Heart and Vessels (2019) 34:948–956
https://doi.org/10.1007/s00380-018-01325-6

ORIGINAL ARTICLE

High-sensitivity cardiac troponin decrease after percutaneous coronary intervention in patients with stable coronary artery disease

Rikuta Hamaya[1] · Tomoki Horie[1] · Taishi Yonetsu[2] · Akinori Sugano[1] · Yoshihisa Kanaji[1] · Eisuke Usui[1] · Masahiro Hoshino[1] · Masao Yamaguchi[1] · Hiroaki Ohya[1] · Yohei Sumino[1] · Masahiro Hada[1] · Hidenori Hirano[1] · Yoshinori Kanno[1] · Haruhito Yuki[1] · Kenzo Hirao[2] · Tsunekazu Kakuta[1]

Received: 10 September 2018 / Accepted: 21 December 2018 / Published online: 1 January 2019

Abstract

Baseline cardiac troponin is a strong predictor of major adverse cardiac events (MACE), and the high sensitive assay can provide risk stratification under the 99th percentile values. Currently, prognostic benefit of PCI has not been established in patients with stable coronary artery disease (CAD), and the influence on baseline troponin levels is unknown. This study aimed to investigate the impact of PCI on baseline high-sensitivity cardiac troponin-I (hs-cTnI) levels and the association with MACE incidence. For 401 patients with stable CAD who were indicated for PCI, baseline hs-cTnI levels were measured before PCI for two times (the average: pre-PCI hs-cTnI) and 10 months after PCI (post-PCI remote hs-cTnI). Hs-cTnI day-to-day variability was assessed based on the pre-PCI values and patients were divided into three groups (Increase/No change/Decrease group) according to the extent of hs-cTnI change (post-PCI remote hs-cTnI minus pre-PCI hs-cTnI) considering the day-to-day variability. A total of 77 patients were categorized into Decrease group. Although Decrease group had significantly higher pre-PCI hs-cTnI levels compared to the other groups, this group had lowest incidence of MACE ($p < 0.001$). Hs-cTnI changes were independently associated with MACE incidence after adjustment (HR 2.069, 95% CI 1.032–4.006, $p = 0.041$ for Increase group vs. No change group; HR 0.143, 95% CI 0.008–0.680, $p = 0.009$ for Decrease group vs. No change group). Hs-cTnI change following PCI was significantly predicted by pre-PCI hs-cTnI, hs-cTnI variability, the presence of dyslipidemia, multivessel disease, and lesions with chronic total occlusion or low quantitative flow ratio. In conclusion, PCI could lower hs-cTnI levels in a certain subset of patients, in whom prognostic benefit might be expected by the intervention.

Keywords Percutaneous coronary intervention · High-sensitivity cardiac troponin · Stable coronary artery disease · Multivessel disease · Quantitative flow ratio

Introduction

Cardiac troponin is a specific marker of myocardial injury and the baseline level is associated with future cardiovascular events. High-sensitivity cardiac troponin assay can detect subtle myocardial injury in healthy individuals and provide risk stratification toward such population with under the 99th percentile value [1]. A recent study has shown the effect of statin in reducing baseline high-sensitivity cardiac troponin-I (hs-cTnI) level, which could be related to favorable clinical outcome [2]. To date, no other intervention has been proved to lower baseline hs-cTnI level.

Percutaneous coronary intervention (PCI) could be safely performed in the majority of patients with stable coronary artery disease (CAD) owing to the development of the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00380-018-01325-6) contains supplementary material, which is available to authorized users.

✉ Tsunekazu Kakuta
kaz@joy.email.ne.jp

[1] Division of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, 4-1-1, Otsuno, Tsuchiura, Ibaraki, Japan

[2] Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan

instruments and technique. However, previous studies have hardly demonstrated the benefit of PCI in terms of lowering major adverse cardiac events (MACE) over optimal medical therapy (OMT) alone [3]. Furthermore, a recent double-blind, randomized controlled trial has shown no advantage of PCI in reducing angina symptoms compared to OMT [4]. Although these reports negate the prognostic benefit of PCI for stable CAD, some studies could identify the subset of patients who could benefit from PCI for avoidance of MACE [5, 6].

The present study focused on the change in baseline hs-cTnI levels following PCI in patients with stable CAD. The aim is to determine the prevalence, clinical implication and predictors of hs-cTnI decrease after PCI. Furthermore, we sought to investigate the relationships between hs-cTnI change after PCI and coronary physiology, using quantitative flow ratio (QFR) that could be assessed retrospectively and show good agreement with fractional flow reserve (FFR) [7], to assess if hs-cTnI change is associated with pre-PCI functional ischemic burden and if hs-cTnI change might identify patients who could expect benefit of PCI.

Methods

Patient population

From June 2014 to December 2017, patients with stable CAD who underwent elective PCI at Tsuchiura Kyodo General Hospital were identified from the institutional database. From the population, the study protocol included patients whose pre-PCI baseline hs-cTnI and post-PCI remote hs-cTnI levels were determined. The exclusion criteria were the presence of unstable symptoms (worsening angina or rest angina within 1 month), PCI failure, myocardial infarction (MI) episode or cardiac catheterization within 30 days before baseline hs-cTnI assessments, decompensated heart failure (HF), cardiogenic shock, severe valvular disease, and patients on hemodialysis. To evaluate the pure effect of PCI on baseline hs-cTnI value, patients were also excluded if they experienced worsening HF or MI after PCI and before post-PCI remote hs-cTnI evaluation. The institutional ethics committee approved the study protocol. Before catheterization, all patients provided written informed consent for enrollment in the institutional database for potential future investigations. All patient data and procedural details were obtained from medical records.

Troponin measurement

Baseline hs-cTnI levels were determined from blood samples obtained in the morning in clinically stable patients at a fasting state, to reduce the diurnal variations [8]. Prior to PCI, blood samples were obtained twice, the date of admission and the next day before coronary angiography. Pre-PCI baseline hs-cTnI was defined as the average value of the two measurements. Post-PCI peak hs-cTnI was determined as the maximum value after PCI during the admission period. Post-PCI remote hs-cTnI levels were determined 10 months after PCI [median 10.0 (inter quartile range, IQR: 8.5–11.2) months] at an outpatient clinic. Hs-cTnI was measured using the ARCHITECT $i2000_{SR}$ STAT hs-cTnI assay (Abbott Laboratories, North Chicago, IL, USA).

Assessment of hs-cTnI change following PCI

Changes in hs-cTnI following PCI were assessed on the basis of day-to-day variability of pre-PCI hs-cTnI levels. We calculated the absolute difference of two measurements of pre-PCI hs-cTnI (AD) as evaluation of the day-to-day variability. Patients were categorized into three groups as follows: Decrease group, post-PCI remote hs-cTnI smaller than pre-PCI baseline hs-cTnI minus AD; Increase group, post-PCI remote hs-cTnI higher than pre-PCI baseline hs-cTnI plus AD; and No change group for the others.

Angiographic analysis and QFR computation

SYNTAX score was defined using the online, most recently updated calculator (SYNTAX SCORE I from https://www.SYNTAXscore.com). Multivessel disease was defined as the presence of ≥ 2 vessels with the diameter stenosis $>$ 50% by off-line quantitative angiography (QAngio XA 7.3; Medis, Leiden, The Netherlands). The three-dimensional quantitative angiography (3D-QCA) analysis and QFR computation were performed using a validated software (QAngio XA 3D 1.1.0 Medis Medical Imaging System, Leiden, The Netherlands) by 2 independent investigators (MH and YK) who were blinded to the patient information and were well trained before this analysis. Two angiographic projections acquired at different angles $\geq 30^\circ$ apart were transferred by local network to the QFR system. From 2 end-diastolic frames, the investigator identified 1–2 anatomical landmarks as reference points for matching location information and vessel contours were automatically delineated. Following a standard operation procedure, manual correction was allowed in case of suboptimal angiographic image quality. 3D-QCA analysis and the QFR computation were performed based on the reconstructed 3D anatomical vessel model. The contrast flow model was applied for QFR computation in the present study, in which contrast-flow QFR (cQFR) was computed by the contrast flow velocity based on the thrombolysis in myocardial infarction (TIMI) frame count analysis [7]. In the presence of multiple coronary stenoses, a single vessel with the most severely decreased cQFR value was used for the present analysis [9].

Clinical follow-up

Clinical follow-up data were collected via a review of the medical records and/or telephone interviews. Spontaneous MI was diagnosed based on the third universal definition of MI. Target vessel revascularization (TVR) was applied to ischemia-driven revascularization of PCI-targeted vessels based on the positive results of scintigraphy, myocardial perfusion imaging, stress electrocardiogram or coronary physiological assessment. MACE was defined as a composite of all-cause death, non-fatal spontaneous MI and TVR.

Statistical analysis

Categorical data, expressed as frequencies and percentages, were compared using the χ^2 test or Fisher's exact test, as appropriate. Normality of the variances was tested using Shapiro–Wilk tests. Continuous biochemical or physiological data were expressed as median (IQR) and analyzed using Mann–Whitney test or Kruskal–Wallis test for variables with non-normal distribution, or using Student's *t* test or analysis of variance for those with normal distribution. Event rates over time were estimated using the Kaplan–Meier method and linear trends were tested with log-rank tests. A Cox proportional hazards regression model was used to identify independent predictors of MACE. The covariates used in multivariable analysis were selected with the criterion of $p < 0.10$ in the univariable analysis. A collinearity index was used for checking linear combinations among covariates and the Akaike information criterion for avoiding overfitting. Multinominal logistic/linear regression analyzes were performed to determine the hs-cTnI changes following PCI. The outcomes were categorical changes in hs-cTnI and delta hs-cTnI for the multinominal and regression models, respectively. Variables showing values of $p < 0.05$ on univariable models were incorporated into multivariable models. Statistical analyzes were performed using JMP 11.2.0 (SAS Institute Inc., Cary, NC, USA). Two-sided $p < 0.05$ was considered statistically significant.

Results

Effects of PCI on baseline hs-cTnI level

From 412 patients with stable CAD who underwent elective PCI and hs-cTnI evaluation, 3 patients with PCI failure, 6 patients with spontaneous MI and 2 patients with acute HF within 10 months after PCI were excluded. A total of 401 patients (mean age was 67.4 ± 9.7 years and 79% were male) were finally analyzed in the present study. All patients had high rates of antiplatelet therapy and statin during hospital stay, at discharge, and during follow-up, with no differences observed among the groups. Baseline pre-PCI hs-cTnI levels were 5 (3–10) ng/l with day-to-day variability of 1 (0–2) ng/l. There were no significant differences between two measurements of pre-PCI hs-cTnI levels ($p = 0.99$). Pre-PCI baseline hs-cTnI was significantly correlated with the day-to-day variability (Pearson correlation coefficient = 0.70, $p < 0.001$), which underscored the importance of the variability in defining change in hs-cTnI following PCI. Post-PCI remote hs-cTnI levels were 5 (3–9) ng/l.

Patient subset exhibiting decrease in hs-cTnI after PCI

Patients were categorized into three groups according to the changes of hs-cTnI and the day-to-day variability. A total of 75, 263, 63 patients were assigned to Decrease, No change and Increase group, respectively. Patient clinical characteristics are summarized in Table 1. Decrease group had lowest prevalence of dyslipidemia and highest levels of N-terminal pro brain natriuretic peptide or pre-PCI baseline hs-cTnI. Post-PCI remote hs-cTnI values were lowest in No change group [4 (3–8) ng/l] and highest in Increase group [9 (4–14) ng/l].

Clinical outcomes

During the observational periods of 1.9 (1.3–2.8) years after PCI, 38 patients (9.5%) met clinical endpoints. Supplemental Table 1 describes the detail of the outcome in every group, and Supplemental Table 2 shows the comparison of clinical characteristics between patients with MACE and those without. Figure 1 demonstrates survival from MACE after post-PCI remote hs-cTnI measurement in patients according to the changes of hs-cTnI. Decrease group had most favorable clinical course and the categorization significantly stratified patient future risk for MACE ($p < 0.001$). Since Decrease group had highest pre-PCI baseline hs-cTnI level, which should lead to highest incidence of future events, the favorable clinical course might demonstrate the positive effects of PCI on clinical outcomes in this patient subset.

Clinical impacts of changes of baseline hs-cTnI

In this cohort consisting of only patients undergoing PCI, pre-PCI baseline hs-cTnI levels were not associated with MACE incidence (HR 0.993, 95% CI: 0.960–1.014, $p = 0.64$). Also, post-PCI peak hs-cTnI levels were not related to the outcome. In a multivariate COX regression model, age (HR 1.052, 95% CI 1.012–1098, $p = 0.009$) and delta hs-cTnI (HR 1.098, 95% CI 1.037–1.174, $p < 0.001$) were remained as the independent predictors for MACE (Table 2). When the categorization of hs-cTnI change was used, compared to No change group, Increase group (HR

Table 1 Patient characteristics

	Decrease group ($n = 75$)	No change group ($n = 263$)	Increase group ($n = 63$)	p
Demographics				
Age, years	66.2 ± 11.0	67.3 ± 9.7	69.3 ± 7.5	0.17
Male	63 (84.0)	208 (79.1)	47 (74.6)	0.39
Hypertension	47 (62.7)	189 (71.9)	48 (76.2)	0.19
Dyslipidemia	36 (48.0)	170 (64.6)	43 (68.3)	0.019
Diabetes mellitus	37 (49.3)	121 (46)	32 (50.8)	0.74
Smoking	12 (16.0)	48 (18.3)	16 (25.4)	0.35
Chronic heart failure	15 (20.0)	27 (10.3)	4 (6.3)	0.033
Atrial fibrillation	8 (10.7)	19 (7.2)	8 (12.7)	0.33
Prior myocardial infarction	17 (22.7)	40 (15.2)	11 (17.5)	0.33
Biomarkers				
Estimated GFR, ml/min/1.73m^2	69 (55–84)	67 (58–81)	67 (57–81)	0.94
LDL cholesterol, mg/dl	85 (69–107)	90 (77–113)	92 (74–107)	0.19
NT-proBNP, ng/l	231 (69–516)	103 (49–232)	158 (58–408)	< 0.001
Ejection fraction, %	62 (53–68)	64 (59–70)	65 (59–70)	0.030
Medicine at discharge				
Statin	71 (94.7)	229 (87.1)	57 (90.5)	0.13
Dual antiplatelet therapy	74 (98.7)	261 (99.2)	62 (98.4)	0.81
Beta-blocker	49 (65.3)	137 (52.1)	30 (47.6)	0.068
Angiotensin inhibitor	48 (64.0)	192 (73.0)	37 (58.7)	0.054
PCI information				
PCI to multiple vessels	12 (16.0)	24 (9.0)	9 (14.0)	0.19
PCI target				
RCA	34 (45.3)	86 (32.7)	27 (42.9)	0.075
LAD	40 (53.3)	156 (59.3)	29 (46.0)	0.14
LCx	13 (17.3)	45 (17.1)	17 (27.0)	0.21
Bypass graft	1 (1.3)	1 (0.4)	0 (0)	0.49
Troponin data				
Pre-PCI baseline hs-cTnI, ng/l	10 (6.5–19.5)	4.5 (3–9)	4 (3–8.5)	< 0.001
Hs-cTnI day-to-day variability, ng/l	1 (0–2)	1 (1–3)	0 (0–2)	< 0.001
Post-PCI peak hs-cTnI, ng l	441 (170–1172)	317 (122–1065)	467 (142–1345)	0.19
Post-PCI remote hs-cTnI, ng/l	5 (3–11)	4 (3–8)	9 (4–14)	< 0.001

Variables are expressed as *n* (%), median (interquartile range), or mean ± standard deviation

PCI percutaneous coronary intervention, *GFR* glomerular filtration rate, *LDL* low-density lipoprotein, *NT-proBNP* N-terminal pro brain natriuretic peptide, *hs-cTnI* high-sensitivity cardiac troponin-I, *RCA* right coronary artery, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery

2.069, 95% CI 1.032–4.006, $p = 0.041$) and Decrease group (HR 0.143, 95% CI 0.008–0.680, $p = 0.009$) were independently related with low MACE incidence after adjustment.

Identification of patients showing hs-cTnI change after PCI

Supplemental Table 3 describes angiographic and QFR characteristics in each group. Decrease group had highest prevalence of lesions with chronic total occlusion (24%) and lowest rate of multivessel disease (24%). No significant difference was documented in SYNTAX score.

QFR computations were completed in 307 patients (77%) because of the exclusions by chronic total occlusion (CTO) (55 patients), severe tortuousness (13 patients), arrhythmia during coronary angiography (15 patients), PCI to lesion in bypass graft or grafted main branch (2 patients), aortic ostial lesion (1 patient), and insufficient angiogram quality (8 patients). Median and mean cQFR in the total cohort were 0.70 (0.63–0.75) and 0.68 ± 0.12, respectively. Decrease group had lowest cQFR levels in three groups [median 0.66 (0.58–0.69)].

Independent predictors for hs-cTnI decrease following PCI were identified by multinominal and linear logistic

Table 2 COX proportional hazard models for predicting MACE

	Univariable models			Multivariable models 1			Multivariable model 2		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.049	1.011–1.093	0.010	1.052	1.012–1.098	0.009	1.043	1.004–1.089	0.030
Remote hs-cTnI	1.025	0.999–1.046	0.059	1.001	0.956–1.036	0.98	1.018	0.991–1.040	0.17
Delta hs-cTnI	1.096	1.051–1.135	< 0.001	1.098	1.037–1.174	< 0.001			
No change group	–	–	–				–	–	–
Increase group	2.415	1.212–4.639	0.013				2.069	1.032–4.006	0.041
Decrease group	0.151	0.008–0.717	0.012				0.143	0.008–0.680	0.009

The prognostic effects of hs-cTnI change following PCI were examined by using delta hs-cTnI (multivariable model 1) and patient categorization defined in this study (multivariable model 2). For the latter model, No change group was used as a reference. Factors showing $p < 0.10$ in the univariate models were incorporated into multivariate analyses. Abbreviations as in Table 1.

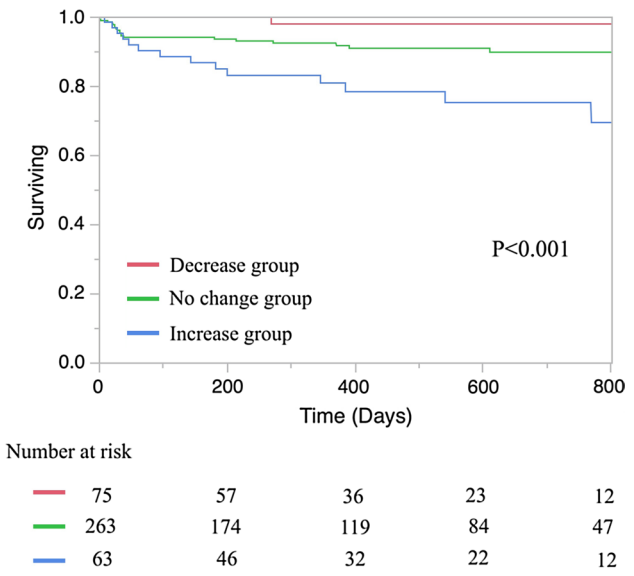

Fig. 1 Survival from MACE in patients according to the change in hs-cTnI after PCI. Kaplan–Meier curves showing survival from major adverse events (MACE) in patients divided according to high-sensitivity cardiac troponin-I (hs-cTnI) change following percutaneous coronary intervention (PCI). Decrease group had most favorable clinical outcomes ($p < 0.001$)

analyzes (Table 3). In total cohort, pre-PCI baseline hs-cTnI and the day-to-day variability, multivessel disease, and the presence of CTO lesions were independently associated with hs-cTnI change after PCI (Table 3A). For patients with lesions of cQFR analysis completed, pre-PCI baseline hs-cTnI, hs-cTnI day-to-day variability, and cQFR remained as the independent predictors (Table 3B). The linear change in hs-cTnI levels was predicted by pre-PCI hs-cTnI, hs-cTnI variability, the presence of dyslipidemia, and cQFR (Table 3C, D). PCI to lesions with CTO or low cQFR and single-vessel disease were significantly associated with subsequent decrease in hs-cTnI.

Discussion

This is the first report providing evidence of the effect of PCI on baseline hs-cTnI value and the clinical implication. The novel findings of the present study were: (1) PCI could decrease baseline hs-cTnI in 19% of patients with stable CAD even after considering the day-to-day variability; (2) MACE rate was significantly lower in patients with decreased hs-cTnI following PCI, while these patients had high pre-PCI hs-cTnI values; and (3) Decrease in hs-cTnI after PCI was associated with high pre-PCI hs-cTnI, single-vessel disease, and lesions with CTO or low QFR of the culprit vessels. In patients with these characteristics, prognostic benefit of PCI might be expected.

Previous studies have consistently demonstrated comparable effects of PCI on clinical outcomes to OMT in patients with stable CAD [3, 10]. Although PCI could reduce ischemia, PCI-related complications are inevitable, including increased risk of bleeding with antithrombotic therapy, restenosis and need for repeat revascularization, and stent thrombosis. In these studies, the benefit of PCI could not outweigh the harmful effects; in other words, PCI might positively modify the outcome if the patient's myocardial blood flow could be restored in a large extent [5, 6, 11, 12]. Recently, our group has shown the possibility that patients with worst profile of coronary flow capacity might benefit from PCI because of the great flow improvement by PCI [5]. In accordance, the present study showed patients with lowered hs-cTnI after PCI could benefit from PCI, for this subset had higher pre-PCI hs-cTnI that should be associated with poor clinical outcomes.

QFR is a novel index that is calculated based on 3D-QCA and TIMI frame count. Previous studies have shown the high agreement of QFR with FFR [7, 9]. Although computation of QFR withholds limitations especially when retrospectively investigated, 70% of the patients could be assessed in the present study, and Decrease group was characterized with significantly low QFR. Decrease group also had highest

Table 3 Predictors for hs-cTnI change after PCI

	Univariable models			Multivariable model		
	Estimate	SE	*p*	Estimate	SE	*p*
A						
Pre-PCI hs-cTnI						
Whole model			< 0.001			< 0.001
Decrease group	0.030	0.01	0.003	0.14	0.024	< 0.001
Increase Group	− 0.027	0.02	0.19	0.066	0.029	0.020
Hs-cTnI variability						
Whole model			< 0.001			< 0.001
Decrease group	− 0.068	0.05	0.18	− 0.71	0.14	< 0.001
Increase group	− 0.35	0.11	0.002	− 0.58	0.15	< 0.001
Dyslipidemia						
Whole model			0.019			0.10
Decrease group	− 0.34	0.13	0.010	− 0.29	0.15	0.051
Increase group	0.081	0.15	0.59	0.060	0.16	0.70
CHF						
Whole model			0.033			0.29
Decrease group	0.39	0.18	0.027	0.18	0.22	0.41
Increase group	− 0.26	0.28	0.35	− 0.31	0.29	0.30
EF						
Whole model			0.013			0.39
Decrease group	− 0.032	0.012	0.007	− 0.014	0.015	0.36
Increase group	0.011	0.015	0.48	0.013	0.017	0.44
Multivessel disease						
Whole model			0.039			0.006
Decrease group	− 0.25	0.15	0.096	− 0.35	0.18	0.047
Increase group	0.22	0.14	0.13	0.13	0.15	0.055
CTO						
Whole model			0.019			0.007
Decrease group	0.49	0.17	0.004	0.64	0.20	0.001
Increase group	0.17	0.21	0.42	0.24	0.22	0.28
B						
Pre-PCI hs-cTnI						
Whole model			0.007			< 0.001
Decrease group	0.025	0.011	0.015	0.14	0.029	< 0.001
Increase group	− 0.023	0.023	0.32	0.10	0.034	0.003
Hs-cTnI variability						
Whole model			< 0.001			< 0.001
Decrease group	− 0.017	0.054	0.75	− 0.75	0.17	< 0.001
Increase group	− 0.55	0.16	< 0.001	− 0.86	0.20	< 0.001
CHF						
Whole model			0.018			0.54
Decrease group	0.58	0.21	0.006	0.16	0.27	0.56
Increase group	− 0.14	0.32	0.66	− 0.25	0.35	0.48
EF						
Whole model			0.01			0.26
Decrease group	− 0.042	0.014	0.003	− 0.027	0.017	0.12
Increase group	0.006	0.018	0.75	0.004	0.020	0.84
cQFR						
Whole model			< 0.001			0.006
Decrease group	− 4.72	1.21	< 0.001	− 4.69	1.50	0.002

Table 3 (continued)

	Univariable models			Multivariable model		
	Estimate	SE	*p*	Estimate	SE	*p*
Increase group	− 1.60	1.44	0.27	− 2.29	1.63	0.16
C						
Pre-PCI hs-cTnI	− 0.46	0.024	< 0.001	− 0.35	0.032	< 0.001
Hs-cTnI variability	− 1.53	0.098	< 0.001	− 0.61	0.12	< 0.001
Dyslipidemia	1.42	0.46	0.002	0.55	0.33	0.094
D						
Pre-PCI hs-cTnI	− 0.48	0.025	< 0.001	− 0.3	0.044	< 0.001
Hs-cTnI variability	− 2.18	0.13	< 0.001	− 0.92	0.21	< 0.001
Dyslipidemia	1.61	0.55	0.004	0.32	0.37	0.39
cQFR	17.6	4.42	< 0.001	6.73	3.02	0.027

Models predicting hs-cTnI categorical change in total cohort (A: multinominal models, C: linear models, $n = 420$) and in patients with completed QFR analysis (B: multinominal models, D: linear models, $n = 323$)

The covariates used in multivariable analyses were selected with the criterion of $p < 0.05$ in the univariable analyses. For multinominal analyses, No change group was selected as the reference and the estimates indicate the log odds of the group to the reference

CTO chronic total occlusion, *cQFR* contrast-flow quantitative flow ratio. Other abbreviations as in Table 1

proportion of PCI to CTO lesions. Lesions with low QFR or CTO were anticipated to have larger ischemic myocardium, and several prior studies suggest a correlation between CAD severity and troponin elevation in the stable condition [13, 14]. Larger ischemic burden is known to be associated with poor clinical outcomes [3, 10]; thus, the low MACE rate in the Decrease group suggested that the patients might benefit from successful PCI by the reduction of large myocardial ischemia at risk that was represented as hs-cTnI decrease.

SYNTAX scoring was an established evaluation for CAD severity by integrated assessments of CTO, number of lesions, tortuosity, bifurcation or other lesion characteristics. Interestingly, SYNTAX score was not associated with hs-cTnI change following PCI. Hs-cTnI decrease was likely related to single-vessel, physiologically impaired epicardial stenosis and SYNTAX score could not represent such lesion characteristics. Pre-PCI subclinical cTnI elevation was reported to be associated with optical coherence tomography-derived unstable plaque morphology [15]. Impaired coronary flow reserve (CFR) is associated with elevated cTnI level, and the prognostic values could be incremental [16]. Furthermore, plaque characteristics and regional physiological indices are related with each other [17]. Combined with our results, regional physiological disturbance or plaque features could influence cTn level, measured not by conventional but by high-sensitive assays, and PCI would benefit to such stable patients possibly with preserved CFR which would be related to relatively low atherosclerotic burden or single-vessel disease. The benefit of PCI might be greater for focal stenosis than diffuse disease, partially in line with research by Taqueti et al. [18]. Figure 2 illustrates two typical cases in which hs-cTnI decrease following PCI would be or not be predicted. Larger, prospective studies are warranted to further investigate the clinical impact of PCI on baseline hs-cTnI levels and its prognostic information.

The number of elective PCI to stable CAD is decreasing, especially after emergent of COURAGE (the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, whereas it is essential for improvement of health economics to assess the physiological or clinical impact of PCI and to specify patients who would benefit from the intervention [10]. The present study focused on the decrease of hs-cTnI for this purpose and further research is awaited from different viewpoints.

Study limitations

The results of the present study should be interpreted with consideration of several important limitations. This study included a relatively small number of subjects from a single center, which may not allow extensive subgroup analysis or more reliable multivariable analyzes. To evaluate the effects of PCI on baseline hs-cTnI levels, the protocol excluded patients with PCI failure or MACE before post-PCI remote hs-cTnI measurement, which lead to selection bias and could underestimate the prognostic value of pre-PCI baseline hs-cTnI. Post-PCI remote hs-cTnI levels were determined by single blood samples and the day-to-day variability was not accounted. However, most prior studies used single cTn values and the insight into the variability was novel in the present study. There is no definition of decrease or increase in hs-cTnI following PCI. Our definition was strict in that the day-to-day variability was considered, which limited the number of patients who exhibited hs-cTnI change after

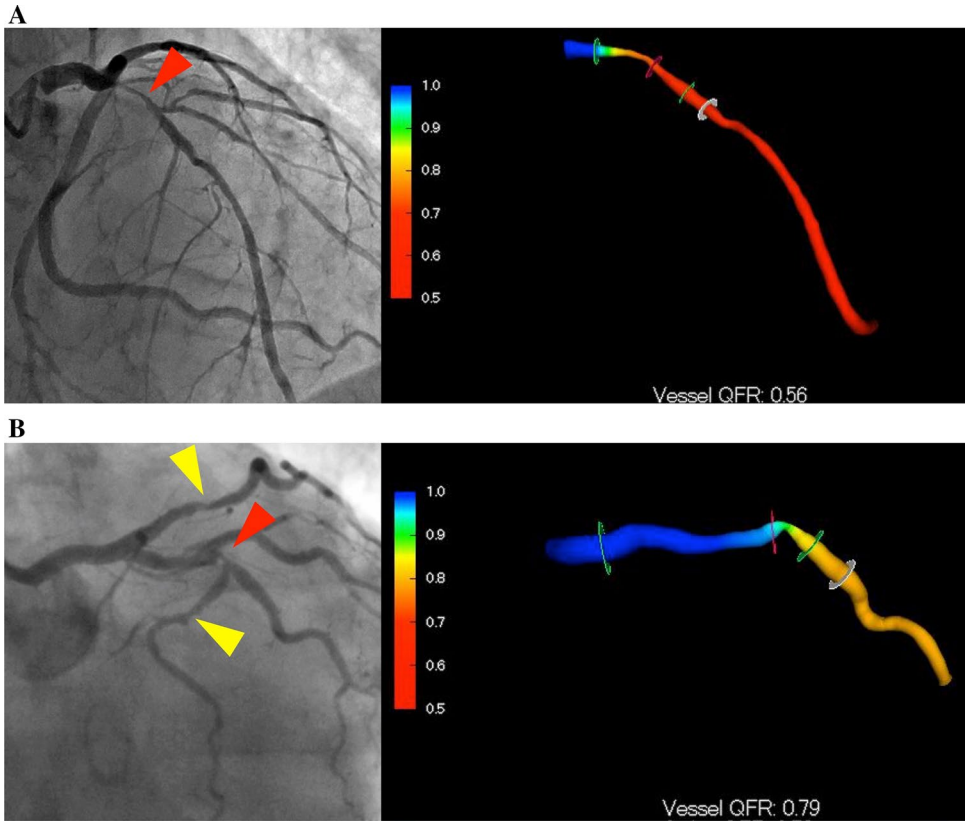

Fig. 2 Representative cases whose baseline hs-cTnI levels were influenced by PCI. Angiograms and QFR computations of two patients with stable coronary artery disease. Red arrows indicate PCI target lesion and yellow arrows deferred lesion. **a** A 63-year-old male with single left anterior descending artery (LAD) lesion His pre-PCI baseline hs-cTnI was 19.5 ng/l with day-to-day variability of 1 ng/l. cQFR of the LAD was 0.56. After PCI, baseline hs-cTnI was decreased to 12 ng/l. **b** A 67 year-old male with left circumflex (LCx) lesion. Multiple lesions were detected in LCx as well as LAD. His pre-PCI baseline hs-cTnI was 4.5 ng/l with day-to-day variability of 1 ng/l. cQFR of the LAD was 0.79. After PCI, baseline hs-cTnI was increased to 8 ng/l. High pre-PCI baseline hs-cTnI, single-vessel disease and low cQFR were the independent predictors for hs-cTnI decrease after PCI. Abbreviations as in Fig. 1

PCI. Nevertheless, the present categorization could efficiently discriminate patient risk for MACE, and reasonably predicted by patient or lesion characteristics. Finally, cQFR analyzes were completed in only 77% of the patients due to the retrospective nature of the study. Although it might cause selection bias, invasive physiological study is more likely to limit the number of subjects and cause bias, because invasive study needs wiring and vasodilation. As high correlations between FFR and cQFR were demonstrated in several prior studies, cQFR computation is an established method for evaluating physiological function of interrogated vessels.

Conclusions

Baseline hs-cTnI level could be lowered after PCI in patients with stable CAD, which might be associated with favorable clinical outcomes. Since such patients had higher pre-PCI hs-cTnI and impaired regional physiological function that are generally associated with poor prognosis, PCI could have led to reduction of future adverse events. Decrease in hs-cTnI after PCI was likely to be achieved in PCI to single vessel disease with CTO or physiologically impaired stenosis.

Acknowledgements We thank all the physicians, nurses, other catheter laboratory staff members, and patients involved in this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Roos A, Bandstein N, Lundback M, Hammarsten O, Ljung R, Holzmann MJ (2017) Stable high-sensitivity cardiac troponin T levels and outcomes in patients with chest pain. J Am Coll Cardiol 70:2226–2236
2. Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, Newby DE, Packard CJ, Mills NL (2016) High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. J Am Coll Cardiol 68:2719–2728
3. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, Erbel R, Legrand V, Gwon HC, Remkes WS, Stella PR, van Schaardenburgh P, Bech GJ, De Bruyne B, Pijls NH (2015) Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J 36:3182–3188
4. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, Ahmad Y, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP (2018) Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet 391:31–40

5. Hamaya R, Yonetsu T, Kanaji Y, Usui E, Hoshino M, Yamaguchi M, Hada M, Kanno Y, Murai T, Hirao K, Kakuta T (2018) Diagnostic and prognostic efficacy of coronary flow capacity obtained using pressure-temperature sensor-tipped wire-derived physiological indices. JACC Cardiovasc Interv 11:728–737
6. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodes-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL (2014) Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol 64:1641–1654
7. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, Fang W, Chen J, Li W, Guan C, Holm NR, Wijns W, Hu S (2017) Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol 70:3077–3087
8. Klinkenberg LJ, van Dijk JW, Tan FE, van Loon LJ, van Dieijen-Visser MP, Meex SJ (2014) Circulating cardiac troponin T exhibits a diurnal rhythm. J Am Coll Cardiol 63:1788–1795
9. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JH, Holm NR, Wijns W (2016) Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR pilot study. JACC Cardiovasc Interv 9:2024–2035
10. Sedlis SP, Hartigan PM, Teo KK, Maron DJ, Spertus JA, Mancini GB, Kostuk W, Chaitman BR, Berman D, Lorin JD, Dada M, Weintraub WS, Boden WE (2015) Effect of PCI on long-term survival in patients with stable ischemic heart disease. N Engl J Med 373:1937–1946
11. Hamaya R, Sugano A, Kanaji Y, Fukuda T, Kanno Y, Yonetsu T, Usui E, Hoshino M, Hada M, Ohya H, Sumino Y, Yuki H, Murai T, Lee T, Kakuta T (2018) Absolute myocardial blood flow after elective percutaneous coronary intervention evaluated on phase-contrast cine cardiovascular magnetic resonance imaging. Circ J 82(7):1858–1865
12. Kanaji Y, Murai T, Yonetsu T, Usui E, Araki M, Matsuda J, Hoshino M, Yamaguchi M, Niida T, Hada M, Ichijyo S, Hamaya R, Kanno Y, Isobe M, Kakuta T (2017) Effect of elective percutaneous coronary intervention on hyperemic absolute coronary blood flow volume and microvascular resistance. Circ Cardiovasc Interv 10:e005073
13. Korosoglou G, Lehrke S, Mueller D, Hosch W, Kauczor HU, Humpert PM, Giannitsis E, Katus HA (2011) Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. Heart 97:823–831
14. Ndrepepa G, Braun S, Schulz S, Mehilli J, Schomig A, Kastrati A (2011) High-sensitivity troponin T level and angiographic severity of coronary artery disease. Am J Cardiol 108:639–643
15. Lee T, Murai T, Yonetsu T, Suzuki A, Hishikari K, Kanaji Y, Matsuda J, Araki M, Niida T, Isobe M, Kakuta T (2015) Relationship between subclinical cardiac troponin I elevation and culprit lesion characteristics assessed by optical coherence tomography in patients undergoing elective percutaneous coronary intervention. Circ Cardiovasc Interv 8:001727
16. Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF (2015) Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 131:528–535
17. Usui E, Murai T, Kanaji Y, Hoshino M, Yamaguchi M, Hada M, Hamaya R, Kanno Y, Lee T, Yonetsu T, Kakuta T (2018) Clinical significance of concordance or discordance between fractional flow reserve and coronary flow reserve for coronary physiological indices, microvascular resistance, and prognosis after elective percutaneous coronary intervention. EuroIntervention 14(7):798–805
18. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, Dorbala S, Blankstein R, Di Carli MF (2015) Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation 131:19–27