

Prognostic value of proximal left coronary artery flow velocity detected by transthoracic Doppler echocardiography☆

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ABSTRACT

Background: Lesions in the proximal left coronary artery (LCA) are associated with a poor prognosis compared with other lesional sites. Transthoracic Doppler echocardiography (TTDE) can help to detect proximal LCA flow, and an accelerated coronary flow velocity (CFV) indicates the presence of proximal LCA lesions. This study aimed to investigate the prognostic value of CFV in the proximal LCA measured by TTDE.

Methods: We enrolled 1472 consecutive hemodynamically stable patients with known or suspected heart disease whose CFV was successfully detected using TTDE accompanied by routine echocardiography between 2008 and 2011. The primary outcome was cardiac death (acute myocardial infarction, heart failure, or sudden cardiac death) and patients were followed up over a median of 6.3 years.

Results: Overall, 42 cardiac deaths (3%) were observed. An increased CFV was significantly associated with the outcome in several models based on potential confounders (age, rate pressure product, Framingham Risk Score, diabetes, coronary artery disease, hemoglobin, brain natriuretic peptide, estimated glomerular filtration rate, left ventricular mass, left ventricular ejection fraction, and E/e'). Using a receiver operating characteristic curve analysis, the optimal cut-off value for the CFV to the association of the outcome was 37 cm/s (area under the curve, 0.70; sensitivity, 82%; specificity, 62%). In sequential Cox proportional hazards models, the CFV added incremental prognostic information to the clinical and basic echocardiographic parameters (chi-squared: 110.7 to 146.6, $P < 0.01$).

Conclusions: An increased CFV in the proximal LCA was associated with cardiac death, incremental to the clinical and basic echocardiographic parameters.

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1. Introduction

Cardiovascular events often occur without prior symptoms [1]. In particular, lesions in the proximal left coronary artery (LCA) are associated with a poor prognosis compared with other lesional sites because it often supplies a large proportion of the left ventricular (LV) myocardium [2–5]. Since effective treatment can prevent cardiovascular events, an accurate and simplified risk assessment is clinically valuable.

Transthoracic Doppler echocardiography (TTDE) can measure the coronary flow velocity (CFV) in various parts of coronary arteries [6,7]. TTDE can be performed quickly and efficiently making it a possible routine echocardiography [8–10]. Recently, several studies have demonstrated the feasibility and usefulness for the detection of significant

proximal LCA stenosis by measuring only the CFV at rest using TTDE in hemodynamically stable patients with coronary artery disease [6,8,9,11,12].

Accordingly, the assessment of fatal coronary lesions using TTDE may provide additive prognostic information over routine clinical and echocardiographic parameters. Therefore, we sought to investigate the prognostic value of the CFV in the proximal LCA, independent of and incremental to clinical and basic echocardiographic parameters in hemodynamically stable patients with known or suspected heart disease who underwent TTDE accompanied by routine echocardiography.

2. Methods

2.1. Study design and subjects

This study was designed as a retrospective cohort study. We identified 3998 consecutive patients without duplication (age, 20 to 89 years) who underwent TTDE accompanied by routine echocardiography for the assessment of known or suspected heart disease between April 2008 and December 2011. They were found to have a hemodynamically stable condition that would not affect the CFV in the absence

Abbreviations: ADPV, averaged diastolic peak velocity; CAG, coronary angiography; CFV, coronary flow velocity; CI, confidence interval; LCA, left coronary artery; LV, left ventricular; TTDE, transthoracic Doppler echocardiography.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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of significant LV hypertrophy (wall thickness > 12 mm), hypertrophic cardiomyopathy, severe valvular heart disease, decompensated heart failure at TTDE, acute myocardial infarction within 30 days of TTDE, history of cardiac resynchronization therapy, and history of coronary artery bypass graft surgery [6,7,13]. In 2779 patients (70%), CFV was successfully detected in the proximal LCA using TTDE. Of these, patients with a life expectancy less than one year due to a known life-threatening malignant disease and patients with no follow-up data were excluded. Of the remaining 2299 patients, 1472 patients with a complete dataset were enrolled in the study. The process of patient selection is presented in Online Fig. 1. The study was approved by the Ethics Committee of Ehime University Graduate School of Medicine (# 1512001).

2.2. Echocardiography

TTDE was performed, followed by routine echocardiography, using Vivid 7 or Vivid E9 Ultrasound Systems (GE Vingmed, Horten, Norway) with an M4S-probe (Vivid 7) or M5S-probe (Vivid E9) by five experienced sonographers all having previously performed >500 TTDE studies. The detailed settings for the TTDE are shown in Online Table 1. After a routine examination, the root of the aorta was imaged in the parasternal short axis view, and the proximal coronary flow was observed under color Doppler guidance (Fig. 1 and Online Video). The color Doppler velocity range was set to ± 19.0 cm/s. If proximal coronary flow could not be visualized after 3 min of examination, the measurement was judged a failure based on the sonographer's decision.

The CFV measurement was performed using a pulsed Doppler as previously described [7,8,10]. The averaged diastolic peak velocity (ADPV) was measured as a characteristic determinant of the CFV. Using the analysis program of the ultrasound system, ADPV was determined from the velocities of >3 cardiac cycles. When proximal coronary flow was detected, the sample volume was placed at that point, and the CFV was recorded. The highest ADPV among several measurements at the proximal LCA was recorded and used in the present study analysis. An effort was made to set the smallest possible correction angle. The median correction angle for the proximal ADPV measurement was 28° [interquartile range (IQR), 17–33].

Conventional echocardiographic parameters were measured using routine echocardiography according to the recommendations of the American Society of Echocardiography [14,15]. The LV mass was calculated according to the American Society of Echocardiography formula and normalized to the body surface area. The LV ejection fraction was calculated by method of discs using two-dimensional images (apical four-chamber and two-chamber views). The transmitral early diastolic velocity (E) at the level of the mitral valve tips was assessed using pulsed wave Doppler, and the early diastolic mitral annular tissue velocity (e') at septal mitral annular velocities was assessed using pulsed tissue Doppler in the apical four-chamber view, and E/e' was calculated.

2.3. Clinical data

Using individual patient medical records, we assessed comorbidities, medical history, and the most recent medications and laboratory data at the time of the TTDE examination. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dl and hemoglobin A1c $\geq 6.5\%$, or use of insulin or antidiabetic medicine. Dyslipidemia was defined as low-density lipoprotein cholesterol ≥ 140 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl, triglyceride ≥ 150 mg/dl, or use of statin or fibrates. A current smoker was considered someone who smoked within the last month. Valvular heart disease was defined as moderate. The Framingham Risk Score was calculated as previously described [16].

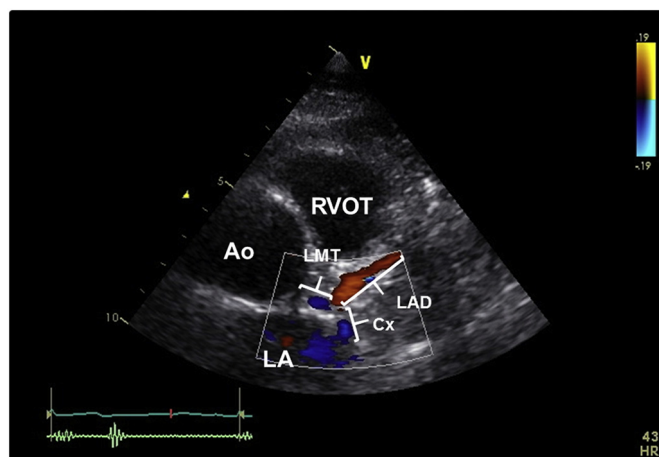


Fig. 1. An example of TTDE in the short axis view with anatomical explanations. Coronary angiography showed no significant stenosis in the proximal left coronary artery. LMT indicates the left main trunk; LAD, left anterior descending coronary artery; Cx, circumflex artery; Ao, aorta; LA, left atrium; PA, pulmonary artery; TTDE, transthoracic Doppler echocardiography.

2.4. Coronary angiography

Among the enrolled patients, 324 had coronary angiography (CAG) a few days after TTDE. The median interval between CAG and TTDE was two days. The proximal LCA was defined as segments 5, 6, and 11 of the American Heart Association (AHA) classification of CAG [17]. A lesion was defined as a stenosis diameter $\geq 50\%$ in the left main trunk, and $\geq 75\%$ in other segments [4]. The stenosis in each segment was evaluated by two experienced cardiologists both having read >1000 CAG studies. Any disagreement was settled by consensus. The number of coronaries involved was assessed. In addition, the scheduled percutaneous coronary intervention of the proximal LCA (segments 5, 6, and 11 of the AHA classification) or coronary artery bypass grafting for the proximal LCA lesion within three months after CAG were checked.

2.5. Outcomes

The primary outcome was cardiac death (death due to acute myocardial infarction, heart failure, or sudden cardiac death). The secondary outcome was all-cause death. The outcome was followed up using medical records or telephone interviews with the patients or their relatives. Patients were censored at the time of the outcome or at the end of the follow-up (July 1, 2016).

2.6. Statistical analysis

Continuous variables are expressed as mean \pm SD or medians (25th and 75th percentiles) according to their distributions, and qualitative data are presented as numbers or percentages. The significance of differences between the groups was assessed using the Mann-Whitney *U* test. For categorical variables, the chi-square test was used. Univariate linear regression analyses were used to evaluate the associations between the CFV and the study parameters to check the confounders of the CFV. For multiple comparisons, the Kruskal-Wallis test was used followed by a Bonferroni correction. The Jonckheere–Terpstra test was used to test the trend among the groups. Univariable and multivariable Cox proportional hazards models were used to determine whether the CFV was independently associated with the outcomes. No significant violations of the proportional hazards assumption were noted. To increase external validation, the candidate covariates for the multivariable models were selected based on the clinically relevant variables that were expected to confound the association between the CFV and the primary outcome as follows: age, rate pressure product, Framingham

Risk Score, diabetes, coronary artery disease, hemoglobin, estimated glomerular filtration rate, brain natriuretic peptide, LV mass index, LV ejection fraction, and E/e' [6,13,18]. As this is a retrospective study, important unmeasured confounders may exist. Five models for the assessment of the independent association of ADPV with the primary outcome were created to avoid overfitting. A receiver operating characteristic curve was used to determine the optimal cut-off value of the ADPV for the prediction of cardiac death. Survival was estimated by the Kaplan–Meier method, and differences in survival between groups were assessed by the log-rank test. We tested for interactions to explore whether the prediction of primary outcome by higher CFV in the proximal LCA differs on the basis of etiology. The incremental value of the ADPV was assessed in three modeling steps using nested models. The change in the overall log-likelihood ratio was used to assess the increase in predictive power. Harrell's C statistic was used to evaluate model performance [19]. Inter- and intraobserver reliability of ADPV was also assessed using interclass correlation coefficients. In a group of 20 randomly selected patients, 2 experienced observers (RH and SN) alternately performed 2 ADPV measurements using TTDE, then 1 observer repeated the measurements 3 days later; all the measurements were blinded. $P < 0.05$ and P -value for interaction < 0.1 were considered to be statistically significant. Statistical analyses were performed using R software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The clinical characteristics of the study cohort are summarized in Table 1. The median ADPV was 24 cm/s. During follow-up, over a median of 6.3 years, 191 (13%) all-cause deaths were observed, of which 42 (3%) were cardiac deaths. The most frequent cause of cardiac death was heart failure ($n = 18$, 43%), followed by sudden cardiac death ($n = 16$, 38%) and acute myocardial infarction ($n = 8$, 19%). Of 324 patients who underwent CAG, 106 patients had proximal lesions, 91, 60, and 26 patients had one-, two-, and three-vessel diseases, respectively. Fifty-one patients took coronary intervention for the proximal LCA lesions within three months after CAG and of whom only one cardiac death (2%) was observed during the follow-up.

3.1. Factors associated with ADPV

Online Table 2 shows the univariate linear regression analysis between ADPV and the study parameters. ADPV was positively associated with age, systolic blood pressure, heart rate, rate pressure product, Framingham Risk Score, hypertension, dyslipidemia, diabetes, coronary artery disease, brain natriuretic peptide, hemoglobin A1c, E/e', and LV mass index, and negatively associated with hemoglobin, estimated glomerular filtration rate, and high-density lipoprotein cholesterol. In the subgroup of patients having CAG, ADPV was significantly associated with the proximal LCA lesions and each number of coronaries with significant stenosis. Interestingly, as the number of coronaries involved increased, ADPV significantly increased (median values of ADPV: none: 22 cm/s, one-vessel disease: 27 cm/s, two-vessel disease: 34 cm/s, and three-vessel disease: 44 cm/s) (Online Fig. 2).

3.2. Associations of ADPV with outcomes

In the univariate analysis, age, Framingham Risk Score, atrial fibrillation, coronary artery disease, hemoglobin, estimated glomerular filtration rate, brain natriuretic peptide, lipid parameters, E/e', LV ejection fraction, LV mass index, and ADPV were significantly associated with cardiac death (Online Table 3). Furthermore, ADPV was significantly associated with cardiac death in all models after the adjustment of clinical and echocardiographic parameters, with similar hazard ratios (Online Table 4). Similarly, ADPV was independently associated with all-cause death in the model based on all 11 covariates (hazard ratio, 1.01; 95% confidence interval [CI], 1.00–1.01; $P < 0.01$).

Table 1
Clinical characteristics of the study cohort.

Variables	
Age, years	72 [62, 79]
Male	878 (59.6)
Body mass index, kg/m ²	24.2 ± 3.6
Systolic blood pressure, mm Hg	134 ± 20
Diastolic blood pressure, mm Hg	75 ± 12
Heart rate, beats/min	68 [60, 77]
Rate pressure product	9008 [7667, 10522]
Framingham risk score, %	13 [8, 20]
<i>Comorbidities</i>	
Hypertension	990 (67.3)
Dyslipidemia	814 (55.3)
Diabetes	229 (20.3)
Current smoker	113 (7.7)
Coronary artery disease	553 (36.7)
Valvular heart disease	489 (33.2)
Atrial fibrillation	261 (17.7)
Stroke	138 (9.4)
<i>Medications</i>	
ACE inhibitors/ARB	775 (52.6)
β-blockers	436 (29.6)
Calcium antagonists	778 (52.9)
Diuretics (loop or thiazide)	367 (24.9)
Diuretics (spironolactone or eplerenone)	156 (10.6)
Statins	504 (34.2)
<i>Serum makers</i>	
Hemoglobin, mg/dl	13.1 [11.9, 14.3]
Estimated glomerular filtration rate, ml/min/1.73 m ²	66 [55, 78]
Brain natriuretic peptide, pg/ml	39 [17, 86]
Total cholesterol, mg/dl	179 [157, 204]
Triglyceride, mg/dl	100 [76, 144]
High-density lipoprotein cholesterol, mg/dl	51 [42, 61]
Low-density lipoprotein cholesterol, mg/dl	103 [83, 122]
Hemoglobin A1c, %	5.8 [5.6, 6.2]
<i>Coronary angiographic parameters (n = 324)</i>	
Proximal LCA lesions	106 (32.7)
One-vessel disease	91 (28.1)
Two-vessel disease	60 (18.5)
Three-vessel disease	26 (8.0)
PCI or CABG for proximal LCA lesions within 3 months after CAG	51 (15.7)
<i>Echocardiographic parameters</i>	
LV ejection fraction, %	65 [59, 70]
E/e'	10.4 [8.3, 13.1]
LV mass index, g/m ²	89 ± 22
ADPV, cm/s	24 [18.0, 33.0]

Data are expressed as mean ± SD, as median (interquartile range), or as number (percentage). ACE = angiotensin-converting enzyme; ADPV = averaged diastolic peak velocity; ARB = angiotensin receptor blocker; CABG = coronary artery bypass grafting; CAG = coronary angiography; LCA = left coronary artery; LV = left ventricular; PCI = percutaneous coronary intervention.

3.3. Discrimination by ADPV

Based on the receiver operating characteristic curve analysis, the optimal cut-off value of ADPV to the association of cardiac death was 37 cm/s (area under the curve, 0.70; sensitivity, 82%; specificity, 62%) (Online Fig. 3). In the Kaplan–Meier curves, the incidence of cardiac death in the group with ADPV ≥ 37 cm/s was significantly higher than in the group with ADPV < 37 cm/s. Similarly, all-cause mortality was higher in the group with higher ADPV than the group with lower ADPV ($P < 0.01$) (Fig. 2).

3.4. Impact of ADPV in the proximal LCA by etiology

We performed subgroup analyses to confirm the impact of higher ADPV in the proximal LCA on primary outcome by etiology (Online

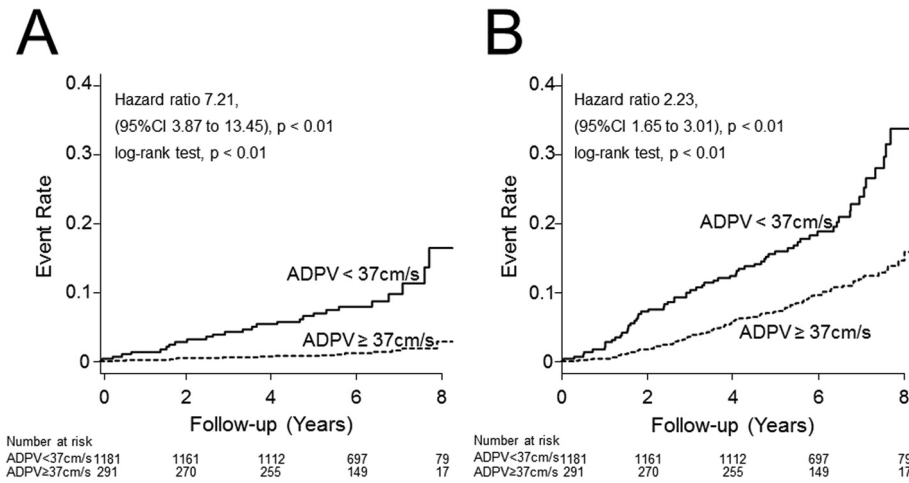


Fig. 2. Kaplan–Meier curves of (A) cardiac death and (B) all-cause death using the cut-off value of the averaged diastolic peak velocity. ADPV indicates the averaged diastolic peak velocity.

Fig. 4). Higher ADPV was significantly associated with higher incidence of cardiac death regardless of the etiology. All the etiologies, except for atrial fibrillation, had similar prognostic impacts of higher ADPV.

3.5. Incremental value of ADPV

In sequential Cox models, the predictive power of a model based on clinical variables (chi-squared = 103.4) significantly improved by the addition of basic echocardiographic variables (chi-squared = 110.7, $P = 0.01$). Furthermore, by adding ADPV to the model, its predictive power significantly improved (chi-squared = 146.6, $P < 0.01$) (Fig. 3).

3.6. Exploration of the selection bias

Due to concern regarding referral bias in the dataset completion, the differences in patient characteristics with and without a complete dataset is shown in Online Table 5. Patients with a complete dataset were significantly older and obese with a higher Framingham Risk Score, higher frequency of comorbidities, increased use of medication, and more deteriorated cardiac function than those with an incomplete dataset. In patients with missing data ($n = 2299$), 59 (3%) patients had cardiac deaths. These results suggest that the patients with an incomplete dataset had less advanced cardiac diseases. Despite that, ADPV was independently associated with cardiac death (Online Table 6). In addition, ADPV demonstrated an incremental benefit for predicting the primary outcome over the model based on clinical and basic echocardiographic parameters (chi-squared: 111.1 to 152.4, $P < 0.01$), which is similar to the results of patients with a complete dataset.

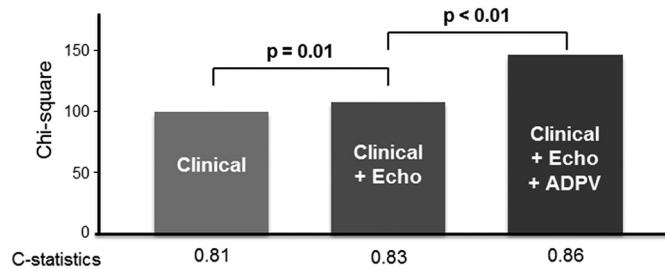


Fig. 3. Incremental value of the averaged diastolic peak velocity over the model based on clinical and basic echocardiographic parameters. The clinical model consists of seven parameters, including age, rate pressure product, Framingham Risk Score, diabetes, coronary artery disease, estimated glomerular filtration rate, and brain natriuretic peptide. Echo indicates basic three echocardiographic parameters, including the left ventricular mass index, E/e' , and left ventricular ejection fraction. ADPV indicates the averaged diastolic peak velocity.

3.7. Inter- and intraobserver variability of ADPV

Median values of ADPV measured by the first observer at the first time, the second observer, and the first observer at the second time were 25 (IQR, 16–33) cm/s, 22 (IQR, 16–36) cm/s, and 24 (IQR, 16–38) cm/s. Inter- and intraclass correlation coefficients were 0.82 (95% CI, 0.61–0.93) and 0.95 (95% CI, 0.89–0.98) for ADPV.

4. Discussion

The present study demonstrated that a higher CFV in the proximal LCA measured using TTDE accompanied by routine echocardiography was significantly associated with cardiac and all-cause mortality in hemodynamically stable patients with known or suspected heart disease, independent of and incremental to the clinical and routine echocardiographic parameters. In addition, a higher CFV in the proximal LCA appeared to be associated with significant stenosis in the proximal LCA, the number of coronary arteries with significant stenosis, higher incidence of risk factors for atherosclerosis, and the surrogate markers for increased myocardial oxygen consumption.

4.1. Possible mechanisms of the association between the prognosis and the CFV in the proximal LCA

Thus far, an increased CFV in the proximal LCA has been associated with a lesion in the proximal LCA [6,8–11], but an association with the prognosis has been uncertain. The following mechanisms can be considered from the present results to explain the association. First, the proximal LCA lesion has been reported to be fatal because it limits coronary flow for a large part of the myocardium, resulting in broad myocardial ischemia [2–4,20]. Similar with previous studies, [8–12] an increased CFV in the proximal LCA was significantly associated with stenosis in the proximal LCA of the CAG in this study.

Second, an increased CFV in the proximal LCA seemed to be associated with an increase in the number of coronary arteries involved in this study. Thus far, several partial atherosclerotic imaging parameters have been reported to be associated with the extent of coronary artery disease [21,22]. Also, an observational study using coronary computed tomographic angiography and coronary angiography revealed that the proximal lesion was observed more often with a multi-vessel disease rather than a single-vessel disease [23,24]. The extent of coronary artery disease could be associated with adverse cardiac events due to an increase in myocardial ischemia [20,25]. In the present study, the most frequent cause of cardiac death was heart failure, followed by sudden cardiac death. Myocardial ischemia can cause cardiac dysfunction and serious abnormal heart rhythms, which are significantly associated

with heart failure and sudden cardiac death [26,27]. Furthermore, such progress of atherosclerosis in the coronary artery could be associated with several systemic atherosclerotic diseases, such as stroke [28]. In addition, the CFV was associated with the Framingham Risk Score and several risk factors for the progress of systemic atherosclerosis in the present study. Accordingly, increased CFV in the proximal LCA may reflect a higher incidence of proximal LCA lesion, which may lead to coronary and systemic atherosclerosis and vice versa and might explain the association between cardiac and all-cause mortality as well as the partial increase in CFV in the proximal LCA.

Finally, an increased CFV in the proximal LCA was significantly associated with several surrogate markers of increased myocardial oxygen consumption, such as rate pressure product, anemia, LV hypertrophy, and E/e' , [29,30] although the hemodynamic condition of the enrolled patients was relatively stable in the present study. Increased myocardial oxygen consumption is associated with deteriorated LV stroke work and adverse events [31–34]. Accordingly, the CFV in the proximal LCA might be secondarily associated with a poor prognosis. In fact, we observed a significant prognostic impact of higher ADPV in the proximal LCA even in the patients without coronary artery disease.

These mechanisms may be complexly intertwined as well as associated with a poor prognosis. Nonetheless, the status of myocardial oxygen consumption may be reflected in several clinical and echocardiographic parameters to a certain extent [13,30,33,35]. Therefore, the unique information gathered regarding the severity of coronary artery disease using TTDE could provide incremental value to clinical and basic echocardiographic parameters for predicting outcomes.

4.2. Limitations

Our data should be interpreted in the context of the limitations of the study. First, CFV measurement in the proximal LCA could not be applied to all the subjects due to anatomical issues [8–10]. In this retrospective real world setting, CFV detected in the proximal LCA failed in 30% of the patients. The success rate might decline in contemporary obese Western populations. To improve the success rate of detecting CFV using TTDE, a peripheral injection of contrast agents may be helpful [36]. Moreover, the significant prognostic information of CFV measurement in the proximal LCA might contribute to justify its routine measurement. Second, CFV increases by narrowing the coronary arteries and increasing the myocardial oxygen consumption, which is closely associated with coronary autoregulation [6,13,37]. Therefore, when myocardial oxygen consumption is expected to increase, an increased CFV should be carefully interpreted because it could indicate increased myocardial oxygen consumption, proximal LCA lesion, or both. In such cases, in addition to several stress tests, an adjustment using the CFV of the adjacent segment might be useful for the discrimination of these patterns [10–12,38]. Nonetheless, we recommend that the present results be applied only to patients with stable myocardial oxygen consumption. Third, CFV at the site other than the proximal LCA was not assessed in this study. However, the prognostic importance of the proximal LCA was evident in comparison with other coronary artery sites [2,5]. Furthermore, the detection of the CFV in the left circumflex coronary artery and the right coronary artery is not easy [6,7]. Also, as we put an importance on the simplicity as a routine procedure, we investigated the implication of only the CFV in the proximal LCA. Nonetheless, the CFV at the distal left anterior descending coronary artery is feasible and would be useful for adjusting the influence of myocardial oxygen consumption, particularly in hemodynamically unstable patients [6,10]. Fourth, although the CFV reserve measurements were established as a clinically useful method for the diagnosis of significant coronary stenosis [6], it was not performed in this study. This is because the measurement requires a hyperemic state induced by pharmacological agents, which could be a barrier to the routine procedure and make patients uncomfortable. Fifth, the precise accuracy of the CFV was unknown because comparison with invasive methods using a Doppler flow wire

was not performed. However, a previous study has shown considerable agreement of the CFV between TTDE and the invasive method [39]. Also, in the present study, we successfully validated ADPV in the proximal LCA with fractional flow reserve in only 10 cases; hence, a modest negative correlation was observed (correlation coefficient: -0.56 , 95% CI: -0.88 to -0.10 , $P = 0.09$). Sixth, although ADPV was determined from the velocities of >3 cardiac cycles in our study, the measurement error based on heart rate variability in atrial fibrillation might weaken the prognostic impact of CFV in the proximal LCA. Finally, this was a single-center, retrospective cohort study. Larger multicenter studies are warranted to confirm these results.

5. Conclusions

A higher CFV in the proximal LCA measured by TTDE at rest yields incremental prognostic information toward the identification of cardiac and all-cause death over the clinical and basic echocardiographic parameters in hemodynamically stable patients with known or suspected heart disease.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2018.04.003>.

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Conflict of interest

None.

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