| | Coronary autoregulation | Abnormal coronary microvascular function | Left ventricle coronary blood flow timing | | Possible paracrine feedback effects | Collateral flow effects |
|---|---|---|---|---|---|---|
| | | | Systole | Diastole | | |
| Vessel → RMP | + | + | | + | + | + |
| Vessel + graft → RMP | + in vessel but not in graft | +/++ | + | + | + in both vessel and arterial grafts | ++ |

Possible coronary physiology principles that influence regional myocardial perfusion changes documented with near-infrared fluorescence imaging at coronary artery bypass grafting surgery. +, Condition is present; ++, condition may be present to greater extent.