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ORIGINAL RESEARCH

Prognostic Implications of Individual and Combinations of Resting and Hyperemic Coronary Pressure and Flow Parameters

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ABSTRACT

BACKGROUND Coronary pressure- and flow-derived parameters have prognostic value.

OBJECTIVES This study aims to investigate the individual and combined prognostic relevance of pressure and flow parameters reflecting resting and hyperemic conditions.

METHODS A total of 1,971 vessels deferred from revascularization after invasive pressure and flow assessment were included from the international multicenter registry. Abnormal resting pressure and flow were defined as distal coronary pressure/aortic pressure $\leq$0.92 and high resting flow (1/resting mean transit time $>$2.4 or resting average peak flow $>$22.7 cm/s), and abnormal hyperemic pressure and flow as fractional flow reserve $\leq$0.80 and low hyperemic flow (1/hyperemic mean transit time $<$2.2 or hyperemic average peak flow $<$25.0 cm/s), respectively. The clinical endpoint was target vessel failure (TVF), myocardial infarction (MI), or cardiac death at 5 years.

RESULTS The mean % diameter stenosis was 46.8% $\pm$ 16.5%. Abnormal pressure and flow were independent predictors of TVF and cardiac death/MI (all $P < 0.05$). The risk of 5-year TVF or MI/cardiac death increased proportionally with neither, either, and both abnormal resting pressure and flow, and abnormal hyperemic pressure and flow (all P for trend < 0.001). Abnormal resting pressure and flow were associated with a higher rate of TVF or MI/cardiac death in vessels with normal fractional flow reserve; this association was similar for abnormal hyperemic pressure and flow in vessels with normal resting distal coronary pressure/aortic pressure (all $P < 0.05$).

CONCLUSIONS Abnormal resting and hyperemic pressure and flow were independent prognostic predictors. The abnormal flow had an additive prognostic value for pressure in both resting and hyperemic conditions with complementary prognostic between resting and hyperemic parameters. (JACC: Asia 2023;3:865–877) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

APV = average peak flow velocity

FFR = fractional flow reserve

MI = myocardial infarction

Pd/Pa = distal coronary pressure/aortic pressure

Tmn = mean transit time

TVF = target vessel failure

Physiological assessment during invasive coronary angiography provides information on risk stratification and decision-making for revascularization.[1] Fractional flow reserve (FFR), measured as the ratio between distal and proximal coronary pressure during maximal hyperemia, has been a reference invasive physiologic index.[2,3] Recently, nonhyperemic pressure ratios that do not require hyperemia were introduced, and similar prognostic implications with FFR have been proposed.[4-7] Therefore, the current recommendation equally considers both resting and hyperemic pressure-derived physiologic indexes as a parameter for invasive physiologic guidance during coronary angiography.[8]

In addition to coronary pressure parameters, a flow-derived parameter, coronary flow reserve (CFR), is also associated with the risk of cardiovascular events.[9,10] Furthermore, CFR has an additive prognostic value over pressure-derived parameters.[11] As CFR represents the ratio between the hyperemic flow and resting flow, its measurement requires flow data or their surrogates in both resting and hyperemic conditions. Nonetheless, whether the flow assessment has incremental value to the pressure assessment under resting or hyperemic conditions and whether identifying resting pressure and flow parameters has a complementary role to hyperemic pressure and flow parameters are unclear in clinical practice. Therefore, we aimed to investigate the relative and additive prognostic implications of resting and hyperemic pressure and flow parameters.

METHODS

STUDY POPULATION. The study population was derived from the ILIAS registry (Inclusive Invasive physiological Assessment in Angina Syndromes; NCT04485234). This international, multicenter registry is a pooled analysis of coronary flow and pressure data and outcome data from Korea, the Netherlands, Japan, Spain, Denmark, Italy, and the United States. All data were collected following the protocol of each study in a prospective manner. The detailed profile of the registry has been previously described in detail.[12-14] Briefly, patients who underwent clinically indicated invasive physiologic assessments of coronary flow and pressure of at least one native coronary artery were enrolled. Individual patient data were gathered using standardized and anonymized spreadsheets and a fully compliant cloud-based clinical data platform (Castor EDC). Among 3,046 vessels from 2,322 patients in the ILIAS registry, a total of 1,971 vessels, in which percutaneous coronary intervention (PCI) was deferred after invasive physiologic assessment, were included after the exclusion of 828 vessels that underwent PCI, 172 vessels with no pressure or flow data, and 75 vessels with no outcome data (Supplemental Figure 1). The study protocol was approved by the institutional review board or ethics committee of each

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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participating center and was conducted according to the principles of the Declaration of Helsinki.

CORONARY ANGIOGRAPHY AND PHYSIOLOGIC ASSESSMENT. Coronary angiography was performed using standard techniques. After diagnostic coronary angiography, an invasive physiologic assessment was performed using a separate pressure- (PressureWire, Abbott Vascular) and Doppler flow velocity sensor-equipped coronary guidewire (FloWire, Philips-Volcano), a dual pressure- and Doppler flow velocity-equipped guidewire (ComboWire, Philips-Volcano), or a pressure-temperature sensor-equipped guidewire (PressureWire, Abbott Vascular). Intracoronary nitrate (100 or 200 μg) was administered before pressure and flow measurements. Hyperemia was induced by intravenous infusion of adenosine or adenosine triphosphate through either a peripheral or central route, or an intracoronary bolus injection of adenosine or nicorandil, depending on the local standards. CFR was measured using the thermodilution technique (52.5%) or the Doppler technique (47.5%). For the former, resting and hyperemic thermodilution curves were obtained using 3 injections of room temperature saline. The mean transit time (Tmn) was derived from each curve, and the inverse of resting Tmn and hyperemic Tmn were labelled as the resting and hyperemic flow, respectively. CFR was calculated as the resting Tmn divided by the hyperemic Tmn. For the latter, the resting and hyperemic average peak flow velocities (APVs) were measured. CFR was estimated as the hyperemic APV divided by the resting APV. For coronary pressure assessment, the resting proximal aortic pressure (Pa) and distal coronary pressure (Pd) were measured. During maximal hyperemia, the FFR was calculated as the ratio of the mean distal coronary pressure to the mean aortic pressure.

PATIENT FOLLOW-UP AND CLINICAL OUTCOMES. Outcome data were obtained during outpatient clinic visits or via telephone contact. The primary outcome was target vessel failure (TVF), which is a composite of cardiac death, target vessel myocardial infarction (MI), and clinically driven target vessel revascularization. The secondary outcome was a composite of cardiac death and target-vessel MI. All clinical outcomes were defined following the Academic Research Consortium.[15]

DEFINITIONS OF ABNORMAL CORONARY PRESSURE AND FLOW PARAMETERS. Abnormal pressure parameters were low resting Pd/Pa (≤0.92) and low FFR (≤0.80) based on previous publications.[3,4] Because the cut-off values for resting and hyperemic flow have not been established, abnormal flow parameters were defined using the optimal cut-off values of 1/Tmn or APV in predicting the primary outcome based on maximal log-rank statistics (Supplemental Figure 2).[16] Accordingly, abnormal flow parameters were high resting flow (ie, 1/resting Tmn >2.4 or resting APV >22.7 cm/s), and low hyperemic flow (ie, 1/hyperemic Tmn <2.2 or hyperemic APV <25.0 cm/s) (Supplemental Figure 3). A sensitivity analysis was performed with cut-off values corresponding to a CFR of 2.0 in defining high resting flow (ie, 1/resting Tmn >2.3 or resting APV >20.2 cm/s), and low hyperemic flow (ie, 1/hyperemic Tmn <3.1 or hyperemic APV <30.0 cm/s), and with optimal cut-off values for resting Pd/Pa and FFR to investigate the prognostic implications of abnormal flow parameters.

STATISTICAL ANALYSIS. Continuous variables are presented as the mean ± SD, and categorical variables as numbers (percentages). The analysis comprised three parts: First, the prognostic value of abnormal pressure and flow parameters was evaluated. Outcome analysis was performed on a per-vessel basis. The cumulative event rates were calculated using Kaplan-Meier censoring estimates. The Breslow test was used to compare survival curves between the groups. Marginal Cox proportional hazards regression was used to derive the HR (95% CI) to account for the interrogated vessels within the same subjects. Multivariable analysis was performed by accounting for clinical and physiologic characteristics. Second, the additive prognostic implications of abnormal flow parameters on pressure parameters were investigated. The trend of the estimated 5-year TVF rate was evaluated using the Jonckheere-Terpstra test according to neither, either, or both of abnormal pressure and flow parameters in each resting and hyperemic condition. Third, the complementary prognostic value between resting and hyperemic parameters was explored. The association of low resting Pd/Pa or high resting flow with clinical outcomes was assessed in vessels with normal FFR or hyperemic flow, and that of low FFR or low hyperemic flow was investigated in vessels with normal resting Pd/Pa or resting flow.

The information gain was used to estimate the importance of each pressure and flow parameter and calculated by subtracting the weighted entropies of individual branches divided by a given variable from the original entropy. The entropy was calculated as the sum of the product of the proportion of a given variable and its logarithmic value. A variable with a

TABLE 1 Baseline Characteristics (N = 1,505)

Age, y	62.8 ± 10.2
Male	1,058 (70.5)
Diabetes	376 (25.1)
Hypertension	855 (57.1)
Hypercholesterolemia	969 (64.6)
Acute coronary syndrome	175 (11.7)
Unstable angina	157 (10.5)
NSTEMI	18 (1.2)
Vessel (N = 1,971)	
Angiographic parameters	
% diameter stenosis	46.8 ± 16.5
Interrogated vessel	
LAD	1,060 (53.8)
LCX	474 (24.0)
RCA	437 (22.2)
Physiologic characteristics	
Resting Pd/Pa ≤0.92	415 (21.1)
FFR ≤0.80	331 (16.8)
High resting flow	381 (19.3)
Low hyperemic flow	208 (10.6)

Values are mean ± SD or n (%).

FFR = fractional flow reserve; LAD = left anterior descending artery; LCX = left circumflex artery; Pd/Pa = distal coronary pressure/aortic pressure; NSTEMI = non-ST-segment elevation myocardial infarction; RCA = right coronary artery.

higher information gain value was considered more important in the prediction of clinical outcomes. Information gain was presented as the mean and 95% CI derived from a bootstrapping method with 10,000 replicates.[17] Mediation analysis using the Cox proportional hazards model was performed as a sensitivity analysis for prognostic implications of abnormal flow parameters. All analyses were conducted using R language, version 4.2.0 (R Foundation for Statistical Computing).

RESULTS

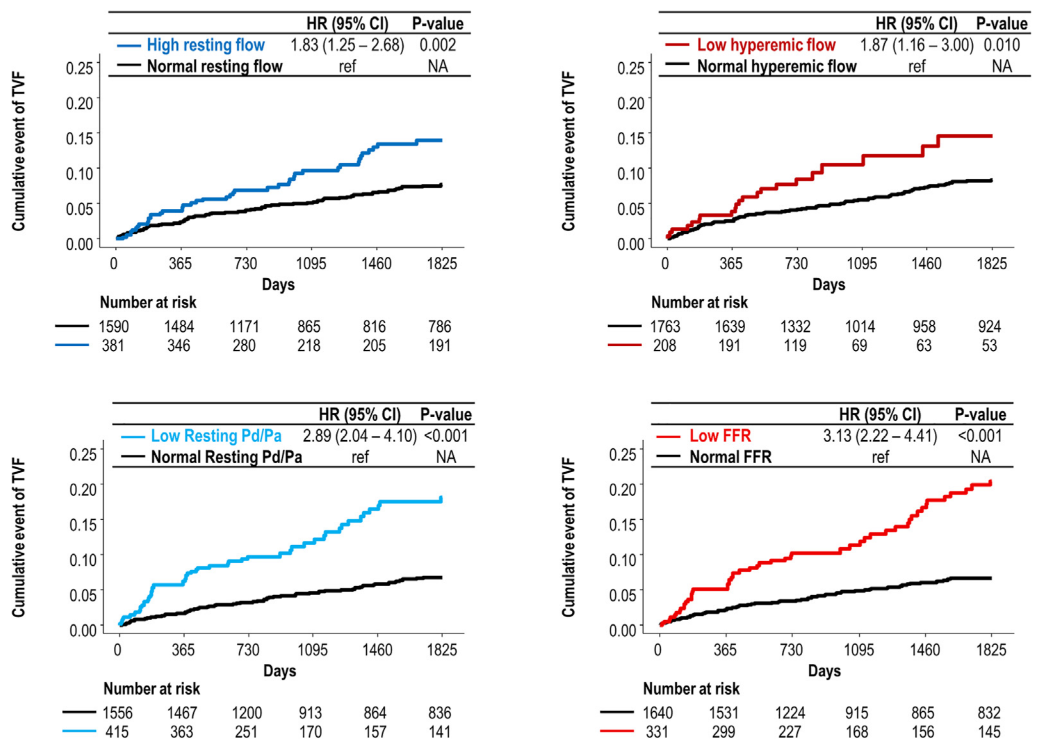
BASELINE CHARACTERISTICS. The baseline characteristics of 1,971 vessels from 1,505 patients are presented in Table 1. The mean age of the patients was 62.8 ± 10.2 years, and 70.5% were male. The mean % diameter stenosis was 46.8% ± 16.5%, and the mean resting Pd/Pa, and FFR were 0.96 ± 0.05 and 0.88 ± 0.08, respectively. The proportions of the vessels with a low resting Pd/Pa and low FFR were 21.1% and 16.8%, respectively, whereas the proportions of those with a high resting flow and low hyperemic flow were 19.3% and 10.6%, respectively.

PROGNOSTIC IMPLICATIONS OF ABNORMAL CORONARY PRESSURE AND FLOW PARAMETERS. During a median follow-up duration of 4.8 years, all abnormal pressure and flow parameters were associated with an increased risk of TVF: high resting flow (HR: 1.83; 95% CI: 1.25-2.68; $P = 0.002$), low resting Pd/Pa (HR: 2.89; 95% CI: 2.04-4.10; $P < 0.001$), low hyperemic flow (HR: 1.87; 95% CI: 1.16-3.00; $P = 0.010$), and low FFR (HR: 3.13; 95% CI: 2.22-4.41; $P < 0.001$) (Figure 1). These associations were similar in the analysis with cardiac death or target vessel MI (HR: 1.99; 95% CI: 1.16-3.42; $P = 0.013$ for high resting flow; HR: 3.28; 95% CI: 1.99-5.39; $P < 0.001$ for low resting Pd/Pa; HR: 2.20; 95% CI: 1.12-4.32; $P = 0.022$ for low hyperemic flow; and HR: 3.11; 95% CI: 1.91-5.07; $P < 0.001$ for low FFR) (Supplemental Figure 4). All abnormal pressure and flow parameters were associated with hard outcomes in the patient-level analysis that the vessel with the lowest FFR value was chosen for the target vessel of the patient (Supplemental Figure 5). The individual components of the TVF, according to the parameters, are shown in Supplemental Table 1, and the patient-level event rates of cardiac death at relevant time points are described in Supplemental Table 2. After adjusting for clinical data, physiologic data, and medication data, all abnormal pressure and flow parameters were still associated with a higher risk of clinical outcomes (Table 2, Supplemental Table 3).

INCREMENTAL OUTCOME TRENDS ACCORDING TO A COMBINED PRESSURE AND FLOW. Outcome trends according to abnormal pressure and flow parameters under resting or hyperemic conditions in Figure 2. In the order of neither, either, and both low resting Pd/Pa and high resting flow, the estimated event rate of the 5-year TVF proportionally increased (*P* for trend < 0.001) (Figure 2A). This finding was consistent with that of the hyperemic condition (*P* for trend < 0.001) (Figure 2B). These results were similar for the risk of cardiac death or target vessel MI (Figures 2C and 2D) after adjusting for clinical and physiologic data (Table 3). The predictability for the primary outcome was significantly increased when abnormal flow parameters were added to abnormal pressure parameters and vice versa (Supplemental Figure 6).

COMPLEMENTARY PROGNOSTIC VALUE BETWEEN RESTING AND HYPEREMIC PARAMETERS. Figure 3 depicts the prognostic value of abnormal resting pressure and flow parameters in vessels with a normal FFR. A higher clinical event rate was observed when the vessels had a high resting flow (HR: 2.08; 95% CI: 1.28-3.37; $P = 0.003$ for TVF; HR: 2.11; 95% CI: 1.04-4.27; $P = 0.039$ for MI or cardiac death) or low resting Pd/Pa (HR: 3.14; 95% CI: 1.90-5.19; $P < 0.001$

FIGURE 1 Prognostic Value of Abnormal Resting and Hyperemic Pressure and Flow



Cumulative events of target vessel failure (TVF) according to high resting flow, low hyperemic flow, low resting distal coronary pressure/aortic pressure (Pd/Pa), and low fractional flow reserve (FFR) are presented. NA = not available; ref = reference.

for TVF; HR: 3.49; 95% CI: 1.70-7.18; $P < 0.001$ for MI or cardiac death) in 1,640 vessels with a normal FFR (**Figure 3**). This association was similar in vessels with a normal hyperemic flow (Supplemental Figure 7). Similarly, **Figure 4** shows the prognostic impact of abnormal hyperemic pressure and flow parameters in vessels with a normal resting Pd/Pa. A higher event rate was related to a low hyperemic flow (HR: 2.13; 95% CI: 1.17-3.84; $P = 0.014$ for TVF; HR: 2.73; 95% CI: 1.16-6.33; $P = 0.021$ for MI or cardiac death) or low FFR (HR: 3.86; 95% CI: 2.35-6.34; $P < 0.001$ for TVF; HR: 3.50; 95% CI: 1.71-7.19; $P < 0.001$ for MI or cardiac death) in 1,556 vessels with a normal resting Pd/Pa. This relationship was consistent in vessels with a normal resting flow (Supplemental Figure 8).

When the information gain of abnormal pressure and flow parameters in the prediction of TVF was evaluated, low FFR was found to be the most important, followed by low resting Pd/Pa, high resting flow, and low hyperemic flow (**Figure 5A**). When vessels were classified by the number of 4 abnormal resting and hyperemic pressure and flow parameters, the risk of 5-year TVF or cardiac death/MI proportionally increased in the order of the presence of 0, 1, 2, and 3 out of high resting flow, low hyperemic flow, low resting Pd/Pa, and low FFR (**Figure 5B**, Supplemental Table 4).

In the sensitivity analysis, the prognostic value of high resting flow and low hyperemic flow was consistent after adjustment for continuous FFR and resting Pd/Pa (Supplemental Table 5). In the mediation analysis, abnormal flow parameters showed a direct prognostic impact on clinical outcomes not mediated by continuous FFR and resting Pd/Pa (Supplemental Figure 9). Overall prognostic implications of flow parameters were similar when different cut-off values (ie, corresponding to CFR of 2.0) were applied in defining high resting flow and low hyperemic flow (Supplemental Figures 10 to 12), or optimal cut-off values for FFR (≤0.78) and resting Pd/Pa (≤0.92) were applied (Supplemental Figures 13 and 14).

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TABLE 2 Relationship of Abnormal Resting and Hyperemic Pressure and Flow Parameters With Clinical Outcomes

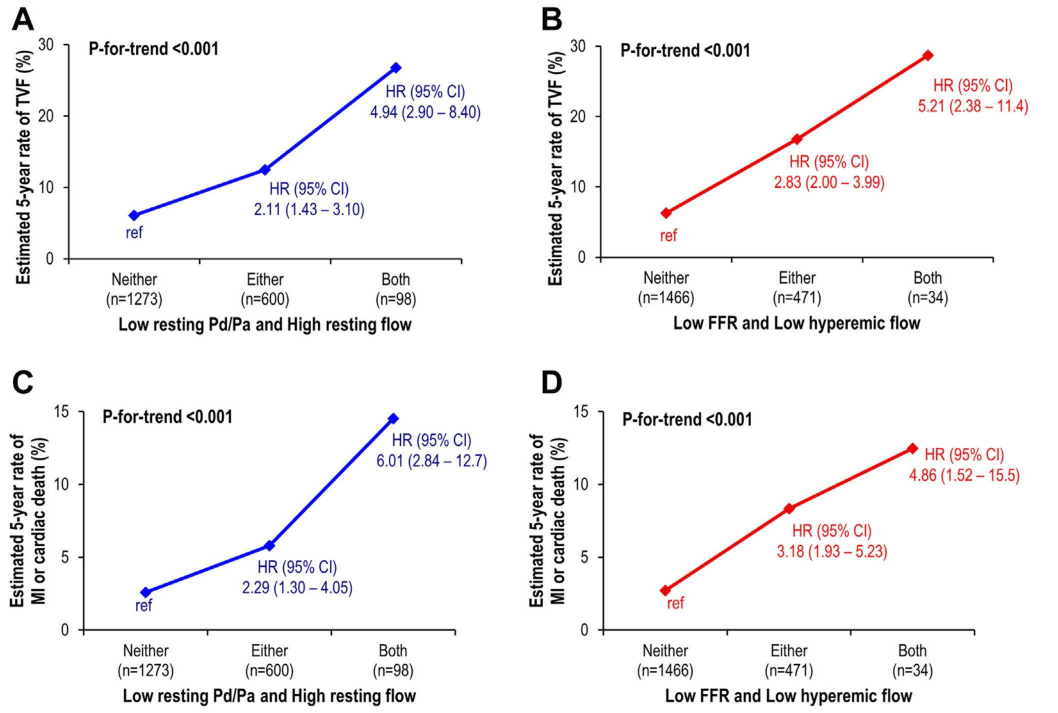
	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value	Adjusted HR[b] (95% CI)	*P* Value	Adjusted HR[c] (95% CI)	*P* Value
TVF								
Low resting Pd/Pa	2.89 (2.04-4.10)	<0.001	2.86 (1.93-4.23)	<0.001	1.91 (1.16-3.15)	0.011	–	–
High resting flow	1.83 (1.25-2.68)	0.002	1.83 (1.25-2.68)	0.002	1.94 (1.30-2.90)	0.001	–	–
Low FFR	3.13 (2.22-4.41)	<0.001	3.07 (2.13-4.43)	<0.001	–	–	2.17 (1.36-3.46)	0.001
Low hyperemic flow	1.87 (1.16-3.00)	0.010	1.68 (1.03-2.73)	0.038	–	–	1.90 (1.14-3.17)	0.013
MI or cardiac death								
Low resting Pd/Pa	3.28 (1.99-5.39)	<0.001	3.49 (2.02-6.04)	<0.001	2.39 (1.15-4.95)	0.019	–	–
High resting flow	1.99 (1.16-3.42)	0.013	2.00 (1.18-3.41)	0.010	2.19 (1.25-3.83)	0.006	–	–
Low FFR	3.11 (1.91-5.07)	<0.001	3.29 (2.00-5.39)	<0.001	–	–	2.06 (1.06-3.99)	0.033
Low hyperemic flow	2.20 (1.12-4.32)	0.022	1.86 (0.92-3.76)	0.084	–	–	2.19 (1.05-4.57)	0.037

[a]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, and target vessel. [b]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, target vessel, low FFR, and low hyperemic flow. [c]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, target vessel, low resting Pd/Pa, and high resting flow.
MI = myocardial infarction; TVF = target vessel failure; other abbreviations as in Table 1.

DISCUSSION

This study aimed to investigate the prognostic implications of individual and combined coronary resting and hyperemic pressure and flow parameters. The main findings are as follows. 1) High resting flow, low resting Pd/Pa, low hyperemic flow, and low FFR were independent prognostic indicators of TVF or MI/cardiac death. 2) The event rate of TVF or MI/cardiac death proportionally increased according to the

FIGURE 2 Incremental Outcome Trend According to Abnormal Pressure and Flow Parameters



The trends of the estimated 5-year rate of TVF according to (A) low resting Pd/Pa and high resting flow and (B) low FFR and low hyperemic flow are shown. The estimated 5-year rate of hard outcomes according to (C) low resting Pd/Pa and high resting flow and (D) low FFR and low hyperemic flow are presented. MI = myocardial infarction; other abbreviations as in Figure 1.

TABLE 3 Prognostic Implications of Abnormal Pressure and Flow Parameters in Resting and Hyperemic Conditions

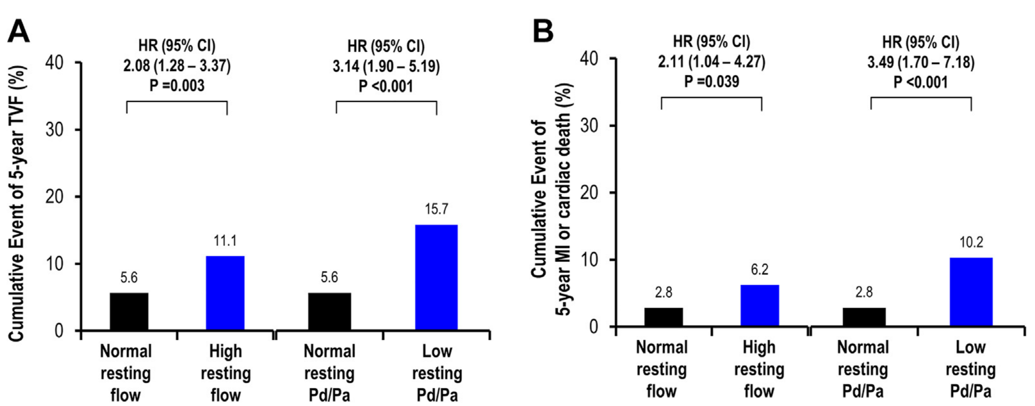
	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value	Adjusted HR[b] (95% CI)	*P* Value	Adjusted HR[c] (95% CI)	*P* Value
TVF								
Low resting Pd/Pa and high resting flow								
Neither	ref	NA	ref	NA	ref	NA	ref	NA
Either	2.11 (1.43-3.10)	<0.001	2.07 (1.40-3.07)	<0.001	1.70 (1.09-2.65)	0.019	–	–
Both	4.94 (2.90-8.40)	<0.001	4.90 (2.73-8.77)	<0.001	3.79 (1.95-7.36)	<0.001	–	–
Low FFR and low hyperemic flow								
Neither	ref	NA	ref	NA	ref	NA	ref	NA
Either	2.83 (2.00-3.99)	<0.001	2.69 (1.87-3.86)	<0.001	–	–	2.20 (1.46-3.33)	<0.001
Both	5.21 (2.38-11.4)	<0.001	4.45 (1.95-10.2)	<0.001	–	–	3.80 (1.55-9.31)	0.004
MI or cardiac death								
Low resting Pd/Pa and high resting flow								
Neither	ref	NA	ref	NA	ref	NA	ref	NA
Either	2.29 (1.30-4.05)	0.004	2.41 (1.36-4.25)	0.002	2.02 (1.08-3.77)	0.027	–	–
Both	6.01 (2.84 - 12.7)	<0.001	6.09 (2.70-13.7)	<0.001	4.94 (1.92-12.8)	<0.001	–	–
Low FFR and low hyperemic flow								
Neither	ref	NA	ref	NA	ref	NA	ref	NA
Either	3.18 (1.93-5.23)	<0.001	3.08 (1.85-5.11)	<0.001	–	–	2.38 (1.30-4.36)	0.005
Both	4.86 (1.52-15.5)	0.008	4.42 (1.30-15.0)	0.017	–	–	3.57 (0.97-13.1)	0.056

[a]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, and target vessel. [b]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, target vessel, low FFR, and low hyperemic flow. [c]Adjusted for age, sex, diabetes mellitus, hypertension, dyslipidemia, clinical diagnosis, target vessel, low resting Pd/Pa, and high resting flow.
NA = not available; ref = reference; other abbreviations as in Tables 1 and 2.

presence of neither, either, or both of abnormal pressure and flow parameters at each resting and hyperemic condition. 3) Abnormal resting parameters were associated with a higher rate of TVF or MI/cardiac death in vessels with normal hyperemic parameters and vice versa (Central Illustration).

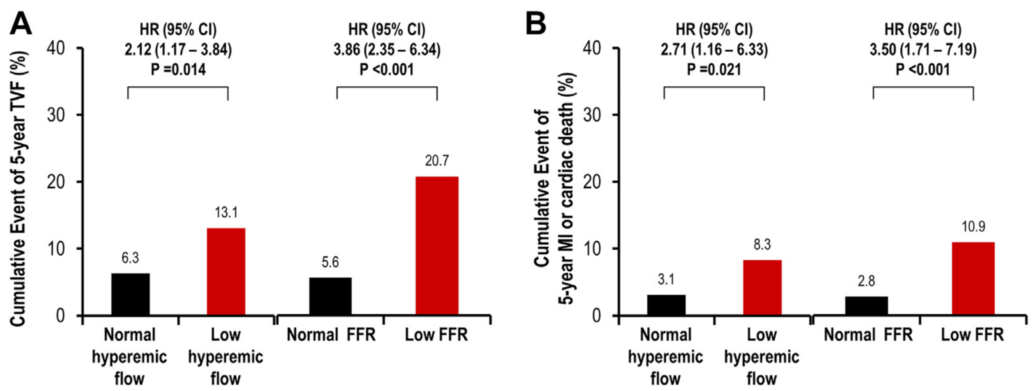
PROGNOSTIC VALUE OF RESTING AND HYPEREMIC CORONARY FLOW AND PRESSURE. Myocardial ischemia is one of the most significant prognostic factors in patients with coronary artery disease.[18,19] Direct blood flow measurement can determine the presence of myocardial ischemia, and the pressure-

FIGURE 3 Prognostic Value of Abnormal Resting Parameters in Normal FFR



In 1,640 vessels with normal FFR, the risks of (A) TVF or (B) hard outcomes according to high resting flow and low resting Pd/Pa are presented. Abbreviations as in Figures 1 and 2.

FIGURE 4 **Prognostic Value of Abnormal Hyperemic Parameters in Normal Resting Pd/Pa**

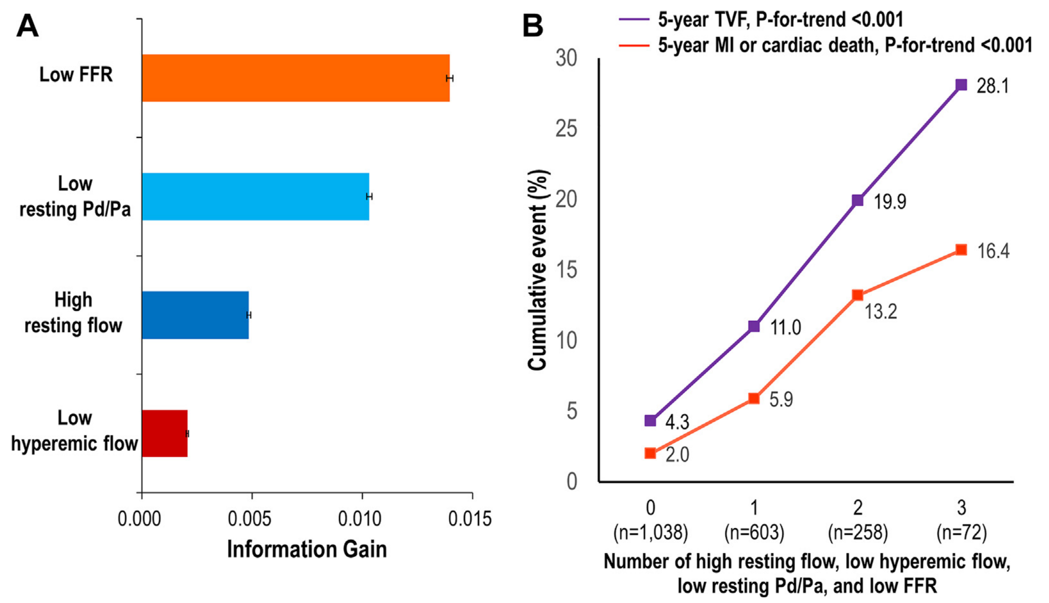


In 1,556 vessels with normal resting Pd/Pa, the risks of (A) TVF or (B) hard outcomes according to low hyperemic flow and low FFR are presented. Abbreviations as in Figures 1 and 2.

derived parameter during maximal vasodilation, such as FFR, can be used as a surrogate for flow impairment.[1] Resting pressure parameters can also represent the functional significance of coronary lesions with similar clinical value to hyperemic parameters.[7] Although the coronary pressure-flow relationship in obstructive atherosclerosis in the resting and hyperemic states has been well-defined, the individual and combined prognostic benefits centered on clinical outcomes have not been comprehensively evaluated.[20,21] In the current study, we defined 4 abnormal physiologic parameters according to coronary flow and pressure under resting and hyperemic conditions (ie, low resting Pd/Pa [≤0.92], low FFR [≤0.80], high resting flow [1/resting Tmn >2.4 or resting APV >22.7 cm/s], and low hyperemic flow [1/hyperemic Tmn <2.2 or hyperemic APV <25.0 cm/s]), and found that all 4 parameters independently predicted a higher risk of TVF or even hard outcomes. This finding is supported by the proposed prognostic value of impaired stress myocardial blood flow, Pd/Pa ≤0.92, and FFR ≤0.80.[22-28] Although there has been sparse data on the association of high resting flow with clinical outcomes, our result is supported by prior studies reporting the relationship of increased resting myocardial blood flow at ^{82}Rb positron emission tomography with an increased risk of major adverse cardiovascular events (MACE), or that a higher resting coronary sinus blood flow, reflective of total blood flow to the myocardium, was observed in patients with MACE than in those without MACE.[29,30] Therefore, abnormal resting and hyperemic coronary pressure and flow may be considered as a prognostic indicator as well as a surrogate for myocardial ischemia.

ADDITIVE PROGNOSTIC IMPLICATIONS OF FLOW TO PRESSURE PARAMETERS UNDER RESTING AND HYPEREMIC CONDITIONS. Coronary pressure measurement has been the gold standard for physiologic assessment in the catheterization laboratory.[8] Although pressure-derived estimates have been developed as surrogate markers for flow impairment based on the assumption of constant microvascular resistance during maximal hyperemia or a certain period of the cardiac cycle, a larger pressure drop occurs across the lesion with a higher coronary flow, which leads to an inevitable 30% to 40% of discordance between abnormal coronary pressure and flow parameters.[31] Given that myocardial function and ischemia are determined by coronary flow, not by perfusion pressure, whether coronary pressure measurement can be replaceable to coronary flow or whether they have synergistic impact in terms of patient's outcome should be elucidated.[32] In the current study, we observed that the risk of TVF proportionally increased in the order of neither, either, and both abnormal pressure and flow parameters at each resting and hyperemic condition. Importantly, this observation was consistent with the analysis of hard outcomes. Our finding is in line with the association of impaired flow measurement along with the preserved pressure parameter, and extends the prior knowledge that coronary pressure and flow have

FIGURE 5 Importance and Additive Value Among Pressure and Flow Parameters



(A) The information gain of individual abnormal pressure and flow parameters in the prediction of TVF is presented. (B) The cumulative event of 5-year TVF or MI/cardiac death is presented according to the number of high resting flow, low hyperemic flow, low resting Pd/Pa, and low FFR. Abbreviations as in Figures 1 and 2.

complementary prognostic value in both resting and hyperemic states.[11,13,33] Thus, regardless of which condition physicians choose for invasive physiologic assessment, both pressure and flow measurements may provide better risk prediction for future clinical events than individual measurements alone.

SYNERGISTIC PROGNOSTIC ROLE BETWEEN RESTING AND HYPEREMIC PARAMETERS. Although coronary pressure-derived measurements can identify intermediate stenosis that can be safely deferred without revascularization, clinical events still occur in lesions with preserved pressure parameters.[34,35] Considering the independent prognostic role of resting and hyperemic pressure and flow parameters, we examined the association of abnormal resting and hyperemic parameters with clinical outcomes in preserved hyperemic and resting conditions, respectively. High resting flow and low resting Pd/Pa were significantly related to a higher risk of TVF or hard outcomes in vessels with normal FFR, whereas low hyperemic flow and low FFR were predictive of clinical events in vessels with normal resting Pd/Pa. Our findings indicate a complementary prognostic role of resting and hyperemic parameters. Although the exact mechanism should be investigated in future studies, a possible explanation is the different physiologic properties of resting and hyperemic parameters of coronary lesions; hyperemic parameters may correlate with the possibility of exertion-triggered events whereas resting parameters may depict the degree of flow turbulence and pressure gradient across the stenosis exposed most of the time.[36-38] The risk of 5-year TVF or hard outcomes increased with an increase in the number of integrative 4 abnormal physiologic parameters. Therefore, the maximal benefit of invasive physiologic assessments may be achieved with the incorporation of flow and pressure parameters derived from resting and hyperemic conditions.

STUDY LIMITATIONS. First, we used a pooled registry-based analysis, which might have caused potential bias during data collection. Second, the physiologic data were not blinded to physicians, which might have affected the occurrence of target vessel revascularization events. Nonetheless, our findings are consistent with those of analyses with hard outcomes. Third, plaque burden, characteristics and lesion-specific hemodynamic parameters were

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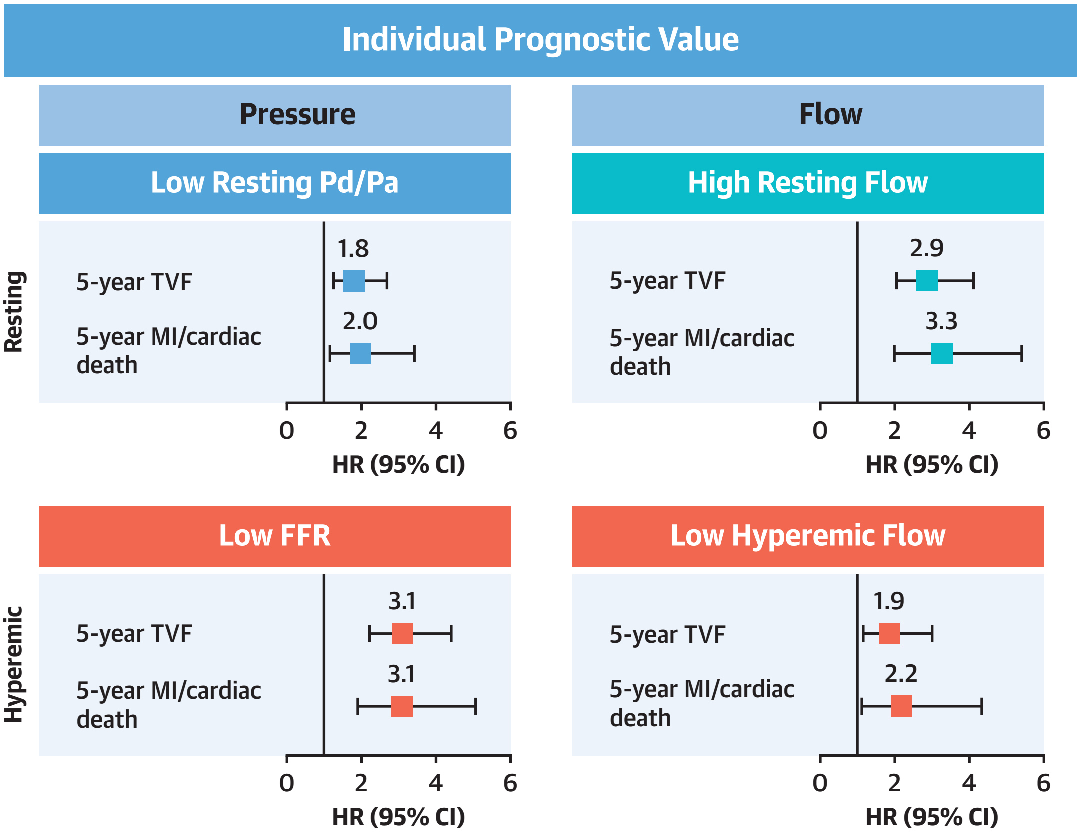
CENTRAL ILLUSTRATION Comprehensive Prognostic Implications of Resting and Hyperemic Pressure and Flow



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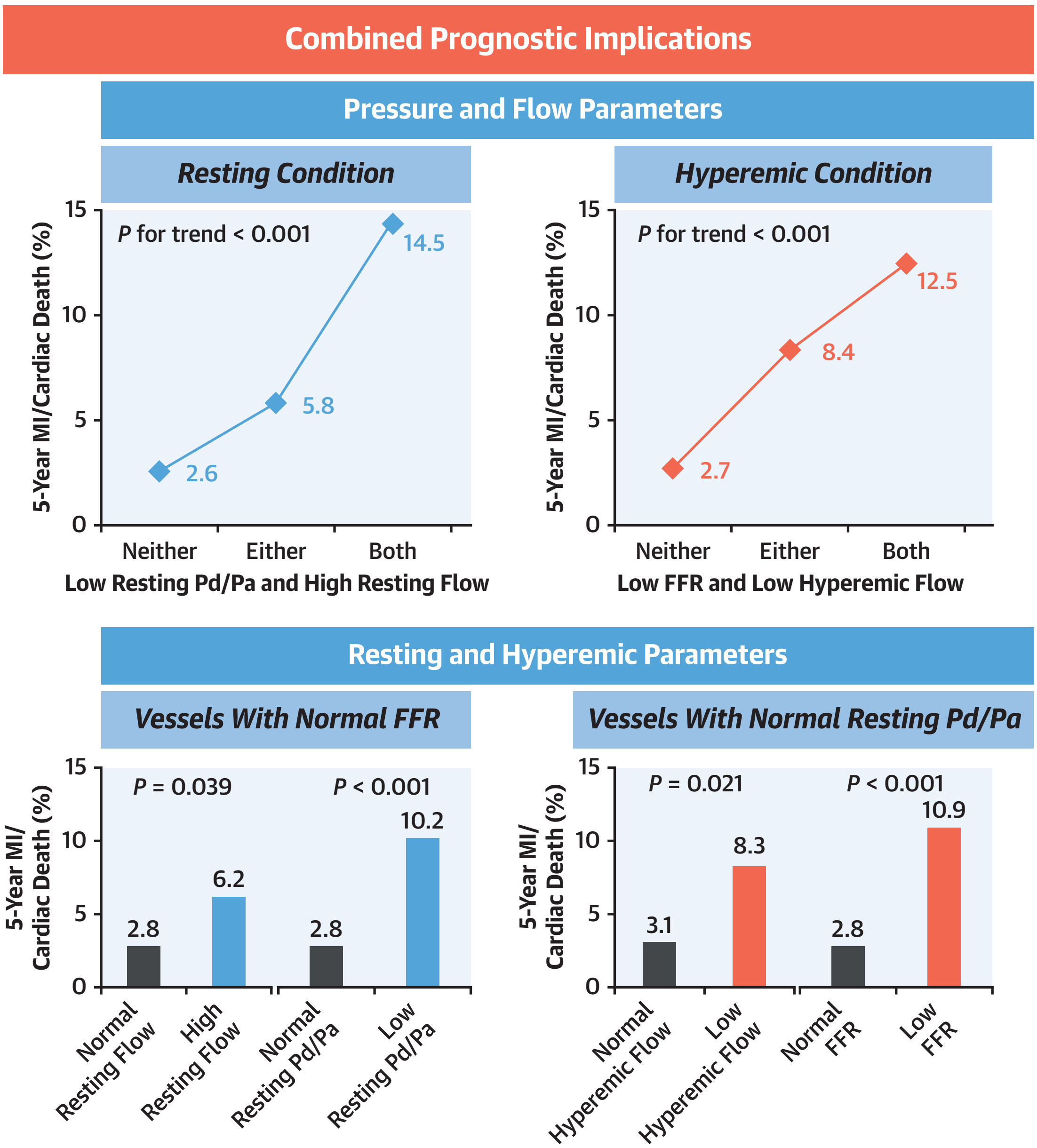
Abnormal resting and hyperemic pressure and flow parameters had independent prognostic values for the prediction of target vessel failure (TVF) or myocardial infarction (MI)/cardiac death. There was an increasing outcome trend according to abnormal pressure and flow parameters in each resting and hyperemic condition. In vessels with normal fractional flow reserve (FFR), resting parameters (ie, high resting flow and low resting distal coronary pressure/aortic pressure [Pd/Pa]) were associated with a higher risk of MI/cardiac death, and in vessels with normal resting Pd/Pa, hyperemic parameters (low hyperemic flow and low FFR) were related to a higher risk of MI/cardiac death.

Continued on the next page

not investigated, and future studies are needed to confirm the current findings using these measurements. Fourth, several findings confirm prior knowledge of the additive prognostic value between resting and hyperemic parameters. Nonetheless, our study comprehensively shows the individual and combined prognostic implications of resting/hyperemic flow and pressure in the large dataset with long-term outcomes, including hard clinical endpoints. Fifth, residual confounders could not be fully accounted for, and the causal relationship of physiologic parameters with clinical outcomes could not be determined in the current analysis. In particular, myocardial oxygen consumption may link the association between resting flow and clinical outcomes, which was not adjusted for in the current study. Sixth, the study population only represented those who underwent invasive physiologic assessment among patients with coronary artery disease, which would be a significant confounder. Seventh, the individual reason for deferral of PCI with FFR ≤0.80 could not be identified, which might be a potential confounder. Nevertheless, the deferral rate in vessels with FFR ≤0.80 (16.8%) in the current analysis was similar to the prior report from other publications representing real world practice.[27,39] Eighth, the

CENTRAL ILLUSTRATION Continued



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medication data and information on risk factor control during the follow-up were not available.

CONCLUSIONS

In the prediction of TVF or hard outcomes, including cardiac death/MI, abnormal resting and hyperemic pressure and flow parameters had independent prognostic values. Moreover, flow parameters provided an additive value to pressure parameters in both resting and hyperemic conditions, and resting and hyperemic physiologic parameters had a complementary prognostic impact on each other. Therefore, integrative assessment of these parameters can improve risk stratification and may help select appropriate treatment strategies for patients with coronary artery disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Abnormal resting and hyperemic pressure and flow were independent prognostic predictors for target vessel failure or hard outcomes. Abnormal flow parameters had an additive prognostic value for abnormal pressure parameters in both resting and hyperemic conditions and resting and hyperemic parameters showed complementary prognostic implications.

TRANSLATIONAL OUTLOOK: Integrative assessment of resting and hyperemic pressure and flow can improve risk stratification in patients with coronary artery disease.

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KEY WORDS coronary blood flow, coronary flow reserve, fractional flow reserve, ischemia

APPENDIX For supplemental tables and figures, please see the online version of this paper.