The predictive factors affecting false positive in on-site operated CT-fractional flow reserve based on fluid and structural interaction

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ARTICLE INFO

ABSTRACT

Background: A novel algorithm has been developed for the on-site analysis of CT-fractional flow reserve (CT-FFR) using fluid structural interactions. There have been no reports on the factors affecting the diagnostic performance of CT-FFR using this algorithm. We evaluated the factors predictive of false-positive CT-FFR findings compared to invasive FFR as a reference standard.

Methods: The subjects were 66 consecutive cases (81 vessels) who underwent invasive FFR assessment within 90 days of the detection of 30–90% stenosis of one vessel of the major coronary artery, from among patients with suspected coronary arterial disease who underwent one-rotation scanning by 320-row coronary CT angiography (CCTA). The prospective CCTA mode was used for all patients, with the X-ray exposure set in a range of 70–99% of the RR interval. The FFR was calculated on-site from multiple cardiac phases. Factors associated with a false-positive finding of functional stenosis on CT-FFR, defined as an invasive FFR of ≤0.80, were evaluated using logistic regression analysis.

Results: Thirty-nine vessels (48.1%) had an invasive FFR of ≤0.80. CT-FFR and invasive FFR values disagreed in 13 vessels in 13 patients. The values were false positive in 12 of the vessels. In an analysis of patient characteristics, the body mass index (odds ratio, 1.33; 95%CI, 1.06–1.67; p = 0.01) and Image noise (odds ratio, 1.18; 95%CI, 1.01–1.40; p = 0.04) were predictive of false-positive findings. The presence of calcified plaque (odds ratio, 5.16; 95%CI, 1.06–20.85; p = 0.01) was the only significant predictive factor in a vessel-based analysis of lesion characteristics.

Conclusions: The presence of calcified plaque exerted a significant effect on the diagnostic performance of CT-FFR, and did so independently of the degree of calcification indicated by the Agatston score.

1. Introduction

A method has been developed to calculate the fractional flow reserve (FFR) by applying the principle of computational fluid dynamics based on conventional coronary computed tomography angiography (CCTA) images (FFR_{CT}). A CT-derived FFR can be expected to be more clinically practical than the conventional invasive FFR. The method can be performed on an outpatient basis with a lower radiation exposure dose through a set of relatively simple procedures. In one large-scale multi-center study, FFR_{CT} was demonstrated to add incremental diagnostic value to the findings of conventional CCTA performed using invasive FFR values as reference [1–3]. Evaluation by FFR_{CT} has also been reported to preempt unnecessary invasive coronary angiography [4] and to cost less than invasive coronary angiography as an initial evaluation [5] for patients with suspected coronary artery disease. Several factors, however, have been reported to influence the diagnostic performance of FFR_{CT} [6–8]. Careful interpretation in individual patients is therefore necessary for clinical use.

An algorithm has recently been developed to calculate the FFR from CCTA based on the fluid structure interactions (CT-FFR). Patient-specific conditions can be set when calculating CT-FFR by performing the analysis according to the Hierarchical Bayes & Markov-Chain Monte Carlo method in consideration of changes in the shape, movement, cross-sectional area, and volume of the coronary artery determined using several optimal cardiac phases to acquire 70–99% of the cardiac phase data [9,10]. Further, on-site analysis can be achieved by calculating the 1D computational fluid dynamics. CT-FFR using this algorithm can add an incremental diagnostic value to the findings of

conventional CCTA performed using invasive FFR values as reference [11, 12]. The specificity and positive predictive value of this CT-FFR are low relative to its sensitivity and negative predictive value, which increases the likelihood of false-positive results [11,12]. While it will be important to evaluate factors that affect the false-positive results of CT-FFR and to use the technique in real clinical situation based on this evaluation, the factors influencing the diagnostic performance may diverge as the algorithm differs from that for conventional FFR_{CT}. The objective of this study was to identify factors leading to false-positive findings on CT-FFR calculations based on fluid structure interactions using invasive FFR as a per-patient and per-vessel reference in patients with 30–90% stenosis on CCTA.

2. Methods

2.1. Study population

This was a prospective study. One beat scanning using 320-row coronary CT was performed on 864 consecutive patients with suspected coronary artery disease between December 1, 2015 and July 23, 2018. Out of this population, 75 consecutive patients with 30–90% stenosis of at least one major epicardial vessel of 2-mm or larger who gave consent to evaluation by invasive FFR within 90 days were selected as subjects. Among these 75 patients, no target vessel was indicated for CT-FFR measurement in 1, consent was withdrawn during the study in 2, ventricular tachycardia developed during invasive FFR in 1, the stenosis of the lesion exceeded 90% on invasive coronary angiography in 9, and acute coronary syndrome developed before FFR after CCTA in 1. After excluding these 14 patients, 66 remained in the analysis.

The exclusion criteria were renal insufficiency (eGFR <60 mL/min/1.73 m²), bronchial asthma requiring long-term steroid therapy, and contraindications to iodinated contrast medium or known CAD. This study was approved by the institutional human research ethics committee and all participants gave written informed consent.

2.2. CCTA acquisition

Patients with a pre-scan heart rate of ≥60 beats per minute were given 20 to 40 mg of metoprolol orally. If the heart rate remained ≥61 beats per minute after 1 h, they were given an intravenous injection of landiolol (0.125 mg/kg). Patients in whom beta-blockers were contraindicated (due to severe aortic stenosis, systolic blood pressure < 90 mg Hg, bronchial asthma, symptomatic heart failure, or advanced atrioventricular block) did not receive these treatments.

The following devices were used: Aquilion ONE ViSION Edition™ or Aquilion ONE GENESIS Edition™ (320-ADCT, Canon Medical Systems Corporation, Otawara, Japan), a Dual Shot GX 7 (contrast injector, Nemoto Kyorindo Co., Ltd., Tokyo, Japan), a Model 7800 ECG monitor (Chronos Medical Devices Inc., Tokyo, Japan), and a Ziostation image analyzer (Zio M900, Ziosoft Inc., Tokyo, Japan).

Scanning was performed at a tube voltage of 100 kV in patients with body mass indexes of <30 kg/m² and a tube voltage of 120 kV in patients with body mass indexes of >30 kg/m². The mean tube current was calculated with automatic exposure control for a standard deviation (SD) of 20. Starting with a slice width of 0.5 mm and reconstruction interval of 0.25 mm, the minimum number of rows necessary to include all coronary arteries was selected from 200 rows (100 mm), 240 rows (120 mm), 256 rows (128 mm), 280 rows (140 mm), and 320 rows (160 mm), with reference to unenhanced CT images obtained to determine the coronary artery calcium score (CACS). All CACS data were evaluated on a workstation soft ware (Zio M900 or ZioStation, Ziosoft). A calcified lesion was defined as ≥3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units (HU). The CACS was determined using the following parameters: 120 kV, 150 mA, and 3-mm thickness to calculate the Agatston score [13].

The prospective CTA mode was used for all patients, with a range of X-ray exposure of 70–99% of the RR interval. Each patient was injected with the contrast agent iohexol (Omnipaque 350 mg/mL I; Daiichi Sankyo Company, Tokyo, Japan) for 12 s at a rate of 180 mg I/kg/s, followed by 30 mL of saline at the same rate as the contrast agent.

Intermittent prep scanning with bolus tracking at the four-chamber-view level was performed once every 0.5 s, beginning from 10 s after the start of the contrast agent injection. Scanning was commenced when the contrast agent reached 300 HU in the ascending aorta. Adaptive iterative dose reduction by three-dimensional processing (AIDR3D) was used for all patients, with the intensity set at the standard level. Radiation doses were estimated and compared using the extended Dose Length Product (DLPe) from a 320-detector row CT [14]. The effective dose was calculated by multiplying the DLPe by 0.028, based on ICRP publication 103 [15].

2.3. CCTA interpretation

Both cross-sectional and longitudinal curved multiplanar reformation images were analyzed for plaque detection. Coronary artery segments with diameters of ≥2 mm were evaluated for the degree of stenosis. The percent degree of stenosis was determined by obtaining the percent ratio of the stenotic lumen to the normal vessel diameter proximal or distal to the stenosis. The stenosis was measured at the angle showing the narrowest degree of stenosis in still images taken from multiple projections. The degree of stenosis was evaluated by consensus of three experienced cardiologists who were unaware of the clinical data. Lesions with stenosis of >50% were defined as significant. A stenotic lesion was defined as significant if calcification prevented access to the stenosis. The diagnostic accuracy of CCTA in comparison to invasive coronary angiography is described in a Supplemental file.

2.4. CT-FFR analysis

After the data were input into CT-FFR software (Canon Medical Systems Japan), the CT-FFR analysis was performed by skilled analysts who had >50 h of experience in training with the software and were blinded to the invasive angiography and FFR findings. The CT-FFR was calculated after identifying the center line and vascular wall of the blood vessel and making manual corrections. The calculation was performed in a series of steps previously reported [9,10]: identifying the borderline conditions based on variations in the vascular cross-sectional areas in images of several phases, performing a fluid analysis based on the borderline conditions identified, and identifying pressure and flow in the blood vessel at each position. No patient was excluded from the calculation of CT-FFR due to image quality.

A senior cardiologist and radiologist, both of whom had >10 years of experience in CT post-processing, reviewed all the processed images to revise the centerline and contour if necessary.

2.5. Invasive coronary angiography, FFR

Detailed information is provided in a supplemental file.

2.6. Definition of vessel characteristics

A coronary plaque was defined as a structure of >1 mm² in area located within the vessel wall. A calcified lesion was defined as a structure with a CT attenuation number of ≥130 HU on the plain image or >130 HU on the contrast-enhanced image. Calcified plaque was defined as an atherosclerotic plaque wholly manifesting as calcium density. Partially calcified plaque was defined as atherosclerotic plaque in which there were 2 visible plaque components, of which 1 was calcified. Noncalcified plaque was defined as an atherosclerotic plaque that was wholly devoid of calcium density.

Positive remodeling was defined when the coronary diameter at the plaque site was at least 10% larger than the reference segment (positive remodeling index>1.1). Low-attenuation plaque was defined when the minimum HU among five 0.36 × 0.36-mm regions of interest was <30 [16,17]. Bifurcation was defined when a major side vessel of >5 mm in diameter branched off from the main coronary artery.

2.7. Definition of risk factors

Hypertension was defined as either a systolic or diastolic blood pressure of ≥140/90 mmHg or the use of antihypertensive medications. Diabetes mellitus was defined when any of the following conditions were met fasting blood sugar of ≥126 mg/dl, postprandial blood sugar of ≥200 mg/dl, hemoglobin A1c of ≥6.5% (NGSP), or the use of medications. Dyslipidemia was defined when any of the following conditions were met total cholesterol of ≥220 mg/dl, low-density lipoprotein cholesterol of ≥140 mg/dl, fasting triglycerides of ≥150 mg/dl, high density cholesterol of <40 mg/dl, or the use of lipid-lowering medications. Patients who had smoked during the past 1 year from the time of CCTA acquisition were defined as smokers.

2.8. Evaluation of image noise

CT numbers and SD values were determined in circular 16 mm × 16 mm regions of interest in the ascending aorta at the height of the origin of the left coronary artery in a short-axis image. We defined this SD value as Image noise.

2.9. Statistical analysis

Continuous data were expressed as the mean ± standard deviation (SD). Categorical data were expressed as frequencies (percentages). The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were calculated to predict the ability of CT-FFR to identify FFR≤0.80 on a per vessel and per patient basis. Predictors for false positive findings were determined by a univariate logistic regression analysis. p-Values of <0.05 were considered significant. The statistical analyses were performed using JMP Software for Windows (SAS Institute Inc., USA).

3. Results

3.1. Patient and vessel characteristics

Eighty-one lesions of 66 patients were analyzed. The mean patient age was 67.1 ± 9.7 years old and the mean calcium score was 424.7 ± 554.8. Invasive FFR was calculated in 81 vessels: RCA, 17; LAD, 50; and LCX, 14. Invasive FFR ≤ 0.80 was detected in 28 vessels (34.6%) and CT-FFR ≤ 0.80 was detected in 39 vessels (48.1%). CCTA>50% diameter stenosis and invasive coronary angiography>50% diameter stenosis were detected in 62 vessels (76.5%) and in 45 vessels (55.6%), respectively. In the 81 target lesions of FFR, positive remodeling was noted in 21 vessels (25.9%), low-attenuation plaques were noted in 12 (14.8%), and bifurcation was noted in 37 (45.7%). The morphological classification of the lesions was non-calcified plaque in 19 vessels (23.5%), partially calcified plaque in 28 (34.6%), and calcified plaque in 34 (42.0%). The patient and vessel characteristics are presented in Table 1.

3.2. Scan characteristics

The mean heart rate at the time of acquisition was 54.3 ± 5.0, and nitrates were used in all patients. The tube voltage was set at 120 kV for 8 patients, and the mean effective dose was 5.4 ± 2.6 mSv. The scan characteristics are presented in Table 1.

Table 1
Patient, scan and vessel characteristics of all study patients.
CACS: coronary artery calcium score, DLPe: extended Dose Length Product.
CCTA: coronary CT angiography, FFR: fractional flow reserve.

66 patients	
Age	67.1 ± 9.7
Gender (M/F)	43/23
Body mass index (kg/m²)	24.2 ± 3.4
Diabetes mellitus (%)	34(51.5)
Hypertension (%)	41(62.1)
Dyslipidemia (%)	51(77.3)
Smoking (never/former/current)	25/28/13
Total CACS	424.7 ± 554.8
Mean heart rate	54.3 ± 5.0
Tube voltage(kV)	100 kV:58(87.9%)
	120 kV:8(12.1%)
Tube current (mA)	547.4 ± 15.9
DLPe (mGy·cm)	189.2 ± 86.2
Effective dose (mSV)	5.4 ± 2.6

81 vessels	
Vessels with CCTA maximum stenosis>50%	76.5% (62/81)
Vessels with CT-FFR≤0.8	48.1% (39/81)
Vessels with invasive coronary angiography maximum stenosis>50%	55.6% (45/81)
Vessels with invasive FFR≤0.8	34.6% (28/81)
RCA/LAD/LCX	17/50/14
Positive remodeling	25.9% (21/81)
Low attenuation plaque	14.8% (12/81)
Positive remodeling + low attenuation plaque	7.4% (6/81)
Bifurcation	45.7% (37/81)
Non-calcified plaque	23.5% (19/81)
Partially calcified plaque	34.6% (28/81)
Calcified plaque	42.0% (34/81)

3.3. Diagnostic accuracy of CT-FFR on a per patient basis and per vessel basis

CT-FFR ≤ 0.80 and invasive FFR ≤ 0.80 were mismatched in 13 patients (13 vessels). Nine of the 12 vessels were false positive and 1 was false negative. On a per-patient basis, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of CT-FFR in detecting functional stenosis defined as invasive FFR ≤ 0.80 were 96.8%, 65.7%, 71.4%, 95.8%, and 80.3%, respectively. On a per-vessel basis, the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of CT-FFR in detecting functional stenosis defined as invasive FFR ≤ 0.80 were 96.4%, 77.4%, 69.2%, 96.7%, and 84.0%, respectively. (Table 2) The correlation coefficient between CT-FFR and invasive FFR was 0.55. The AUC to predict FFR ≤ 0.8 on a per-vessel basis in CT-FFR based on the severity of coronary stenosis is provided in a Supplemental file.

3.4. Univariate analysis for prediction of false positive findings on CT-FFR

Factors related to the prediction of false positivity were investigated by logistic regression analysis. In the patient-based univariate analysis,

Table 2
Diagnostic accuracy of CT-FFR on per patient and vessel basis.

	CT-FFR (patient)	CT-FFR (vessel)
True positive	23	27
True negative	30	41
False positive	12	12
False negative	1	1
Sensitivity (%)	96.77	96.43
Specificity (%)	65.71	77.36
Positive predict value (%)	71.43	69.23
Negative predictive value (%)	95.83	97.62
Accuracy (%)	80.30	83.95

Table 3
Univariate analysis on patient base and vessel base for prediction of false positive CT-FFR.
CACS: coronary artery calcium score.

Variable	OR	95%CI	p value
The patient-based univariate analysis			
Age	1.00	0.94–1.08	0.81
Male	0.66	0.18–2.39	0.53
Body mass index	1.33	1.06–1.67	0.01
Diabetes mellitus	3.36	0.82–13.81	0.08
Hypertension	3.55	0.71–17.81	0.09
Dyslipidemia	0.88	0.20–3.77	0.86
Current smoking	0.76	0.15–4.00	0.74
Mean heart rate	0.98	0.87–1.12	0.79
CACS 3groups			
CACS≤100 (reference)	1.00	1.00	N/A
100 < CACS≤400	3.69	0.59–22.94	0.16
CACS>400	4.50	0.81–25.15	0.09
Image noise	1.18	1.01–1.40	0.04
Left ventricular mass	0.99	0.98–1.01	0.37
Left ventricular mass index	0.97	0.94–1.01	017
The vessel-based univariate analysis			
Calcified plaque	5.16	1.06–20.85	0.01
Vessel CACS 3groups			
vCACS≤50 (reference)	1.00	1.00	N/A
50 < vCACS≤100	8.00	0.81–79.02	0.08
vCACS>100	6.28	0.73–54.48	0.10
Positive remodeling	0.23	0.03–1.94	0.11
Bifurcation	0.56	0.15–2.05	0.37
Coronary tree			
RCA + LCX (reference)	1.00	1.00	N/A
LAD	0.86	0.25–3.02	0.82

body mass index (odds ratio, 1.33; 95%CI, 1.06–1.67; p = 0.01) and Image noise (odds ratio, 1.18; 95%CI, 1.01–1.40; p = 0.04) were significant predictors (Table 3). In the vessel-based univariate analysis, the presence of calcified plaque (odds ratio, 5.16; 95%CI, 1.06–20.85; p = 0.01) was significant factor (Table 3).

Data on a representative false positive case are presented in a Supplemental file.

4. Discussion

The results of CT-FFR analysis using fluid structure interaction failed to match the results of invasive FFR in 13 (13 vessels) of the 66 patients (81 vessels) with 30–90% stenosis on CCTA, and were falsely positive in 12 of the patients (12 vessels). We therefore examined the factors associated with the false positive CT-FFR findings. In the per-vessel analysis, the presence of calcified plaques in the vascular lesions was the only factor significantly associated with false positivity. While the optimal cut-off value for deviation of the diagnosis based on the vascular coronary artery calcium score (CACS) was 55 in the ROC curve analysis, the degree of vessel calcification indicated by the Agatston score was not a significant predictor. We previously reported that if invasive FFR was set at ≤0.80 when CACS exceeded 400, the specificity decreased and the diagnostic performance of CT-FFR weakened [11]. In the present study we set both the patient-based and vessel-based CACS into those two categories, but neither of the factors was significantly related to false positivity. Although calcified plaques increase as the CACS increases, these results tell us that the presence of calcified plaques in a vascular lesion targeted by FFR analysis is important even if localized. This limitation of spatial resolution was thought to produce a calcification-induced partial volume and beam-hardening-induced artifacts, resulting in an underestimated tracing of the inner lumen. The analysis employed in the present study was performed on site using a workstation. Automatic analysis software partially combined with manual procedures was used for the centerline and editing of the lumen, enabling simple analyses within a short time. Reproducibility among the analysts was a problem, however, and may have influenced the results of this study. This analysis was performed by skilled analysts who had trained for 50 h or more. The results were reviewed by a radiologist and cardiologist, each of whom had 10 or more years of experience. We previously reported that the correlation coefficient of the CT-FFR value between beginners and skilled analysts increased to 0.83 after specific training with feedback [18]. The inter-observer reproducibility and intra-observer reproducibility have also been found to be favorable among analysts who have trained for a specific time [11], suggesting that results similar to those of this study can be obtained by analysts who undergo specific training.

The BMI and Image noise were significantly related to false positive in the per-patient analysis. In the acquisition protocol used, the tube voltage was set at 120 kV when the patient's BMI exceeded 30, and the tube current was set at an SD value of 20. This tube current had an upper limit, and increases in noise accompanying increases in BMI might have influenced the accuracy of the blood vessel tracing. Although the mean CT number of the ascending aorta at the origin of the coronary artery significantly differed between the false-positive and non-false-positive groups (458.9 ± 62.8 vs 434.0 ± 72.6, p = 0.28, data was not shown), the Image noise was significantly related to false positive. This higher Image noise may have been linked to the positive correlation found between calcification of the coronary artery and BMI even after adjustment for other risk factors [19].

Misalignment, motion artifacts, and the use of β-blockers and nitroglycerin have been reported to influence the diagnostic performance of FFR_{CT} [8]. The use of a 320-row area detector CT, in combination with a low patient HR of 54.3, helped us avoid misalignment in the present study. One-beat scanning was selected for all patients to produce a favorable image quality, and all patients were administered nitroglycerin. These factors were therefore omitted from the analysis.

LV mass and diabetes mellitus are reportedly associated with the deviation of the value between CT-based FFR using the conventional algorithm and invasive FFR [7], but neither was a significant factor in our study. The resting total coronary flow and microvascular resistance in conventional FFR_{CT} are determined according to the allometric scaling laws [20,21]. The reduction of peripheral vascular resistance due to hyperemia in conventional FFR_{CT} is calculated based on a method in which the variation among patients with a normal coronary flow reserve is set at 4% or lower [22], disregarding individual differences among patients [20,21]. The algorithms used in this study do not apply allometric scaling laws or virtual estimates of hyperemia for calculation. Our algorithms may thus explain why the LV mass and diabetes mellitus reported in the past [7] are not discordant with the findings in the present study.

One recent study reported that the FFR value was lower in lesions exhibiting the features of vulnerable plaques even with a similar degree of stenosis [23]. Other studies have reported significantly lower FFR findings in cases exhibiting CT findings consistent with vulnerable plaques, such as positive remodeling and low attenuation, even when the degree of stenosis was similar [24,25]. The addition of these manifestations significantly increased the diagnostic performance of FFR_{CT} [26]. In theory, however, these factors are likely to influence the false negativity of CT-FFR. As most our patients with a divergent diagnosis were falsely positive, we investigated factors related to false positivity. These factors, therefore, may have had no significant association. Positive remodeling was noted in only one vessel, and low-attenuation plaques were absent altogether, in the falsely positive patients. While another study reported that bifurcation lesions influenced the diagnostic performance [8], we found no evidence of such an influence in our study. The patient-specific borderline conditions in the algorithm used for the present study were set by considering changes in the shape, movement, cross-sectional area, and volume of the coronary artery using several cardiac phases. Further investigation will be necessary to clarify whether these differences between our algorithm and the FFR_{CT} algorithm influence the results.

5. Limitations

This study had several limitations. First, this was a single center study investigating only a small number of patients. From a statistical point of view, we therefore relied only on evaluation by univariate analysis for the investigation of the predictors of false positivity using logistic regression analysis. While the per-vessel analysis analyzed multiple vessels from the same patients in several instances, the invasive FFR value in the vessel was thought to be independently defined in each vessel even in the same patients. Further, independent variables in logistic regression analysis could also be considered independent factors in the same patients. We therefore chose not to perform any analysis by a generalized linear mixed model. As a second limitation, patients with stenting and patients treated by bypass surgery were excluded. Third, although factors related to false positivity were examined setting the baseline of invasive FFR at ≤0.80, the factors causing CT-FFR values inconsistent with invasive FFR may have differed. Fourth, a factor in invasive FFR could be a factor of false positivity on CT-FFR. Even so, invasive FFR is now widely used in real-world clinical practice as a gold standard for functional stenosis. We therefore analyzed invasive FFR as a factor of false positivity by treating it as a reference in the present study. Fifth, with regard to the reported effect of image reconstruction on the quantification of coronary artery calcium [27], we took no steps to examine the influences of differences in the image reconstruction. In the present study we used the reconstruction method commonly applied in actual clinical practice. Sixth, while we tried to get the consent of all unknown CAD patients with stenosis of 30–90% on CCTA, optical medical therapy and/or stress myocardial perfusion SPECT were selected for some patients. This may have caused a patient selection bias by precluding the participation of some of the unknown CAD patients with stenosis of 30–90% on CCTA.

6. Conclusion

Most of the cases with mismatched findings between invasive FFR and CT-FFR were false positive. The presence of calcified plaque significantly affected false-positive findings in on-site operated CT-FFR based on the fluid structure interaction, and did so independently of the CACS indicated by the Agatston score.

Funding

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100372.

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