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ORIGINAL ARTICLE
Ischemic Heart Disease

Diagnostic Performance and Pressure Stability of a Novel Myocardial Ischemic Diagnostic Index

— The Intracoronary-Electrocardiogram-Triggered Distal Pressure/Aortic Pressure Ratio —

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Background: We hypothesized that the intracoronary-electrocardiogram (IC-ECG)-based pressure index would be more stable and precise than the instantaneous flow reserve (iFR). We investigated the usefulness of the IC-ECG-based pressure index for diagnosing myocardial ischemia.

Methods and Results: Thirty-seven consecutive patients with coronary stenosis requiring physiological assessment were enrolled in the study. iFR was measured at rest and under hyperemia in 51 and 40 lesions, respectively. The IC-ECG-triggered distal pressure (Pd)/aortic pressure (Pa) ratio (ICE-T) was defined as the mean Pd/Pa ratio in the period corresponding to the isoelectric line. The ICE-T was significantly lower than the iFR both at rest and during hyperemia (P<0.00001 for both). Fluctuations in the ICE-T pressure parameters (Pd/Pa, Pa, and Pd) were significantly smaller than those of iFR both at rest and during hyperemia. The diagnostic accuracy of predicting a fractional flow reserve (FFR) ≤0.80 of the ICE-T at rest was significantly higher than that of iFR (P=0.008). Receiver operating characteristic curve analyses showed that the ICE-T predicts FFR ≤0.80 more accurately than the iFR (area under curve 0.897 vs. 0.810 for ICE-T and iFR, respectively).

Conclusions: We identified the period in the IC-ECG in which resting Pd/Pa was low and constant. The IC-ECG-based algorithm may improve the accuracy of diagnosing myocardial ischemia, without increasing invasiveness, compared with pressure-dependent indices.

Key Words: Coronary artery disease; Diagnostic accuracy; Diastolic fractional flow reserve; Instantaneous wave-free ratio; Intracoronary electrocardiogram

Several clinical trials have demonstrated that the physiological assessment of coronary artery lesions using fractional flow reserve (FFR) in coronary interventions contributes to reducing cardiovascular events.[1–3] Although the non-inferiority of instantaneous flow reserve (iFR) compared with FFR-guided percutaneous coronary intervention (PCI) has been demonstrated, no large-scale studies have established its superiority.[4,5] FFR and iFR are reportedly discordant in up to 20% of cases.[6–12] The iFR is calculated as the coronary artery distal pressure (Pd) to aortic pressure (Pa) ratio (Pd/Pa) in the absence of hyperemia, during the mid- to end-diastolic or the wave-free period (WFP), during which microvascular resistance is recognized as being low and stable.[13–15] Coronary blood flow at rest is slower than that at maximal hyperemia, and the pressure gradient caused by stenosis at rest is limited. Therefore, the resting myocardial ischemic index should capture very slight changes in intracoronary (IC) pressure.[13]

Diastasis during the diastolic phase has considerably less left ventricular (LV) myocardial activity and is concordant with the concept of WFP. However, an increased heart rate shortens the diastasis period to preserve LV stroke

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volume.[16] Other new resting pressure-derived diastolic indices that are not restricted to the WFP did not show any differences in their values and were well correlated with iFR.[17,18] Westerhof et al reported that the assumption of iFR violates physical principles because Ohm's law cannot theoretically be applied under extensive pressure changes.[19] Therefore, the amount of change in the pressure parameter within the analysis interval is important for the resting indices. The currently used iFR algorithm (FFR software 2.5; Volcano Corp., Rancho Cordova, CA, USA) is completely dependent on aortic pressure because the iFR values remain consistent with or without the use of electrocardiogram (ECG), and the initiation of the systolic period can be identified without using the R-wave of the ECG.[20] We previously reported that QTUc prolongation during papaverine-induced hyperemia markedly decreased iFR values,[21] implying that the diagnosis of myocardial ischemia may not be appropriate in some patients because of limitations in the iFR algorithm. Therefore, the diastolic index may be more reliable, because it can extract a low and stable Pd/Pa time phase even under hyperemia with large pressure fluctuations. Furthermore, the diastolic index that can extract an appropriately low and stable Pd/Pa may be applied to diastolic FFR (d-FFR).

IC-ECG findings are reportedly more sensitive and selective for detecting regional myocardial potentials than 12-lead body surface ECG (S-ECG) findings.[22–24] Furthermore, the combined use of FFR and IC-ECG facilitated the understanding of local myocardial viability near the pressure wire tip, containing the pressure sensor.[25] Diastolic indices need to capture delicate changes in IC resistance with every heartbeat. We hypothesized that the interval in which the IC-ECG potential remains low and stable may be used as the low-resistance period in the coronary artery circulation. The aims of the present study were to: (1) investigate whether the IC-ECG-based pressure index, Pa/Pd, was more stable and precise than iFR; and (2) evaluate the potential usefulness of the IC-ECG-based pressure index for diagnosing myocardial ischemia as opposed to iFR.

Methods

Patient Selection

The present prospective single-center study enrolled 37 consecutive patients who had chronic stable angina and were scheduled for coronary angiography at the Todachuo General Hospital between March and October 2018. All patients had at least 1 stenosis in a large epicardial artery that required physiological assessment to determine intervention indications. Exclusion criteria included a history of coronary artery bypass surgery, extremely tortuous coronary arteries, acute coronary syndrome, occluded coronary arteries, left main coronary artery disease, coronary ostial stenosis, congestive heart failure, and an absolute contraindication to adenosine (asthma and bradyarrhythmia).

This study was approved by the Institutional Review Board of Todachuo General Hospital (Reference no. 0362) and was performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants after they had bee provided with a complete explanation of the protocol and potential risks.

Catheterization and Measurement of the Instantaneous Wave-Free Ratio at Rest and During Hyperemia

Physiological measurements of coronary artery stenosis were performed in the standard manner. The Volcano S5 imaging system with the Verrata pressure guide-wire (Phillips, Amsterdam, Netherlands) was used for measuring coronary artery pressure. An IC bolus of nitrates (200–300 μg) was administered to all patients before pressure wires were introduced. After calibration to normal atmospheric pressure and prior to wire insertion, pressure equalization was performed at the catheter tip before advancing the pressure guide-wire into the distal stenotic lesion.

IC-ECG was recorded during physiological measurements by connecting the proximal tip of the 0.014-inch pressure guide wire to a unipolar lead terminal of a multichannel ECG recorder (RMC-4000M Cardio Master with EP amplifier system [JB400G; Nihon Koden, Tokyo, Japan] or AXIOM Sensis HEMO EP128 [Siemens AG, Munich, Germany]) via a sterile double-alligator connector. These systems allowed simultaneous multichannel recordings of limb and chest lead ECGs during IC-ECG recordings. The V1 leads were replaced with IC-ECG waveforms and displayed during iFR measurements. Data were stored digitally for offline analysis.

To confirm that IC-ECG was low and plateaued, iFR was recorded in all patients at rest (iFR-online). In addition, iFR was measured under ATP administration (iFRa) in lesions where the operator considered that maximal hyperemia was necessary for the diagnosis of myocardial ischemia. Specifically, 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ATP was administered intravenously for 3 min until steady state hyperemia was achieved. Phillips iFR computational algorithms, iFR-online and iFRa-online, were used to measure iFR and iFRa online, respectively. Pa and Pd values were automatically recorded every 5 ms during physiological measurements.

Calculation of iFR and Other Diastolic Indices

Pressure data were extracted directly from the digital archive of the Volcano S5 device console. To identify variations in pressure parameters during WFP, iFR and other diastolic indices were calculated as follows, using pressure data from 3 heartbeats, which were included within the data for automatic iFR calculation: iFR-calc=(Pd/Pa)/WFP (from 25% into diastole until 5 ms before end-diastole,[14] where the start of diastole was defined as the nadir of the Pa dicrotic notch and end-diastole was defined as 50 ms before the Pa upstroke from the subsequent ventricular contraction); diastolic pressure ratio (dPR): the entire diastole; diastolic hyperemia-free ratio (DFR): Pa < mean Pa and down-sloping Pa. The whole-cycle Pd/Pa was the Pd/Pa determined for the entire whole cardiac cycle.

IC and S-ECG Analysis and Calculation of Pressure Indices

Both IC-ECG and S-ECG were analyzed using a multichannel ECG recorder. ECGs were examined by scaling up the sampling speed by 100 mm/s and the ECG signal amplitude by 10 mm/mV. The following points were traced on the IC-ECG and S-ECG: the beginning of the P wave, the beginning of the QRS complex, the end of the T wave, the end of the U wave, the beginning of the subsequent P wave, and the beginning of the subsequent QRS complex. The isoelectric line was considered as the T-P segment preceding the QRS (or QS) complex. If some hallmark points were indistinct, the isoelectric line was identified considering that the electrical potential is small and parallel to the baseline. In the S-ECG, the isoelectric lines were

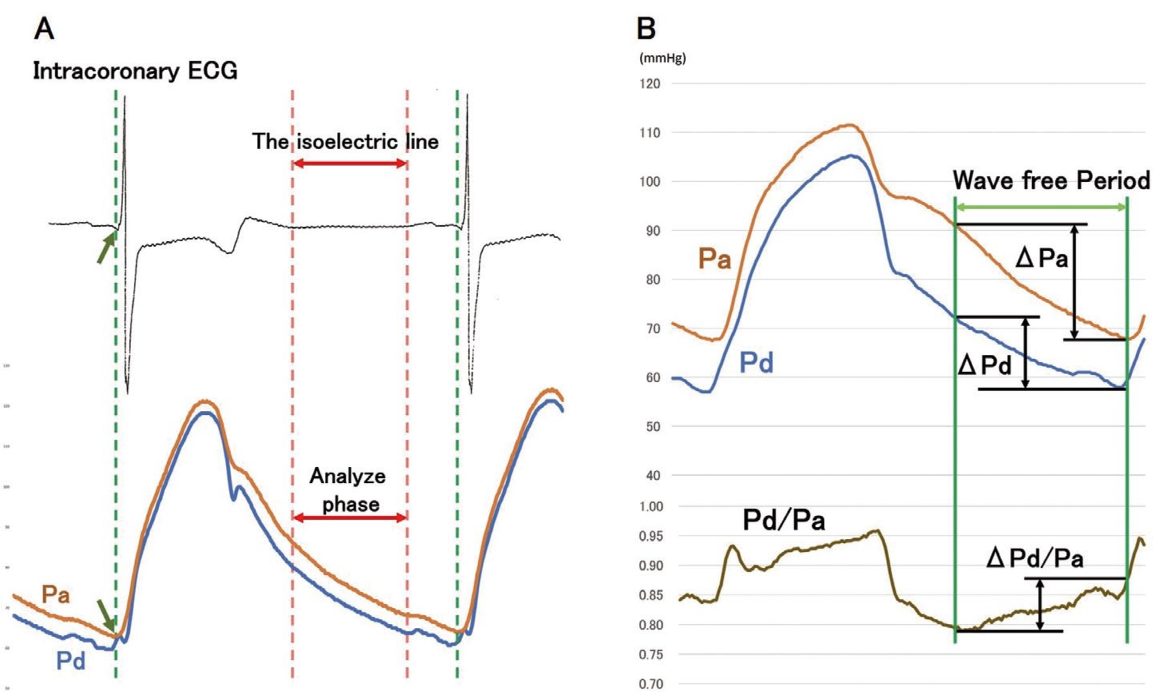


Figure 1. Method of calculation for the intracoronary electrocardiogram (IC-ECG)-based pressure index, and definitions of terms. (**A**) First, the Q point of the IC-ECG is synchronized with the start points of the systolic phase in the pressure waveform. The IC-ECG-triggered distal pressure (Pd)/aortic pressure (Pa) ratio was defined as the average of Pd/Pa in the period corresponding to the isoelectric line. (**B**) ΔPd/Pa is defined as the difference between the minimum and maximum Pd/Pa values during the analysis interval of each index; ΔPa and ΔPd are similarly defined as differences between the minimum and maximum values.

defined as periods with no potential activity in any lead. The time from the Q point to the start and end of the isoelectric line was measured. The IC-ECGs were interpreted by 2 cardiologists, who discussed disagreements to arrive at a consensus.

The start points of the systolic phase in the pressure waveform and the Q point in IC-ECG were regarded as the same point, and time phases were synchronized. The IC-ECG-triggered Pd/Pa ratio (ICE-T) was defined as the mean Pd/Pa ratio in the period corresponding to the isoelectric line (**Figure 1A**). The S-ECG-triggered Pd/Pa ratio (ECG-T) was similarly calculated.

Angiographic Analysis

Quantitative coronary angiography was performed using an auto-edge detection method with CMS version 7.1 (Medis, Leiden, Netherlands). Reference vessel diameter, minimum lumen diameter, and percentage diameter stenosis were measured using the external diameter of the catheter as a scaling device.

Data Analysis

Information regarding patients' clinical characteristics, including the number and locations of stenotic lesions, was collected at baseline. Excel (Microsoft, Redmond, WA, USA) was used to analyze iFR-calc, dPR, DFR, whole-cycle Pd/Pa, ICE-T, and ECG-T values offline. All indices were determined in a fully automated manner for 3 consecutive beats and then averaged. Differences between the minimum and maximum Pd/Pa values during the analysis

Table 1. Patients' Clinical Characteristics

Male sex	37 (34)
Age (years)	68±9
Body weight (kg)	66±11
Body height (cm)	165±8
No. arteries measured at rest/during hyperemia	
Total	51/40
LAD	24 (47.1)/20 (50.0)
LCX	14 (27.5)/8 (20.0)
RCA	13 (25.5)/12 (30.0)
QCA	
Lesion length (mm)	12.5±7.9
Reference diameter (mm)	2.69±0.76
Minimal luminal (mm)	1.4±0.6
Diameter stenosis (%)	49.7±12.9
Medical history	
Hypertension	31 (83.8)
Diabetes	20 (54.1)
Dyslipidemia	28 (75.7)
Current smoker	6 (16.2)
Prior myocardial infarction	4 (10.8)

Unless indicated otherwise, data are given as the mean ± SD or n (%). LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; QCA, quantitative coronary angiography.

Table 2. Comparison of Index Value, Fluctuations in Pressure Parameters, and Analysis Intervals Between iFR and Other Indices

	Index value	P value	ΔPd (mmHg)	P value	ΔPa (mmHg)	P value
At rest (n=51)						
Whole cycle	0.931±0.071	0.344	61.1±17.3	<0.00001	55.4±16.6	<0.00001
Whole diastolic	0.895±0.100	0.305	34.7±11.8	<0.00001	0.113±0.087	<0.00001
DFR	0.893±0.107	0.053	18.2±6.7	0.663	0.089±0.052	0.793
iFR	0.893±0.108		17.9±6.2		22.8±4.7	
ICE-T	0.878±0.119	<0.00001	7.6±3.8	<0.00001	9.3±4.0	<0.00001
ECG-T	0.885±0.112	0.282	13.7±6.8	0.0006	14.8±7.2	<0.00001
ATP (n=40)						
Whole cycle	0.858±0.086	0.181	61.1±15.9	<0.00001	56.6±15.4	<0.00001
Whole diastolic	0.798±0.111	0.029	35.2±10.9	<0.00001	37.0±10.7	<0.00001
DFR	0.795±0.113	0.110	19.7±5.7	0.513	23.4±5.5	0.747
iFR	0.794±0.114		19.3±5.4		23.2±4.2	
ICE-T	0.773±0.120	<0.00001	8.1±3.3	<0.00001	9.5±3.8	<0.00001
ECG-T	0.781±0.120	0.196	14.3±6.4	0.0005	15.3±6.6	<0.00001

	ΔPd/Pa (mmHg)	P value	Analysis interval (ms)	P value	ICC of index value	P value	ICC of analysis interval	P value
At rest (n=51)								
Whole cycle	0.004±0.001	0.039	876±153	<0.00001	0.999	<0.00001	0.979	<0.00001
Whole diastolic	0.014±0.002	0.862	515±124	<0.00001	0.996	<0.00001	0.962	<0.00001
DFR	0.010±0.001	0.103	383±95	0.836	0.998	<0.00001	0.904	<0.00001
iFR	0.083±0.053		382±93		0.997	<0.00001	0.962	<0.00001
ICE-T	0.020±0.011	<0.00001	126±51	<0.00001	0.999	<0.00001	0.946	<0.00001
ECG-T	0.035±0.039	<0.00001	206±97	<0.00001	0.998	<0.00001	0.962	<0.00001
ATP (n=40)								
Whole cycle	0.255±0.103	<0.00001	833±158	<0.00001	0.998	<0.00001	0.995	<0.00001
Whole diastolic	0.148±0.070	0.00002	474±130	<0.00001	0.999	<0.00001	0.984	<0.00001
DFR	0.126±0.061	<0.00001	370±108	0.007	0.997	<0.00001	0.957	<0.00001
iFR	0.115±0.057		352±98		0.999	<0.00001	0.984	<0.00001
ICE-T	0.030±0.014	<0.00001	115±52	<0.00001	0.999	<0.00001	0.906	<0.00001
ECG-T	0.056±0.044	<0.00001	206±123	<0.00001	0.998	<0.00001	0.976	<0.00001

Unless indicated otherwise, data are given as the mean±SD. DFR, diastolic hyperemia-free ratio; ECG-T, electrocardiogram-triggered diastolic pressure (Pd)/aortic pressure (Pa) ratio; ICC, intraclass correlation coefficient; ICE-T, intracoronary cardiogram-triggered pressure ratio; iFR, instantaneous flow reserve.

interval for each index were defined as ΔPd/Pa; ΔPa and ΔPd were similarly defined (**Figure 1B**). The mean Pd/Pa values (i.e., each index value) of dPR, DFR, whole-cycle Pd/Pa, ICE-T, and ECG-T were compared with iFR-online at rest and during hyperemia. ΔPd/Pa, ΔPd, ΔPa, and the period used for analysis of dPR, DFR, whole-cycle Pd/Pa, ICE-T, and ECG-T were compared with iFR-calc at rest and during hyperemia.

Sample Size Calculation

The following parameters were used to calculate the sample size to detect differences in iFR and ICE-T values: α=0.05, β=0.90, and a difference between the groups in the iFR and ICE-T values of 0.02±0.04 at rest estimated from a small pilot study. Using these assumptions, we determined 44 stenoses were needed. However, iFR was measured for patients who had provided informed consent before reaching the target sample size, and we eventually enrolled 37 patients with 51 stenosis.

Statistical Analysis

Numerical data are expressed as the mean±SD. Pearson's test was used to analyze the correlation between iFR-calc and iFR-online. Paired t-tests were used to compare index values between iFR-online and dPR, DFR, whole-cycle Pd/Pa, ICE-T, or ECG-T. Similarly, paired t-tests were used to compare ΔPd/Pa, ΔPd, ΔPa, and the analysis period between iFR-calc and dPR, DFR, whole-cycle Pd/Pa, ICE-T, or ECG-T at rest and during hyperemia. To examine the internal reliability of index values and analyze intervals for each index observed during the 3 beats, we used intraclass correlation coefficients (ICC). ICC values <0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability, and values >0.90 indicate excellent reliability. Receiver operating characteristic (ROC) curve analyses for iFR-online, ICE-T, and ECG-T at rest were performed to determine the best cut-off values for predicting an FFR of ≤0.80 during hyperemia, which is indicative of lesions positive for myocardial ischemia. Areas under the ROC curve (AUCs) were compared using the DeLong

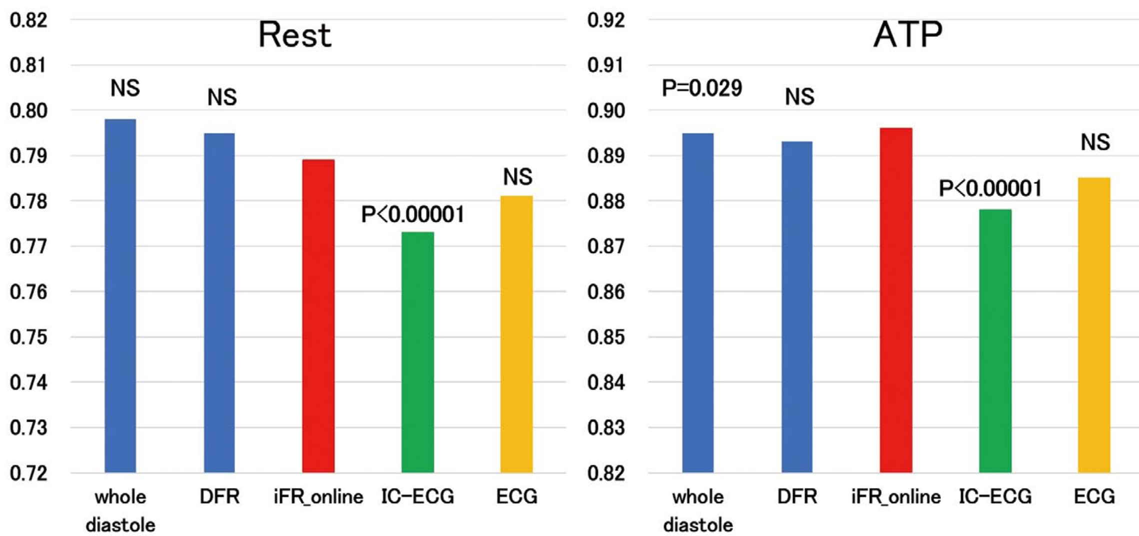


Figure 2. Comparison of intracoronary cardiogram-triggered pressure ratio (ICE-T) and surface electrocardiogram-triggered distal pressure/aortic pressure ratio (ECG-T) values with instantaneous flow reserve recorded at rest (iFR-online). ICE-T values were significantly lower than iFR-online values both at rest and during hyperemia. The ECG-T values were lower than those of automatically calculated iFR (iFR-calc), but the difference did not reach statistical significance. DFR, diastolic hyperemia-free ratio.

method.

The diagnostic performance of ICE-T, ECG-T, and iFR-online for identifying FFR-positive lesions was determined by assessing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. The diagnostic accuracy of ICE-T, ECG-T, and iFR-online was compared with that of FFR using McNemar's test. Furthermore, the analysis of diagnostic accuracy was limited to the adenosine zone (0.86≤iFR-online≤0.93) used in the iFR-FFR hybrid strategy.[26]

Two-sided P<0.05 was considered significant. Statistical analyses were performed using SPSS 19 (IBM Corp., Chicago, IL, USA) and JMP 14 (SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

The clinical characteristics of the 37 patients are given in **Table 1**. iFR was measured in 51 lesions and, of these, iFRa was measured in 40. Physiological assessment was mostly conducted at the left anterior descending artery (LAD; 47.1% at rest, 50.0% during hyperemia). IC-ECG recording was successful and interpretable in all patients. Most patients were men and had hypertension, diabetes, or dyslipidemia; approximately 10% had a history of myocardial infarction. Mean heart rate at rest and during hyperemia was 60.8±10.0 and 64.1±10.3 beats/min, respectively.

Correlation Between iFR-Online and iFR-Calc Values

The relationship between iFR-online and iFR-calc is shown in the **Supplementary Figure**. Superimposition of iFR-online and iFR-calc data (differences: 0.003±0.025 at rest and 0.005±0.024 during hyperemia) yielded a strong correlation (Pearson's r=0.972 at rest and r=0.979 during hyperemia; P<0.001 for both).

Comparison of Index Values, Pressure Parameters, and Analysis Period Between iFR-Calc and Whole-Cycle Pd/Pa, dPR, DFR, ICE-T, or ECG-T

Resting index pressure parameters and the analysis period are given in **Table 2** and shown in **Figure 2**. ICE-T was significantly lower than iFR-online, both at rest and during hyperemia. There were no significant differences between iFR-online and either DFR or ECG-T. ΔPd/Pa, ΔPd, and ΔPa were significantly lower for ICE-T and ECG-T than iFR-calc. The periods used for the ICE-T and ECG-T analyses were significantly shorter than those used for the iFR-calc analysis. ΔPd/Pa, ΔPd, and ΔPa were significantly lower for ICE-T than ECG-R, both at rest and during hyperemia (P<0.001). Although the index value of the ICE-T was lower than that of ECG-T, there was no significant difference between them either at rest (P=0.347) or during hyperemia (P=0.465).

Scatter plots of resting ICE-T and iFR, as well as resting ICE-T and iFR relative to FFR, are shown in **Figure 3**. iFR and ICE-T showed a good correlation (r=0.866, P<0.001), and the correlation coefficients of the 2 resting indices relative to FFR were similar (ICE-T, r=0.711; iFR, r=0.718, P<0.001). The index values of both other diastolic indices and the ICE-T had excellent reproducibility of more than 0.99, and the analysis interval ICC for the ICE-T was excellent (0.946 at rest), although it was slightly lower than that of the existing diastolic indices. The ICC was excellent for both the index value and the analysis interval for ICE-T (0.999 and 0.906, respectively), even during hyperemia.

An example of a pressure waveform and IC-ECG recorded in the LAD under maximum hyperemia with ATP is shown in **Figure 4**. The ICE-T value calculated based on the IC-ECG isoelectric line was smaller than the

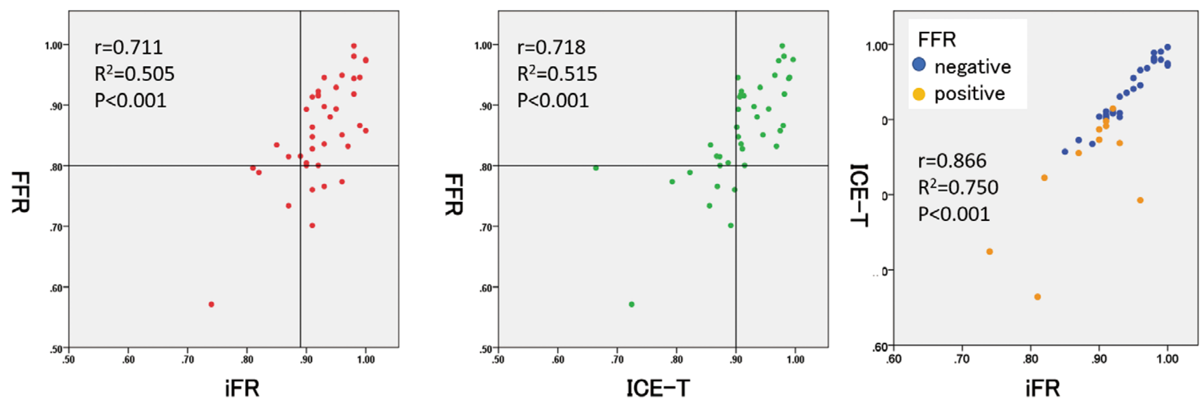
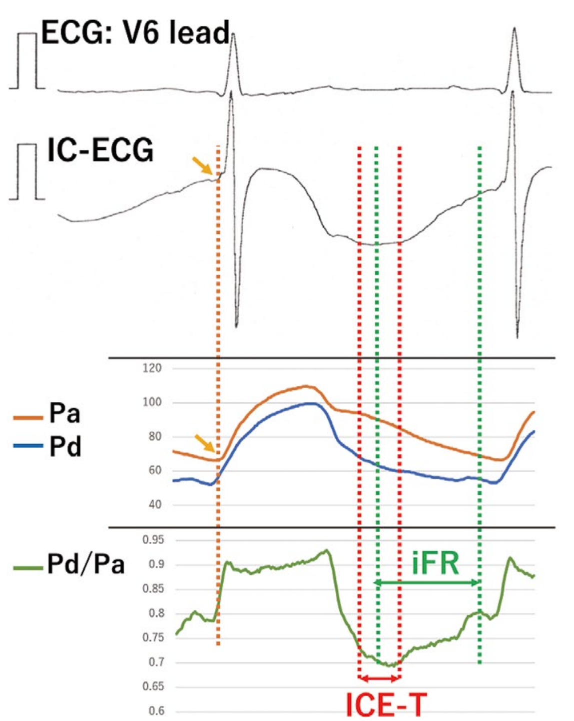


Figure 3. Scatter plots of resting intracoronary cardiogram-triggered pressure ratio (ICE-T) and instantaneous flow reserve (iFR), as well as resting ICE-T and iFR relative to fractional flow reserve (FFR). There was a good correlation between iFR and ICE-T (r=0.866, P<0.001), and the correlation coefficients of the 2 resting indices relative to FFR were similar (ICE-T, r=0.711; iFR, r=0.718, P<0.001).



	Index value	ΔPd/Pa	ΔPd (mmHg)	ΔPa (mmHg)
iFR-calculation	0.756	0.123	20.83	26.25
ICE-T	0.707	0.013	9.00	9.08

Figure 4. Example of an intracoronary electrocardiogram (IC-ECG) and pressure waveform recorded in the left anterior descending coronary artery under maximum hyperemia. The intracoronary cardiogram-triggered pressure ratio (ICE-T) value is smaller than the calculated instantaneous flow reserve (iFR) value by 0.049. The fluctuations in the distal pressure (Pd)/aortic pressure (Pa) ratio, Pa, and Pd during ICE-T analysis intervals are smaller than those based on the wave-free period. The IC-ECG-based analysis could identify the low and stable Pd/Pa phase, even under hyperemia.

iFR value by 0.049. Values of ΔPd/Pa, ΔPd, and ΔPa calculated based on IC-ECG in the ICE-T were lower than those calculated based on WFP in iFR. IC-ECG-based analysis could identify the low and stable Pd/Pa phase, even during hyperemia.

Diagnostic Accuracy of ICE-T and IC-ECG vs. iFR

The sensitivity, specificity, NPV, PPV, and diagnostic accuracy of the ICE-T and ECG-T exceeded those of iFR-online (**Table 3**). The diagnostic accuracy of ICE-T, ECG-T, and iFR-online was 90.0%, 85.0%, and 72.5%, respectively, with ICE-T having the highest accuracy. The diagnostic accuracy of ICE-T was superior to that of iFR-online (P=0.008). ROC curve analysis revealed that an ICE-T cut-off of ≤0.897 was strongly correlated with an FFR value of ≤0.80 (AUC 0.897; 95% confidence interval [CI] 0.886–0.930). Although not statistically significant, ECG-T was better correlated with FFR than was iFR-online (for ECG-T, best cut-off value 0.899, AUC 0.865, 95% CI 0.890–0.933; for iFR-online, best cut-off value 0.91, AUC 0.810, 95% CI 0.907–0.942; DeLong method, iFR vs. ICE-T P=0.114, iFR vs. ECG-T P=0.368, ICE-T vs. ECG-T P=0.369; **Figure 5**). ICE-T and ECG-T in the adenosine zone (0.86≤iFR-online≤0.93), an ambiguous value for a diagnosis of ischemia with iFR, were not statistically significant, but sensitivity, specificity, NPV, PPV, and diagnostic accuracy were higher than for iFR-online (diagnostic accuracy: iFR-online vs. ICE-T P=0.105, iFR-online vs. ECG-T P=0.709, ICE-T vs. ECG-T P=0.509). The clinical or angiographic characteristics of the patients and vessels with a discordance between iFR and ICE-T could not be clarified because of the limited number of cases in the present study.

Discussion

Herein we identified the period in which the resting Pd/Pa was low and constant using the IC-ECG signal, and the accuracy of the IC-ECG-triggered resting index (ICE-T) was found to be superior to that of iFR for diagnosing myocardial ischemia. An ICE-T cut-off of ≤0.897 strongly correlated with an FFR ≤0.80 (AUC 0.897, 95% CI 0.886–

Table 3. Agreement of Dichotomous Classification With Combined Reference Standard for Detection of Myocardial Ischemia

	All data (n=40)			0.86≤iFR-online≤0.93 (n=20)		
	iFR-online	ICE-T	ECG-T	iFR-online	ICE-T	ECG-T
Best cut-off value	0.91	0.897	0.899			
Sensitivity (%)	72.7	90.9	81.8	42.9	75.0	80.0
Specificity (%)	72.4	89.7	86.2	76.9	83.3	80.0
Positive-predictive value (%)	50.0	76.9	69.2	50.0	75.0	57.1
Negative-predictive value (%)	87.5	96.2	92.6	71.4	83.3	92.3
Diagnostic accuracy (%)	72.5	90.0	85.0	65.0	80.0	80.0

ECG-T, electrocardiogram-triggered pressure ratio; ICE-T, intracoronary cardiogram-triggered pressure ratio; iFR-online, instantaneous wave-free ratio online.

0.930). Analysis using the IC-ECG-based period reduced the fluctuations in Pa, Pd, and Pd/Pa. Resting-state and hyperemic ICE-T were significantly lower than those of iFR. No previous study has reported the resting index ICE-T or demonstrated its superior accuracy compared with iFR.

Differences Between ICE-T and the Aortic Pressure-Dependent Diastolic Index

The present study showed that ICE-T was significantly lower than iFR. van't Veer et al reported a good correlation among diastolic index values, although that study did not examine the significance of differences (e.g., by using paired t-tests).[17] In addition, Svanerud et al showed that the lowest point of Pd/Pa was variable, even when limited to diastole.[18] In the present study, Pd/Pa values varied within the WFP by 0.083±0.053. The ICE-T showed significantly shorter analysis intervals and significantly smaller ΔPd/Pa compared with iFR. This suggests that the ICE-T selectively detected the interval with lower Pd/Pa, leading to a significantly lower index value for ICE-T compared with iFR.

Selectivity and Sensitivity of IC-ECG and S-ECG

The ICE-T value was significantly lower than the iFR-online value, but ECG-T was marginally lower than iFR-online. The 12-lead S-ECG facilitates the recognition of myocardial ischemia, injury, and infarction. However, not all cardiac abnormalities can be detected using 12-lead ECG. Indeed, approximately 25% of myocardial infarctions are non-ST segment elevation myocardial infarction (NSTEMIs). NSTEMIs are more common in patients with either right coronary artery or left circumflex artery involvement than in those with LAD involvement.[27] The additional use of posterior leads (V7–V9) and right precordial leads (V3R–V5R) may improve the detection of myocardial ischemia.[28,29] However, patients with ischemic heart disease often have myocardial conduction delay.[30] IC-ECG recording is more sensitive and reliable for detecting regional myocardial ischemia than standard S-ECG recording,[31,32] and is useful for predicting myocardial infarction-related microvascular obstruction[33] and post-procedural myocardial injury in angina pectoris.[34] Ikenaga et al reported that the estimation of microvascular perfusion from IC-ECG was consistent with the characteristics of plaque by Fourier-domain optical coherence tomography.[35] These reports led to our hypothesis that the local myocardial condition can be assessed sensitively using IC-ECG. In this study we investigated whether the IC-ECG can selectively detect the potential representative of cardiac muscle activity around the pressure sensor of the pressure wire. The IC-ECG requires a shorter analysis period than S-ECG because it can detect finer electrical potential. Indeed, the ICE-T analyzed using IC-ECG data exhibited excellent accuracy. Petraco et al reported that the overall ischemia diagnostic rate is similarly high for iFR and FFR but is significantly reduced in borderline ischemic cases.[36] Similarly, in the present study, the diagnostic accuracy of iFR in the adenosine zone was reduced to 65.0%, whereas that of the ICE-T was maintained at 80%. The superiority diagnostic accuracy of ICE-T may be due to the accurate ischemic diagnosis of borderline cases. However, the factors responsible for the discrepancy in ischemia diagnosis between ICE-T and iFR could not be elucidated in the present study and should be investigated in future studies with larger sample sizes.

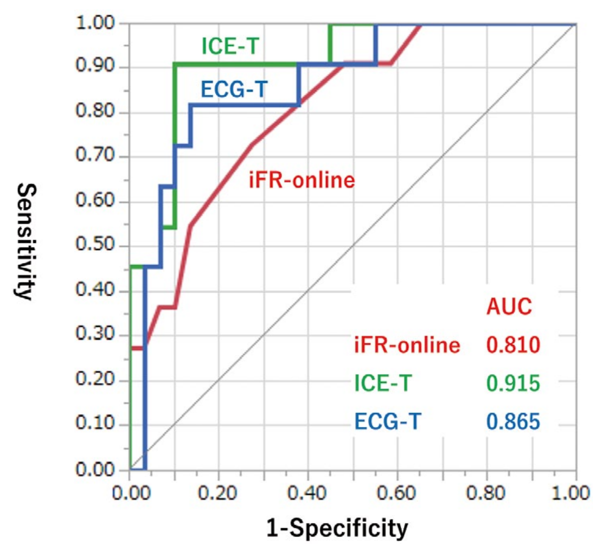


Figure 5. Receiver operating characteristic (ROC) curve analysis of resting indices for predicting a fractional flow reserve (FFR) of ≤0.80. The area under the ROC curve (AUC) indicates that the intracoronary cardiogram-triggered pressure ratio (ICE-T) is more accurate than instantaneous flow reserve recorded at rest (iFR-online) for predicting FFR positivity.

Application to Mid-d-FFR

To the best of our knowledge, there have been no large-scale trials that have shown the superiority of iFR over FFR.

The d-FFR reported by Abe et al was calculated with LV pressure, using the whole diastolic phase.[37] Although both the present study and that of Abe et al had small sample sizes, d-FFR was useful for diagnosing ischemia and understanding blood-flow compared with whole-cardiac cycle FFR. We speculate that d-FFR in the LAD may facilitate appropriate diagnosis of myocardial ischemia because most coronary blood flow occurs during diastole. However, d-FFR requires simultaneous measurement of IC and LV pressure; thus, it is not widely used because it requires 2 arterial punctures and is more invasive. In the present study, the isoelectric line could be specified in all stenoses during hyperemia, and the ICE-T value could be calculated. The ICE-T value was statistically and clinically significantly lower than the iFR-online value (0.77±0.12 vs. 0.79±0.12, respectively; P=0.0001). In the present study, ICE-T selectively extracted the low and stable Pd/Pa value and could be measured even during hyperemia. Although further studies of clinical significance are needed, the hyperemic ICE-T may represent a novel d-FFR index for which no additional puncture is required. However, the widespread use of the ICE-T will require the development of an automated analysis system for IC-ECG.

Study Limitations

This study has some limitations. First, it included a relatively small number of patients for comparisons of the AUC and diagnostic accuracy. Differences in AUC and diagnostic accuracy may have been due to the high proportion of borderline cases in this study. Second, the pressure wire may capture the electrical potential proximal to the stenosis. However, we recently reported that the IC-ECG was captured near the pressure wire tip.[25] Moreover, this system selectively extracts the low myocardial electrical activity phase. Therefore, although the analysis interval is short, due to potential noise from the proximal coronary arteries, the influence on the index value is minor. Furthermore, it is necessary to verify that the ICE-T analysis period is extracted from the low and stable resistance period. Future studies on ICE-T that measure both blood flow and pressure are needed. Third, to record IC-ECG, the V1 lead was removed, which could result in differences to determinations of the analysis interval by 12-lead ECG. However, the QT interval and P waves are generally evaluated in limb leads.[38] Therefore, the effect of the absent V1 lead would be very small.

Conclusions

In this study we identified the period in which resting Pd/Pa was low and constant, based on IC-ECG, and demonstrated that the accuracy of this new ICE-T was superior to that of iFR for predicting positive FFR. The IC-ECG-based period for ICE-T analysis was less variable than iFR, resulting in reduced Pa, Pd, and Pd/Pa variation. The use of an isoelectric period of IC-ECG is in concordance with the iFR concept of selecting the low and stable resistance phase, rather than using the pressure waveform-based index. ROC curve analysis showed that an ICE-T cut-off of 0.897 was strongly correlated with an FFR cut-off of 0.80. The resting and hyperemic ICE-T values were significantly lower than those of iFR. This study indicated that the IC-ECG-based algorithm may improve the accuracy of myocardial ischemia diagnosis, without increasing invasiveness, compared with pressure-dependent indices. The d-FFR using ICE-T may facilitate appropriate diagnosis of myocardial ischemia, particularly diagnoses in lesions in the LAD. Further multicenter studies are needed to confirm the clinical significance of the new index, ICE-T.

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IRB Information

This study was approved by Todachuo General Hospital (Reference no. 0362).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

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