T1 mapping improvement using stretched-type adiabatic locking pulses for assessment of human liver function at 3T

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$T_{1\rho}$ mapping improvement using stretched-type adiabatic locking pulses for assessment of human liver function at 3 T

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ABSTRACT

Purpose: The purpose of this study is to investigate the performance of stretched-type adiabatic spin lock pulses for homogeneous spin locking with a flexible spin lock time (TSL) setting.

Methods: $T_{1\rho}$ values were obtained from 61 patients and five normal volunteers who were categorized using the Child–Pugh classification and scanned using each spin lock pulse type. The pulses used were the block and two kinds of hyperbolic secant (HS); HS8_10, and HS8_5. Visual scoring was categorized using a four point scale (1:Severe, 2:Moderate, 3:Mild and 4:None) to evaluate the homogeneity of the $T_{1\rho}$ map and the source images obtained by each spin lock pulse. Mean $T_{1\rho}$ values among the patient groups with different Child–Pugh classification were compared.

Results: The visual assessment scores were 1.98 ± 1.05 for block pulse locking, 3.87 ± 0.39 for HS8_10 pulse locking, and 3.83 ± 0.45 for HS8_5 pulse locking, respectively. The scores between block pulse and HS8_10 were significantly different ($p < 0.001$), as were those between block pulse and HS8_5 ($p < 0.001$). The median $T_{1\rho}$ values of normal liver function, Child–Pugh A, and Child–Pugh B or C were 37.00 ms, 40.77 ms, and 42.20 ms for block pulse, 46.75 ms, 50.78 ms, and 55.60 ms for HS8_10, and 48.80 ms, 55.42 ms, and 57.80 ms for HS8_5, respectively.

Conclusion: The spin locking sequence using stretched-type adiabatic pulses provides homogeneous liver $T_{1\rho}$ maps with reduced artifact and is necessary for a robust evaluation of liver function using $T_{1\rho}$.

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1. Introduction

Assessment of liver function is essential for the management of patients with liver disease and for the prevention of postoperative hepatic failure. Liver function is frequently estimated by measuring biochemical parameters in the blood, such as bilirubin, aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, albumin, and prothrombin activity [1]. The Child–Pugh classification [2,3] is based on a combination of serum albumin, serum bilirubin, prothrombin activity, ascites, and hepatic encephalopathy to reflect liver functional reserve more accurately than by using any of these biological factors alone [3]. Previous

reports using magnetic resonance imaging (MRI) state that T1 mapping and T2* mapping can be used to assess liver function [4,5]. Liver fibrosis is a common feature of most chronic liver diseases and ultimately progresses to liver cirrhosis with the accumulation of proteoglycans and collagen and other macromolecules in the extracellular matrix [6–8]. Conventional MRI cannot evaluate liver fibrosis directly. Liver biopsy is carried out for the diagnosis and monitoring of progression as a standard of reference; however, liver biopsy is an invasive procedure, is prone to error, and involves the risk of complications [9,10]. Another approach, magnetic resonance elastography (MRE), is a noninvasive method for the detection of fibrotic liver and staging of liver fibrosis [9–11]; however, additional equipment is required for MRE, especially the transducer to generate a vibrational wave [12].

Recently, $T_{1\rho}$ measurement has been widely applied to investigate diseases of the cartilage [13–17], prostate, disc [18], myocardium [19], and liver [7,8,20–23]. With regard to the liver, Wang et al. reported that in an animal model $T_{1\rho}$ relaxation was used successfully to detect early liver fibrosis and that increased liver collagen results in an increase

Abbreviations: MRE, magnetic resonance elastography; RF, radio frequency; TSL, spin lock time; HS, hyperbolic secant; MLEV, Malcolm H. Levitt; IDL, Interactive Data Language; ROI, region of interest.

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of the $T_{1\rho}$ value [20]. Contrary to that report, Sirlin et al. suggested that $T_{1\rho}$ relaxation does not directly reflect liver fibrosis [8]. Moreover, Allkemper et al. and Rauscher et al. reported that $T_{1\rho}$ values were prolonged proportional to the progression of the Child–Pugh grade and liver cirrhosis [24,25].

In most of these studies, a block pulse was used as a spin lock pulse. However, at 3 T, severe artifacts due to B0 and B1 inhomogeneity were observed, especially for a larger organ like the liver. Furthermore, these artifacts not only cause artefactual $T_{1\rho}$ images but also hamper accurate measurement of the $T_{1\rho}$. Such artifacts are caused by inhomogeneous B0 and B1 and therefore imperfect excitation pulses in the spin lock pulse train. Witschey et al. [26] reported an improved spin locking pulse, namely the echo locking method, to remediate these artifacts in a phantom and the human brain but not in the liver.

Adiabatic pulses are characterized by the simultaneous modulation of radio frequency (RF) wave amplitude and frequency. Well-chosen modulation wave forms result in insensitivity to a broad range of B0 and B1 inhomogeneity [27–31].

A few papers reported application of adiabatic pulses for spin locking. Taheri S et al. and Michaeli S reported a simulation study [32, 33], Mangia S et al. studied the brain at 4 T [34], Casula V et al. studied knee cartilage [35] and Yang Q et al. applied them to liver [22].

The purpose of this study was to investigate the performance of the stretched-type adiabatic spin lock pulses for homogeneous spin locking with a flexible spin lock time (TSL) setting. Moreover, we aimed to investigate the clinical usefulness of the $T_{1\rho}$ value acquired using the improved spin locking pulses for the assessment of liver function.

2. Materials and methods

2.1. Subjects

This study was approved by our Institutional Review Board; it complied with the standards of the Ethics Committee.

Between June 2013 and July 2014, 69 patients underwent MRI of the liver, including $T_{1\rho}$ maps, because a liver tumor was suspected due to chronic liver disease or malignant disease in other organs. We excluded eight patients with difficulty to determine Child–Pugh classification. Of the remaining 61 patients, 51 patients were categorized as Child–Pugh A (age range, 40–83 years; mean age, 63.4 years) and 10 as Child–Pugh B or C (age range, 43–74 years; mean age, 61.3 years). As the control, five normal volunteers (age range, 50–55 years; mean age, 52.6 years) were scanned.

2.2. Imaging protocols

MRI data acquisition was performed on a 3 T clinical scanner (Achieva TX; Philips Healthcare, Best, Netherlands). A 32-channel phased-array receiver coil was used.

Three types of rotary echo spin lock pulses were generated to achieve $T_{1\rho}$ -weighted images (Table 1). The non-selective block pulse was used as a conventional spin lock pulse (Fig. 1). The spin lock pulse amplitude was set at 500 Hz, following the literature [20,36]; the TSLs were 1, 20, and 40 ms. Two different types of spin lock pulses type

Fig. 1. Scheme of the $T_{1\rho}$ spin lock RF cluster using block pulse. The RF pulse train is $90^\circ(+x) - SL(+y) - SL(-y) - 90^\circ(-x)$. Magnetization is nutated into the x axis by the initial 90° pulse. The magnetization vector is then spin locked by two block pulses, locking first along the $+y$ and then the $-y$ axis. Finally, the magnetization is nutated back into the z axis by the 90° pulse along the $-x$ axis.

were used, namely the block pulse and the stretched-type adiabatic preparation pulses.

The hyperbolic secant (HS) pulse, known to be insensitive to variations of B1 intensity approaching several orders of magnitude, was used as a base. The time variation of the wave form modulations was modified to further optimize the performance of the pulse.

An effective magnetic field ($\omega_{eff} = \gamma B_{eff}$) is induced by the pulse, where B_{eff} is the effective magnetic field vector and γ is the gyromagnetic ratio. The time-dependent magnitude of the effective field is:

$$\omega_{eff}(t) = \sqrt{\omega_1^2(t) + (\omega_0 - \omega_{RF}(t))^2}$$

where;

$$\omega_1(t) = \omega_1^{max} \text{sech}(\beta t^n),$$

$$(\omega_0 - \omega_{RF}(t)) = A \text{fsech}^2(\beta \tau^n) d\tau,$$

where ω_1^{max} is the maximum amplitude. A determines the frequency sweep amplitude and is equal to $\mu\beta$, μ is a dimensionless parameter and β is a modulation angular frequency. ω_0 is the on-resonance frequency equal to γB_0 and ω_{RF} is the frequency modulation. For the original HS pulse, n equal to 1, whereas the stretched adiabatic pulse is generated by $n > 1$ (Fig. 2). We applied a high n factor ($n = 8$) to generate two types of adiabatic spin locking pulse from the original pulse, which was characterized by $\mu = 5$ and $\beta = 4$ rad/s. The parameters of the first pulse type were pulse duration 10 ms, frequency sweep 636.6 Hz, and maximum amplitude 6.37 μT (HS8_10). The second pulse type had a pulse duration 5 ms, frequency sweep 1273.2 Hz, and maximum amplitude 13.48 μT (HS8_5). The B_{eff} change during the two types of adiabatic pulse is indicated in Fig. 3; the average B_{eff} field of HS8_10 and HS8_5 was 500 Hz and 1000 Hz, respectively. For these adiabatic pulses, the rotating frame relaxation time was measured using a pulse module consisting of consecutive identical HS pulses. The number of pulses was increased to obtain the $T_{1\rho}$ images with different TSLs for fitting from two to four for HS8_10 and from four to eight for HS8_5, with MLEV phase cycling [37] (Fig. 4). The TSL was set to 0, 20, and 40 ms by increasing the number of pulses. TSL = 0 represents the absence of a spin lock pulse.

Table 1
Design parameters for the spin lock pulses.

Spin lock pulse	Pulse type	Pulse duration per pulse (ms)	Frequency sweep (Hz)	Spin lock frequency (Hz)	B1max (μT)	TSL (ms)
Block	Block	–	–	500	11.7	1,20,40
HS8_10	Stretched-type adiabatic ($n = 8$)	10	636.6	500.0*	6.73	0,20,40
HS8_5	Stretched-type adiabatic ($n = 8$)	5	1273.2	1000.0*	13.48	0,20,40

*average effective SL frequency.

Fig. 2. Scheme of the amplitude and frequency modulation function for HS1 and HS8. HS8 is the stretched-type version of HS1. Time is shown on the horizontal axis.

We simulated the efficiency of these three types of spin lock pulse in function of B_0 and B_1 using Bloch equations at TSL 20 ms (Fig. 5). The simulation was based on the Bloch-equations, solved using the ordinary differential equation function of Matlab (Mathworks, Natick, MA, USA). We did not take relaxation effects into account. The figures show the final magnetization, in function of B_0 and B_1 , after presenting each type of spin lock pulse combination to the equilibrium magnetization.

The spin locking block pulse combination nutates the equilibrium magnetization into the x axis by the initial 90° pulse and is then spin locked by two block pulses that have opposite phases. After the spin locking the magnetization is nutated back into the z axis by a -90° pulse (Fig. 5 a).

For the two types of stretched-type adiabatic pulse, the magnetization is spin locked by an even number of adiabatic pulses (Fig. 5 b and c).

In case of perfect locking, and ignoring relaxation, the final magnetization is equal to the equilibrium magnetization.

In the figures we show the final magnetization as a fraction of the equilibrium magnetization, in function of both B_0 and B_1 .

For imaging, a three-dimensional turbo field echo sequence using the parallel imaging technique was employed with breath holding.

Volume shimming was used to minimize B_0 inhomogeneity. Other imaging parameters were as follows: repetition time 2.1 ms, echo time 0.98 ms, field of view $360 \times 306 \text{ mm}^2$, matrix 256×205 , slice thickness 10 mm, slice gap 0 mm, number of slices 3, number of acquisitions 1, shot interval 5000 ms, and scan time of $T_{1\rho}$ -prepared image with each TSL 11.7 s. Scanned slices were set at the level of the hepatic hilum.

2.3. $T_{1\rho}$ image analysis

$T_{1\rho}$ maps were generated on a pixel-by-pixel basis using in-house developed software program written in Interactive Data Language (IDL 6.3; ITT, Boulder, CO) using a mono-exponential decay model: $M(\text{TSL}) = M_0 \times \exp(-\text{TSL}/T_{1\rho})$, where M_0 and $M(\text{TSL})$ denote the equilibrium magnetization and $T_{1\rho}$ spin lock prepared magnetization for each TSL, respectively. $T_{1\rho}$ maps were generated for each spin lock type with a Levenberg–Marquardt fitting algorithm [38]. For quantification of liver $T_{1\rho}$ value, three regions of interest (ROIs) were manually placed on the liver parenchyma; the sizes of the ROIs were as large as possible, approximately $50\text{--}150 \text{ mm}^2$, avoiding blood vessels, tumors, and artifacts.

2.4. Visual assessment

Evaluation of the homogeneity of the $T_{1\rho}$ maps and the $T_{1\rho}$ source images was scored through visual evaluation by two MR clinical scientists (T.O. and M.O.) with 10–16 years of experience. Visual scoring was categorized using a 4-point scale as 1 severe, 2 moderate, 3 mild, and 4 none. The definition of visual scoring was as follows:

- 1: Severe: Severe artifacts, difficult to evaluate $T_{1\rho}$ values;
- 2: Moderate: Mildly severe artifacts. Artifacts should be avoided to measure the $T_{1\rho}$ value, however, the fitting to calculate $T_{1\rho}$ values is acceptable using a limited area;
- 3: Mild: Some artifacts on the image;
- 4: None: No artifacts on the image.

2.5. Statistical analysis

We employed the Tukey–Kramer method to compare visual scoring between the image qualities and the Friedman test to compare the mean $T_{1\rho}$ values of each spin locking pulse (the block pulse, HS8_10, and HS8_5).

Mean $T_{1\rho}$ values among the patient groups with different Child–Pugh classifications were compared using the Kruskal–Wallis test followed by Tukey's post hoc test. Statistical analysis was performed

Fig. 3. The amplitude, frequency and effective frequency change during two types of adiabatic pulses: HS8_10 a) and HS8_5 b).

Fig. 4. Scheme of the amplitude and frequency modulation function for HS8_10 and HS8_5 locking of 20 ms duration. HS8_10 locking consists of two segments a) and HS8_5 consists of four segments b), with an MLEV-type phase cycle.

using EZR free software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [39]. A P value <0.01 was considered significant.

3. Results

The simulation suggested that the HS8_5 pulses would perform better as a locking pulse, given that for a broad range of B_0 and B_1 values the equilibrium magnetization is restored after the locking.

Two cases of typical source images and $T_{1\rho}$ maps are shown in Fig. 6a and b. There were artifacts on most of the spin locking images using the block pulse; however, the artifact level on the source images and $T_{1\rho}$ mapping obtained with the adiabatic spin locking pulses was significantly reduced.

3.1. Visual assessment

The intraclass correlation coefficient of visual scoring between the two readers was 0.90, indicating good concordance in the readers' visual scoring.

The visual assessment score (mean $\pm$ standard deviation) of the homogeneity of the $T_{1\rho}$ maps resulted in 1.98 ± 1.05 for block pulse locking, 3.87 ± 0.39 for HS8_10 pulse locking, and 3.83 ± 0.45 for HS8_5 pulse locking, respectively. Both types of adiabatic spin locking-derived maps scored significantly better than the block pulse locking-derived maps (Fig. 7). The visual assessment score showed significant differences between the block pulse and HS8_10 ($P < 0.001$) and

between block pulse locking and HS8_5 ($P < 0.001$). There was no significant difference between HS8_10 and HS8_5 ($P = 0.792$).

3.2. $T_{1\rho}$ values

It was not possible to draw an ROI avoiding the artifacts in all source images for some $T_{1\rho}$ maps using block pulse because artifacts appeared in different locations in each source image. This resulted in a limited area where the $T_{1\rho}$ value could be calculated to generate a reliable $T_{1\rho}$ map. In contrast, there were no severe artifacts in most of the source images using adiabatic pulses.

The $T_{1\rho}$ values calculated using each spin lock type are shown in Table 2. The mean $T_{1\rho}$ values for normal tissue of block, HS_10, and HS_5 were 37.07 ms (range: 32.47–42.41 ms), 46.12 ms (range: 44.03–48.77 ms), and 49.99 ms (range: 47.97–51.43 ms), respectively. $T_{1\rho}$ values were significantly different between each spin lock type (Friedman test, $P < 0.0001$).

The $T_{1\rho}$ values for each spin lock type are shown in Fig. 8. The median $T_{1\rho}$ values of normal liver function, Child–Pugh A, and Child–Pugh B or C were 37.00 ms, 40.77 ms, and 42.20 ms for block pulse; 46.75 ms, 50.78 ms, and 55.60 ms for HS8_10; and 48.80 ms, 55.42 ms, and 57.80 ms for HS8_5, respectively.

$T_{1\rho}$ values were not significantly different between normal liver function and Child–Pugh B or C using block pulse (Kruskal–Wallis, $P = 0.038$). We found a significant difference between normal liver function and Child–Pugh B or C using the HS8_10 pulse as well as the HS8_5 pulse, with a high significance level (Kruskal–Wallis, $P < 0.01$).

Fig. 5. Simulated longitudinal magnetization after each spin lock pulse at TSL 20 ms: a) block pulse, b) HS8_10, and c) HS8_5. Relative B1 amplitude is on the vertical axis, and ΔB_0 is on the horizontal axis, in kHz units. The final longitudinal magnetization after locking with HS8_10 and HS8_5 is shown to be more homogeneous for a wide range of relative B1 amplitude and ΔB_0 compared to using block pulses. The contour lines in the plot are per 0.2 Meq interval, with dark blue equal to $-Meq$ and yellow equal to $+Meq$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 6. Source images for each TSL and the calculated $T_{1\rho}$ maps. The typical source images for each spin lock type are shown: block pulse (top), HS8_10 (middle), and HS8_5 (bottom) with the resulting $T_{1\rho}$ map (right). Using the block pulse, there are severe artifacts in segment 3 and segment 4 on each TSL image (white arrow a), and severe artifacts in segment 7 and segment 8 on each TSL image (white arrow b).

4. Discussion

We investigated the effectiveness of applying a module consisting of stretched adiabatic pulses as a locking pulse to acquire robust $T_{1\rho}$ maps at 3 T. Using the block pulse, which is standard in most spin locking

sequences for whole body systems, we found severe artifacts on the source images. The use of adiabatic pulses reduces B1 inhomogeneity-related artifacts, which cause fatal errors in calculating $T_{1\rho}$ values. Witschey et al. reported a spin locking pulse that mitigates B0- and B1-type artifacts at all field strengths [26]. This type of B0 and B1

Fig. 7. Results of visual scoring. The asterisk (*) represents a value of $P < 0.001$ between block and HS8_5 and between block and HS8_10. There is no significant difference between HS8_10 and HS8_5 ($P = 0.792$).

insensitive spin lock pulse ($90_{(x)} - \tau/2_{(y)} - 180_{(y)} - \tau/2_{(-y)} - 90_{(x)}$) was used for a neurological study. However, in our experience, it is not well suited for the liver due to the size of the field of view of the liver compared to the brain and the heart.

The diagram of the final longitudinal magnetization simulated using the Bloch equations after presenting each type of spin lock pulse to the equilibrium magnetization clearly shows that the block pulse is very sensitive to B0 and B1 inhomogeneity (Fig. 5). This will cause severe artifacts on the image. In contrast, adiabatic spin locking results in a homogeneous final magnetization for a wide range of B0 and B1 fields. In particular, HS8_5 maintains homogeneity; therefore, it is useful for big organs, like the liver, where B0 and B1 are inhomogeneous, especially

at 3 T and higher field strengths. However, there is no significant difference in visual scoring between HS8_10 and HS8_5. Thus, we can conclude that the HS8_10 is working as well as the HS8_5 within the range of B0 and B1 variations expected for a liver examination on a clinical 3 T system like the one we used. The difference in visual scoring between the block and the two types of adiabatic spin locking pulse corroborates the findings from the simulation. The stretched-type adiabatic spin locking pulse was able to provide homogeneous $T_{1\rho}$ images. Spin locking using adiabatic pulses represents a promising improvement to overcome B1 and B0 inhomogeneity, especially for body $T_{1\rho}$ imaging.

Both mean $T_{1\rho}$ values obtained from the block and the two types of adiabatic spin locking pulse increased as liver function worsened. This result was similar to those previously reported [20,21,24]. However, the fundamental mechanisms leading to $T_{1\rho}$ prolongation in liver fibrosis and cirrhosis have not been fully investigated [24]. Wang et al. [20] described the usefulness of $T_{1\rho}$ relaxation for the evaluation of liver fibrosis in a rat biliary duct ligation model. Takayama et al. [40] claimed that $T_{1\rho}$ relaxation of the liver was not significantly correlated with liver fibrosis or with necro-inflammation. Thus, they concluded that $T_{1\rho}$ has potential as a biomarker for the assessment of liver function, although it may not be suitable to estimate liver fibrosis or necro-inflammation. The present study did not investigate the mechanisms of $T_{1\rho}$ prolongation with liver dysfunction. Liver dysfunction may contribute to $T_{1\rho}$ prolongation through combined mechanisms, such as biological, chemical, and physical factors, as Takayama et al. suggested.

The obtained $T_{1\rho}$ values using the adiabatic pulses were longer than those using the block pulse, similar to the results obtained by Jokivarsi et al. [41] in normal rat brain parenchyma, even if the average B_{eff} is equal, as for the HS8_10 pulse. We conjecture that this difference in $T_{1\rho}$ is because the B_{eff} of the adiabatic pulse is continuously changing during the pulse (Fig. 3), in contrast to the block pulse. The HS8_5 has a higher average B_{eff} , therefore a different $T_{1\rho}$ can be expected [32,42]. Furthermore, temporal and spatial variation of B_{eff} will result in a varying $T_{1\rho}$ relaxation rate, which is difficult to control or predict. One must be aware of this when interpreting the $T_{1\rho}$ values, and this should thus be done with extreme caution. Moreover, liver tissue contains a variety of macromolecules causing a mix of $T_{1\rho}$ values within the voxels. Further, it is known that exchange and diffusion effects occur during

Table 2
Difference in mean $T_{1\rho}$ values and range for normal tissue between each spin lock type.

Spin lock pulse	Block	HS8_10	HS8_5
Mean $T_{1\rho}$ (ms)	37.07*	46.12*	49.99*
Range of $T_{1\rho}$ (ms)	32.47–42.41	44.03–48.77	47.97–51.43
Standard deviation (ms)	± 3.30	± 1.78	± 2.14

* $P < 0.0001$.

Fig. 8. Comparison of $T_{1\rho}$ values between block, HS8_10, and HS8_5. The graphs indicate mean liver $T_{1\rho}$ values and standard deviation of Child–Pugh A, Child–Pugh B or C, and normal using each spin lock pulse. Each spin lock type is shown on the horizontal axis; $T_{1\rho}$ values are on the vertical axis.

locking and can affect the final signal. We did not study this aspect within the scope of this project.

It is thus difficult to achieve a meaningful absolute quantitative $T_{1\rho}$ in the clinical setting because the B_{eff} varies temporally and spatially. However, using adiabatic locking pulses provides a locking that is effective over a large field of view and thus enables the calculation of homogeneous $T_{1\rho}$ maps. The visual scores of the $T_{1\rho}$ maps acquired with adiabatic pulse locking are indeed higher compared to traditional block pulse locking. The visual scores for the respective Child–Pugh grades were not significantly different between HS8_10 and HS8_5. Furthermore, the use of HS8_10 and HS8_5 pulses allows to differentiate between normal and Child–Pugh B or C with high statistical significance.

There is a limitation in the present study. The pulse duration of the adiabatic pulse was determined by the modulation function and optimal adiabatic condition. The total locking pulse is limited to an even number of adiabatic pulse segments (Fig. 4), and thus the TSL duration was restricted to an even multiple of that segment duration. In this study, HS8_10 uses 10 ms per adiabatic pulse segment, and the TSLs were set to 20 ms and 40 ms. However, we believe that this restriction to the TSLs was not disadvantageous for the calculation of the $T_{1\rho}$ value of the liver, as mentioned in previous research [20,21,24].

In conclusion, we demonstrated that the stretched-type adiabatic spin locking method provides homogeneous and reduced artifact $T_{1\rho}$ liver images and is useful for a robust evaluation of liver function using $T_{1\rho}$.

Disclosure of conflicts of interest

The authors have a conflict of interest to declare. Tomoyuki Okuaki and Marc Van Cauteren are Philips Healthcare employee. Tetsuo Ogino and Makoto Obara are Philips Electronics Japan employee. Yukihisa Takayama, Akihiro Nishie, Hiroshi Honda and Toshiaki Miyati have no relevant conflicts of interest to disclose.

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