The impact of tissue-tracking strain on the left atrial dysfunction in the patients with left ventricular dysfunction

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1. Introduction

Recently, several studies focus on the importance of left atrial (LA) function. LV diastolic dysfunction increases the left ventricular (LV) preload and affects the LA structure and function [1]. Furthermore, myocardial scars, caused by myocardial infarctions, etc., frequently lead to an impaired LV filling and result in LA enlargement and an impaired LA function [2,3]. Therefore, the LA function reflects the effect of the LV filling and function. Generally, LA fibrosis increases in patients with LV dysfunction compared to that in those with a normal LV function [1–3].

Cardiac magnetic resonance (CMR) is useful for assessing the LV function and fibrosis [4,5]. There have been many reports regarding late gadolinium enhancement (LGE), T1 mapping, and tissue-tracking strain using CMR.

Some studies have indicated the association between the LA function and fibrosis and tissue tracking observed by cine CMR [1,6]. However, using the LGE and T1 mapping to assess LA fibrosis is controversial because of CMR's spatial resolution. Further, there are few studies regarding the LA extracellular volume (ECV) calcu-
lated by T1 mapping and there are no studies regarding the relationship among T1 value, ECV, and strain in LA.

It is already revealed that LV dysfunction decreases LA functions [1–3]. Therefore, we hypothesized that there may be significant differences in the LA function parameters, such as T1 values and strain, compared to those in the low left ventricular ejection fraction (LVEF) patients with those in normal LVEF patients.

The present study aimed to investigate the usefulness of CMR for evaluating the LA function using tissue-tracking strain and the T1 mapping. Furthermore, the relationship between LA-ECV and LA-strain was analyzed.

2. Methods

2.1. Study population and study design

This study prospectively enrolled 65 consecutive patients who underwent CMR using contrast agents to evaluate LV function and cardiomyopathy between January 2017 and April 2018 at our institute (Mitsui Memorial Hospital, Tokyo, Japan). They were the patients whose abnormalities were pointed out with their health checkups; echocardiography, or electrocardiography. The LGE, T1 mapping, and tissue-tracking strain using CMR were evaluated to examine their cardiological abnormalities. Among the 65 patients, 15 patients had no history of hypertension, diabetes, or atrial fibrillation (AF) and their body mass index (BMI) was less than 25 kg/m². They underwent CMR for electrocardiogram abnormalities, such as premature ventricular contractions (PVCs) or abnormal T waves. However, no coronary stenosis or cardiomyopathy was determined by the CMR or other modalities. Therefore, those 15 patients were defined as the healthy group. The remaining 50 patients had cardiological abnormalities detected by the CMR. Further, they were divided into two groups according to a left ventricular ejection fraction (LVEF) of <50% or ≥50% on echocardiography. Because the echocardiography is generally used to evaluate cardiac function in clinical practice. The classification of an impaired LVEF (LVEF < 50%) was defined according to the previous study [7]. Therefore, the patients finally were divided into three groups; LVEF < 50% group (n = 20), LVEF ≥ 50% group (n = 30), and healthy group (n = 15).

We assessed the LA-CMR parameters to evaluate the differences in LA functions among the three groups. For the CMR parameters, the T1 values, ECV, and longitudinal or circumferential strain were investigated to assess the myocardial function and fibrosis. The ECV was calculated by the measuring the myocardial and blood T1 values before and after the administering contrast agents. The study protocol was approved by the institutional review board of Mitsui Memorial Hospital. The study was in compliance with the principles outlined in the Declaration of Helsinki.

2.2. Echocardiography protocol

Echocardiography was performed in all patients. The echocardiographic parameters were measured in the standard parasternal long-axis and apical 2-chamber and 4-chamber views. The LVEF was calculated by the modified Simpson method. The LV diastolic function was evaluated using a transmitral flow profile in the apical 4-chamber view measured on pulsed and tissue Doppler as E/e'.

2.3. CMR protocol

CMR was performed on a 1.5-Tesla scanner (Vantage Titan, Canon Medical Systems Ltd., Tochigi, Japan). Electrocardiogram (ECG)-gated cine CMR, T1 mapping, and an LGE study were performed. The cine CMR images were obtained in the short axis and long axis 2- and 4-chamber views using a steady-state free precession (SSFP) sequence (repetition time/echo time [TR/TE] 4.2/2.1 ms, flip angle 65°, matrix size 160 × 240, field of view 360 × 360 mm, spatial resolution 1.2 × 0.8 mm, and slice thickness 8 mm). For the native T1 mapping, the short axis and long axis 2- and 4-chamber views were acquired using a high-resolution 5(3)3 modified Look-Locker inversion recovery (MOLLI) sequence (initial inversion recovery times 140, 280 ms), and after administering contrast agents, those views were acquired using a high-resolution 4(1)3(1)2 MOLLI sequence (initial inversion recovery times 140, 280, 420 ms). The sequence parameters were as follows: TR/TE 3.4/1.4 ms, flip angle 13°, matrix size 120 × 192, field of view 350 × 360 mm, spatial resolution 1.5 × 1.0 mm, and slice thickness 10 mm. The MOLLI sequence was obtained during ventricular diastole or atrial systole. The LGE images were acquired within 15 min after injecting 0.2 nmol/kg of gadobutrol (Gadovist, Bayer, Germany) using a high-resolution ECG-triggered 3D inversion recovery. The sequence parameters were as follows: TR/TE 5.2/2.2 ms, flip angle 13°, matrix size 130 × 256, field of view 380 × 380 mm, spatial resolution 1.5 × 0.75 mm, and slice thickness 10 mm. The optimal inversion time was determined in each patient.

2.4. CMR analysis

The presence of LGE in the contrast-CMR was determined visually and if there were not any LGE that indicated fibrosis, we defined those patients as LGE-negative.

The T1 maps were realigned offline and the images were measured to quantify the fibrosis using QMass MR software (Medis Medical Imaging Systems, Leiden, the Netherlands). This method was previously reported and validated with reproducibility [8,9]. This analysis was performed by one cardiologist with sufficient experience in analyzing T1 mapping images. The endocardial and epicardial contours were manually determined in the short axis and 4-chamber views at end-systole. For a motion correction, the LA walls were manually drawn by polygon regions of interest and carefully reconstructed throughout the MOLLI data (Fig. 1A). T1 mapping and LGE were evaluated in the same views.

For the ECV measurement, a region of interest was defined in each of the 4 required areas: native myocardial T1 values, native blood T1 values, and those post-contrast T1 values. The hematocrit was measured in all subjects immediately before each CMR study. The ECV was calculated by the following formula [10]:

\[
\text{Myocardial ECV} = (1 - \text{hematocrit}) \\
\times \left( \frac{1}{\text{post. contrast T1 myocardium}} - \frac{1}{\text{native T1 myocardium}} \right) \\
\left( \frac{1}{\text{post. contrast T1 blood}} - \frac{1}{\text{native T1 blood}} \right)
\]

For the myocardial tissue tracking strain, MR-Wall Motion Tracking software (Vitrea, Canon Medical Systems Ltd., Tochigi, Japan) was used to semi-automatically draw around the LV and LA walls and divide them into 6 segments on the mid one slice. This slice was the same position slice which was measured in T1 mapping. The circumferential strain was calculated from the global values within every 6 segments using an automated frame-to-frame pixel pattern-matching technique [1,11]. On the 4-chamber view, the endocardial and epicardial borders in LV and LA were manually defined in the end-diastolic frame. Those were automatically propagated through the cardiac cycle by matching individual patterns. Then, the 4-chamber cine image was divided into 6 segments. Finally, the longitudinal strain for the 4-chamber cine images was calculated within each of the 6 segments (Fig. 1B).
2.5. Statistical analysis

All continuous data were expressed as the mean ± standard deviation or numbers (%). Comparisons among the groups were analyzed using a univariate analysis (one-way ANOVA, post-hoc test, and Fisher’s exact test). Multivariable linear regression models were used to assess the relationship between each CMR parameter. The models included the age, types of cardiomyopathy, LVEF on echocardiography, and LA volume.

The intra-observer agreement for the LA measurements was determined for 20 randomly selected patients. One reader remeasured the same cases one month later after the first measurement for the intra-observer variability. Bland-Altman plots were computed to assess the intra-observer variability. The statistical analyses were performed using EZR software, a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0). Statistical significance was determined at a p < 0.05.

3. Results

3.1. Baseline characteristics

The mean age was 55.7 ± 14.6 years, and 44 (67.7%) were male. Those baseline characteristics are listed in Table 1. The healthy group was significantly younger than the others. The left atrial dimension (LAD) in the LVEF < 50% group was significantly greater, and their E/e’ was worse than that in the healthy group. In patients with an LVEF ≥ 50%, there were 11 (36.7%) with hypertrophic cardiomyopathy, 2 with cardiac sarcoidosis, 6 with left ventricular hypertrophy due to hypertension, and 4 with ischemic heart disease as a medical history. In the patients with an LVEF < 50%, there were 3 with ischemic heart disease, 9 with dilated cardiomyopathy, and 2 with cardiac sarcoidosis.

3.2. Strain and T1 mapping during CMR

The CMR characteristics among the three groups are listed in Table 2. Fig. 2 shows comparisons of the ECV and strain for the LA and LV among the three groups. There was a significantly larger number of LV-LGE positive patients in the LVEF < 50% group. However, the LV-native T1 values in patients with an LVEF < 50% did not significantly differ from that in the others (LVEF < 50%; 968.8 ± 46.0 ms vs. LVEF ≥ 50%; 946.7 ± 24.5 ms vs. Healthy; 954.2 ± 37.3 ms, p = 0.10). On the other hand, in patients with an LVEF < 50%, the LV-post-contrast T1 values were significantly lower and LV-ECV was higher than that in the others. Furthermore, the LV-circumferential and longitudinal tracking strains in patients with an LVEF < 50% was significantly decreased.

In patients with an LVEF < 50%, the left atrial volume was significantly larger, and the LA circumferential and longitudinal strain in those group were significantly lower than that in the other groups. However, both the LA-T1 values (native and post-contrast) and LA-ECV did not differ from that in the others (Fig. 2).

The relationship between the circumferential strain, ECV, and T1 values in the LV is reported as follows. In the LV, the circumferential strain had weak relationships with the LV-ECV (r = 0.29, p = 0.02) and LV-native T1 values (r = 0.35, p = 0.005). The LV-ECV was also related to the LV-native T1 and LV-post-contrast T1 values, but the LV-post-contrast T1 values had a stronger association with the LV-ECV than LV-native T1 values. The relationship among the longitudinal strain, ECV, and T1 values in the LA is shown in Fig. 3. There was no significant relationship between the LA-longitudinal strain, ECV, and T1 values in the LA. However, both the LA-T1 values (native and post-contrast) and LA-ECV did not differ from that in the others (Fig. 3).

Table 3 shows the patients characteristics with and without LA-LGE. There were 19 LA-LGE positive patients. However, almost the
LA-LGE was positive in only the part of the LA wall. There were few patients whose presence of LGE was more than 50% in the LA walls. The number of patients with ischemic heart disease was significantly larger in patients with LA-LGE than that without LGE. However, the LA-LGE was not associated with other non-ischemic cardiomyopathies. We also evaluated the relationship between the LVEF and LA function. Multiple regression models after adjusting for the patient background, such as the age, sex, cardiomyopathies, and LA volume, revealed that the LA longitudinal strain was related to the LVEF, LA systolic volume, and hypertrophic cardiomyopathy. The LA-LGE was related to a low LVEF and ischemic heart disease. Additionally, there were no significant relationships between the LA-ECV and those factors (Table 4).

### 3.3. Variability of the intra-observer measurements

The intra-observer agreement of the LA-longitudinal strain, LA-native T1 values, and post-contrast T1 values was high (bias, −8.77 [−22.01 to 4.47] and correlation, 0.97 for the LA-longitudinal strain; bias, −0.69 [−5.33 to 3.95] and correlation, 0.82 for the LA-native T1 values; and bias, −1.77 [−5.70 to 2.15] and correlation, 0.93 for the LA-post-contrast T1 values) (Fig. 4).

### 4. Discussion

#### 4.1. Major findings

The main findings were as follows. First, the worse LA longitudinal strain was correlated with a lower LVEF and larger LA vol-
volume, however, the LA-ECV was not associated with those parameters. On the other hand, almost the LGE was presented in only the part of the LA wall, therefore, there was only a small LGE volume in the patients with LA-LGE positive. That suggested there was little fibrosis in the LA, despite the presence of primarily LA dysfunction in the patients with LV dysfunction. These findings supported that tissue-tracking strain was more useful for evaluating the LA function than T1 mapping in patients without much LA-LGE or fibrosis.
of LA-LGEs in the MOLLI sequence slice could not have affected positive was in only the part of the LA wall. The small volume LVEF < 50% group, however, those volumes were small, and LGE was because, first, 50% of the LA-LGE positive patients were in the LA-T1 values and LA-ECV among the three groups, regardless of the present study, there were no significant differences in the lower LA strain, the correlation values have been weak [1]. In contrast T1 values are associated with higher LA volumes and although some reports have demonstrated that lower post-

ever, only a few studies have applied T1 mapping to the LA. advantages of T1 mapping over LGE imaging for quantifying LA e'clock [19,20]. Beinart et al. also demonstrated that the post-

contrast LA-T1 relaxation times were decreased in patients with AF and LA fibrosis, as compared to healthy controls [18]. How-

tates in fibrosis regions [13,14]. The ECV is elevated in patients values are decreased because extracellular gadolinium accumu-

lates in fibrosis but not the presence of an LGE [12,13]. Native T1 values are influenced by hypertension and diabetes [16].

Regarding the LA function, previous studies have shown some advantages of T1 mapping over LGE imaging for quantifying LA fibrosis [17,18]. Further, in those studies, the post-contrast T1 values were decreased in those with AF as compared to the controls [19,20], Beinart et al. also demonstrated that the post-

contrast LA-T1 relaxation times were decreased in patients with AF and LA fibrosis, as compared to healthy controls [18]. How-

ever, only a few studies have applied T1 mapping to the LA. Although some reports have demonstrated that lower post-

contrast T1 values are associated with higher LA volumes and lower LA strain, the correlation values have been weak [1]. In the present study, there were no significant differences in the LA-T1 values and LA-ECV among the three groups, regardless of the LA strain, which was decreased in the LVEF < 50% group. That was because, first, 50% of the LA-LGE positive patients were in the LVEF < 50% group, however, those volumes were small, and LGE positive was only in the part of the LA wall. The small volume of LA-LGEs in the MOLLI sequence slice could not have affected

4.2. T1 Mapping and ECV

Some reports pointed out that the LGE cannot absolutely quantify diffuse myocardial fibrosis or non-ischemic patients without focal scars on the LGE [5]. On the other hand, T1 mapping is useful to quantify diffuse myocardial fibrosis [12]. Nakamori et al. showed a univariate correlation between the native T1 values and LV function in patients with a large extent of myocardial fibrosis but not the presence of an LGE [12,13]. Native T1 values are typically higher in diffuse fibrosis, whereas post-contrast T1 values are decreased because extracellular gadolinium accumulates in fibrosis regions [13,14]. The ECV is elevated in patients with extracellular edema or fibrosis [15]. The T1 values and ECV are influenced by hypertension and diabetes [16].

According to the LA function, previous studies have shown some advantages of T1 mapping over LGE imaging for quantifying LA fibrosis [17,18]. Further, in those studies, the post-contrast T1 values were decreased in those with AF as compared to the controls [19,20], Beinart et al. also demonstrated that the post-

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contrast T1 values are associated with higher LA volumes and lower LA strain, the correlation values have been weak [1]. In the present study, there were no significant differences in the LA-T1 values and LA-ECV among the three groups, regardless of the LA strain, which was decreased in the LVEF < 50% group. That was because, first, 50% of the LA-LGE positive patients were in the LVEF < 50% group, however, those volumes were small, and LGE positive was only in the part of the LA wall. The small volume of LA-LGEs in the MOLLI sequence slice could not have affected

| Table 3 | Patients Characteristics with and without LA-LGE. |
|---------|-----------------------------------------------|
| Factor  | LA-LGE (−) (n = 46) | LA-LGE (+) (n = 19) | p-value |
| Past medical history |
| AF (%)  | 4 (8.7) | 4 (21.1) | 0.218 |
| CHF (%) | 7 (15.2) | 5 (26.3) | 0.311 |
| DM (%)  | 3 (6.5) | 6 (31.6) | 0.015 |
| HT (%)  | 12 (26.1) | 5 (26.3) | 0.950 |
| CVD (%) | 2 (4.3) | 5 (26.3) | 0.019 |
| DCM (%) | 5 (10.9) | 3 (15.8) | 0.683 |
| HCM (%) | 8 (17.4) | 4 (21.1) | 0.735 |
| CS (%)  | 1 (2.2) | 3 (15.8) | 0.072 |
| LVEF (%) | 60.50 ± 13.55 | 51.68 ± 20.89 | 0.048 |
| e'     | 6.46 ± 2.70 | 5.51 ± 2.67 | 0.210 |
| e/e'   | 11.12 ± 4.81 | 13.55 ± 8.32 | 0.078 |
|
| LV parameters |
| T1 values (native, ms) | 950.28 ± 30.49 | 967.11 ± 45.49 | 0.087 |
| T1 values (contrast, ms) | 453.80 ± 37.33 | 441.58 ± 52.21 | 0.291 |
| Circumferential strain (%) | −14.27 ± 5.09 | −10.95 ± 5.88 | 0.026 |
| Longitudinal strain (%) | −18.48 ± 5.82 | −16.59 ± 9.97 | 0.304 |
|
| LA parameters |
| LA systolic volume (ml) | 34.57 ± 18.82 | 65.94 ± 50.87 | 0.001 |
| T1 values (native, ms) | 1158.24 ± 71.21 | 1174.68 ± 70.69 | 0.417 |
| T1 values (contrast, ms) | 319.52 ± 27.70 | 327.79 ± 35.67 | 0.319 |
| Circumferential strain (%) | 18.63 ± 8.69 | 15.08 ± 7.44 | 0.124 |
| Longitudinal strain (%) | 24.16 ± 12.26 | 13.76 ± 8.41 | 0.001 |

Values are the mean ± SD or n (%). LA = left atrial; LGE = late gadolinium enhancement; PAF = paroxysmal atrial fibrillation; CHF = congestive heart failure; DM = diabetes mellitus; HT = hypertension; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; CS = cardiac sarcoidosis; LVEF = left ventricular ejection fraction; LV/LA parameters = left ventricular/left atrial parameters; ECV = extracellular volume.

| Table 4 | Multiple Regression Model for the CMR parameters. |
|---------|-----------------------------------------------|
| Factor  | LA-LGE (−) (n = 46) | LA-LGE (+) (n = 19) | p-value |
| LV parameters |
| LVEF (%) | 60.50 ± 13.55 | 51.68 ± 20.89 | 0.001 |
| e'     | 6.46 ± 2.70 | 5.51 ± 2.67 | 0.210 |
| e/e'   | 11.12 ± 4.81 | 13.55 ± 8.32 | 0.078 |
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| LA parameters |
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Values are the mean ± SD or n (%). LA = left atrial; LGE = late gadolinium enhancement; PAF = paroxysmal atrial fibrillation; CHF = congestive heart failure; DM = diabetes mellitus; HT = hypertension; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; CS = cardiac sarcoidosis; LVEF = left ventricular ejection fraction; LV/LA parameters = left ventricular/left atrial parameters; ECV = extracellular volume.

* p < 0.05. adjusted for the age, sex, background of the patients, and EF. The columns show the dependent variables. CI = confidential interval; LA = left atrial; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LV/LA parameters = left ventricular/left atrial parameters; ECV = extracellular volume.
the T1 values. Second, the MOLLI sequence used in this study provided a 2.9 × 1.9 mm resolution, the atrial wall thickness was likely near the spatial resolution limit. The region of interest (ROI) may have included the blood pool or epicardial fat in some cases due to volume effects. Therefore, we analyzed the Bland-Altman plots to avoid any ROI error. Furthermore, there was no significant difference in each plot. It also suggested that the absence of an LA-LGE might have contributed to the lack of a difference in the T1 values.

4.3. Tissue-tracking strain and T1 mapping

Some studies have indicated the usefulness of the LA strain to evaluate LA fibrosis [1,21,22]. CMR has a higher spatial resolution than echocardiography, thus it is capable of achieving a better evaluation particularly of thin LA walls where the fibrosis is located [6]. Imai et al. demonstrated that when using CMR, the LA strain in the myocardial scar group was significantly decreased compared to that in the controls [1]. In this present study, the LA longitudinal and circumferential strain were also associated with the LV function, as well as in the previous studies [1,21,22].

Generally, in impaired LVEF patients, fibrosis presents in the LA and the LA function is decreased [1,2]. In this study, the LA fibrosis in these patients was not directly evaluated, such as by biopsy, and thus we could not deny there was less fibrosis in the LA regions when evaluated by CMR. The LA volume in the LVEF < 50% group was greater and their E/e' was higher than that in the healthy group. That suggested that there was more LA overload in the LVEF < 50% group than in the healthy group. However, LGE positive was in only the part of the LA wall. The LA-global longitudinal and circumferential strains in patients with an LVEF < 50% was significantly decreased compared to that in the healthy group. On the other hand, there was no significant difference in the LA-global strain between the LVEF ≥ 50% group and healthy group. In the LVEF ≥ 50% group, there might have been patients who had little fibrosis in the LA or no LA overload, because there was no significant difference in the number of LA-LGE positive patients, and some patients had only hypertension or diabetes in this group. The presence of those patients might have led to no significant value of the LA-global longitudinal strain between the LVEF ≥ 50% group and healthy group in this study. However, hypertrophic cardiomyopathy caused a decrease in the LA-strain of the same magnitude as that for the LVEF (Table 4). This was because an LA-overload due to hypertrophic cardiomyopathy may decrease the LA-strain, regardless of the no significant difference in the T1 mapping. Kwong RY etc. also showed the LA-LGE and LA function among each LV function. In patients with less LA-LGE, the large LA size was associated with low LA-EF. Further, the LA-EF in patients with more LA-LGE was significantly lower than those in patients with less LA-LGE [23]. On the other hand, the presence of LA-LGE was independent of LVEF.

Those studies and our results indicated that LA enlargement or LA strain decrease may appear in the early stage. On the progression of LA dysfunction, LA-LGE may increase and facilitate more LA dysfunction.

CMR demonstrated that the LA-global longitudinal and circumferential strain significantly decreased in the LVEF < 50% group. The LA-T1 values were not associated with the LA-global strain. Tissue-tracking strain was more useful for evaluating the LA function than the T1 mapping especially in patients who did not have much LA-LGE or fibrosis but had primary or early LA dysfunction due to an increasing volume or LV dysfunction.

4.4. Study limitations

This study had some potential limitations. First, this study was a single center trial. We did not have very many patients. Second, we also considered the spatial resolution of the current 1.5 Tesla CMR, which might have caused a statistical bias. There might have been some artifact in the LA-LGE assessments. The MOLLI sequence has been suggested to be sensitive to the heart rate and rhythm. Therefore, in this study, all patients underwent CMR during sinus rhythm to avoid any artifact and preserve a high-resolution. Additionally, the analysis of the LA function and reproducibility were confirmed by Bland-Altman plots to avoid any ROI bias. Third, no systematic biopsy as a reference standard of the fibrosis assessment was performed. Therefore, we divided the patients into three groups and compared the patients with controls as a healthy group. Further, the results of this study could have estimated their fibrosis because of considering the LA strain, volume, and LGE. Fourth, there were various patient backgrounds in this study. However, the multivariable model after adjusting for the type of cardiac disease revealed the correlation between the CMR parameters in the LA, but that background was weak. However, further research is needed with a greater number of patients to confirm these findings.

5. Conclusions

The LA global strain in patients with LV dysfunction was significantly lower. However, the LA-ECV did not significantly differ from that in those without LV dysfunction. In patients who did not have much LA-LGE, but instead had primary LA dysfunction due to LV dysfunction, the LA-tissue-tracking strain was more useful for evaluating the LA function than LA-T1 mapping.

Declaration of Competing Interest

This research received no grants from any funding agencies in the public, commercial, or not-for-profit sectors. The Authors including the Canon employee declare that there was no conflict of interest.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100453.

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