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CLINICAL RESEARCH

Non-invasive assessment of pulmonary vein isolation durability using late gadolinium enhancement magnetic resonance imaging

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Aims

Electrical reconnection of pulmonary veins (PVs) is considered an important determinant of recurrent atrial fibrillation (AF) after pulmonary vein isolation (PVI). To date, AF recurrences almost automatically trigger invasive repeat procedures, required to assess PVI durability. With recent technical advances, it is becoming increasingly common to find all PVs isolated in those repeat procedures. Thus, as ablation of extra-PV targets has failed to show benefit in randomized trials, more and more often these highly invasive procedures are performed only to rule out PV reconnection. Here we aim to define the ability of late gadolinium enhancement (LGE)-magnetic resonance imaging (MRI) to rule out PV reconnection non-invasively.

Methods and results

This study is based on a prospective registry in which all patients receive an LGE-MRI after AF ablation. Included were all patients that—after an initial PVI and post-ablation LGE-MRI—underwent an invasive repeat procedure, which served as a reference to determine the predictive value of non-invasive lesion assessment by LGE-MRI.: 152 patients and 304 PV pairs were analysed. LGE-MRI predicted electrical PV reconnection with high sensitivity (98.9%) but rather low specificity (55.6%). Of note, LGE lesions without discontinuation ruled out reconnection of the respective PV pair with a negative predictive value of 96.9%, and patients with complete LGE lesion sets encircling all PVs were highly unlikely to show any PV reconnection (negative predictive value: 94.4%).

Conclusion

LGE-MRI has the potential to guide selection of appropriate candidates and planning of the ablation strategy for repeat procedures and may help to identify patients that will not benefit from a redo-procedure if no ablation of extra-PV targets is intended.

Keywords

Durability of pulmonary vein isolation • Pulmonary vein reconnection • Late gadolinium enhancement • Cardiac MRI • Non-invasive ablation lesion assesment • Atrial fibrillation • Catheter ablation

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What's new?

- Non-invasive lesion assessment by post-ablation late gadolinium enhancement (LGE)-magnetic resonance imaging (MRI) predicts pulmonary vein (PV) isolation durability with high specificity but somewhat lower sensitivity.
- LGE-MRI can reliably rule out PV reconnection with a negative predictive value of 97%.
- Patients with complete LGE lesions encircling all four PVs may not benefit from repeat invasive procedures, if ablation of extra-PV targets is not intended.
- LGE-MRI has a clear potential to guide selection of appropriate candidates and planning of the ablation strategy for repeat procedures and may help to avoid unnecessary invasive procedures with all their associated risks and costs.

Introduction

Electrical reconnection of pulmonary veins (PVs) is considered an important determinant of recurrent atrial fibrillation (AF) after pulmonary vein isolation (PVI).[1] To date, an invasive repeat procedure is required to assess durability of PVI. Against this background, in most centres clinically relevant AF recurrences almost automatically trigger repeat ablation procedures aiming at PV re-isolation.[2,3] However, technological and procedural advances have substantially improved efficacy of catheter ablation.[4–10] As a result, it is becoming increasingly common to find all four PVs isolated in those repeat procedures.[11] Thus, as ablation of extra-PV targets has failed to show benefit in large randomized trials, more and more often these highly invasive procedures are being performed only to confirm durable PVI.[3]

Late gadolinium enhancement (LGE)-magnetic resonance imaging (MRI) is the only non-invasive method to assess ablation lesions. While the ability of LGE-MRI to localize functional gaps in ablation lesions after PVI has been investigated in a number of small studies, its predictive value regarding PVI durability and PV reconnection, respectively, has not been specifically defined.[12–20] Here we aim to determine the ability of LGE-MRI to rule out PV reconnection and its potential to guide patient selection for repeat ablation procedures.

Methods

Study design and participants

This was an observational, retrospective analysis of a prospective patient registry conducted at the Arrhythmia Section of Hospital Clínic, University of Barcelona. All patients scheduled for AF ablation enter this registry and receive an LGE-MRI within 4 days prior to ablation, as well as 3 months after ablation. The protocol was reviewed and approved by the local research ethics committee, and written informed consent was obtained from each patient.

All patients from the registry that had undergone a repeat invasive procedure after an initial AF ablation with complete PVI were eligible and included in the analyses if the post-index ablation LGE-MRI was of sufficient quality. The ability of LGE-MRI to determine PVI durability and PV reconnection, respectively, was then investigated using invasive mapping during the subsequent repeat procedure as a reference.

Late gadolinium enhancement-magnetic resonance image acquisition

LGE-MRI was performed as previously described.[12] In brief, MRI studies were performed in sinus rhythm using one of two different 3-Tesla scanners (Magnetom Prisma, Siemens Healthineers, Erlangen, Germany and Signa Architect, General Electric, Chicago, Illinois, USA), both with 32-channel phase array cardiovascular coils.

Inversion recovery prepared T_1-weighted gradient echo sequences were acquired in axial orientation using electrocardiogram gating and a free-breathing 3D navigator, 20 min after administering an intravenous bolus of 0.2 mmol/kg of gadobutrol (Gadovist, Bayer Hispania).

Sequence parameters for magnetom prisma scanner (Siemens Healthineers)

Repetition time 2.3 ms, echo time 1.4 ms, flip angle 11°, bandwidth 460 Hz/pixel, and inversion time (TI) 280–380 ms, acquired voxel size 1.25 × 1.25 × 2.5 mm.

Sequence parameters for signa architect scanner (general electric)

Repetition time 6.4 ms, echo time 2.2 ms, flip angle 20°, bandwidth 244 Hz/pixel, acquired voxel size 1.25 × 1.25 × 2.4 mm.

A TI scout sequence was used in order to determine the optimal TI that nullified the left ventricular myocardial signal (typically 280–380 ms).

Late gadolinium enhancement-magnetic resonance imaging post-processing

LGE-MRI post-processing was performed by two highly experienced experts (E.F. and P.G.), blinded to data from invasive mapping, using ADAS 3D software (Adas3D Medical SL). For semiautomatic 3D reconstruction of left atria and PVs, the atrial wall was manually traced on each axial-plane slice and automatically adjusted to built a 3D shell.

LGE was quantified in a standardized manner based on voxel signal intensities relative to the mean blood pool signal intensity, applying a previously validated signal intensity ratio threshold of ≥1.2 to define LGE indicative of fibrotic tissue.[12,21] The 3D reconstructions were colour-coded accordingly, and an LGE discontinuation of ≥3 mm was considered indicative of PV reconnection (previous studies from our group suggest that LGE discontinuations of <3 mm may not be relevant for clinical outcome and that consideration only of LGE discontinuations ≥3 mm does not significantly lower the sensitivity in the detection of gaps).[12,22]

Invasive assessment of pulmonary vein isolation

For validation, PVI durability was determined based on the subsequent invasive repeat procedures taking into account all available information including electroanatomical mapping and local bipolar PV electrograms. Electrical PV reconnections were defined based on the presence of local PV electrograms recorded by the multipolar mapping catheter without application of a specific voltage threshold. Invasive assessment of PVI was performed exclusively with the following multipolar mapping catheters: LassoNav™ and PentaRay™ (both Biosense Webster Inc.), IntellaMap Orion™ (Boston Scientific Inc.) or Advisor™ HD Grid (Abbott, Inc.).

Statistical analysis

Analysis was performed using SPSS 28.0 software (SPSS Inc, Chicago, IL). Continuous variables are presented as mean ± SD or median (interquartile range), unless otherwise specified. Sensitivity, specificity, and positive, as well as negative predictive value of LGE-MRI were determined with respect to PV reconnection as determined by invasive assessment. In addition, the agreement between the two methods was analysed by calculating Cohen's kappa coefficient (κ) for inter-rater reliability based on the presence or absence of gaps in LGE-MRI using invasive mapping as a reference. A P-value < 0.05 was considered significant.

Results

Screening and baseline characteristics

Of the 1262 patients in the AF ablation registry screened, a total of 159 patients had undergone a post-ablation LGE-MRI and a subsequent invasive repeat procedure. Seven patients (4.4%) had to be excluded because of insufficient MRI quality. Thus, total of 152 patients with PVI index ablation procedure performed between October 2010 and

Table 1 Baseline patient characteristics

Parameter	n = 152
Age, years	57.0 ± 10.7
Female gender	45 (29.6)
CHA_2DS_2-VASc score	1.4 ± 1.1
AF type prior to index PVI	
Paroxysmal AF	62 (41)
Persistent AF	90 (59)
Recurrent arrhythmia type triggering repeat procedure	
Paroxysmal AF	47 (31)
Persistent AF	68 (45)
AT/flutter	37 (24)
Left atrial diameter, mm	42.5 ± 6.4
Left atrial volume index, mL/m^2	39.9 ± 7.3
LVEF, %	55.7 ± 8.6
Congestive heart failure	18 (12)
Systemic hypertension	77 (51)
Diabetes	16 (11)

All values are *n*, (%) or mean ± standard deviation.

Table 2 Index ablation procedural characteristics

Parameter	n = 152
Complete pulmonary vein isolation	152 (100)
Additional extra-PV ablation	10 (7)
Posterior wall isolation (box lesion)	7 (5)
Mitral isthmus line	2 (1)
LGE-MRI-based fibrosis ablation	2 (1)
Radiofrequency ablation	128 (84)
Cryoballoon ablation	24 (16)

All values are *n*, (%).

December 2020, were included in the analysis. Patient and procedural characteristics are displayed in *Tables 1 and 2*. In the vast majority of patients a PVI-only approach was followed and performed by point-by-point radiofrequency ablation. Of note, contact force-sensing catheters were used by default from 2013 onwards, whereas index-guided ablation according to the CLOSE-protocol was introduced in 2018.

Per-pulmonary vein pair analysis

Post-ablation LGE lesions of 304 PV pairs from 152 patients were analysed and validated based on subsequent invasive repeat procedures. The distribution of gaps is displayed in *Figure 1*. LGE-MRI predicted PV reconnection with high sensitivity (98.9%), whereas specificity was rather low (55.6%) (*Table 3*). The agreement between LGE-MRI and invasive assessment of PVI regarding the presence or absence of gaps in a given PV pair was moderate to good (Cohen's kappa coefficients for inter-rater reliability between 0.56 and 0.61). Of note, complete circumferential LGE lesions without discontinuation were encountered in 64 PV pairs (21.1%) and ruled out electrical reconnection of the respective PV pair with a negative predictive value of 96.9% (*Figure 2*).

Per-patient analysis

The per-patient analysis yielded similar results with very high sensitivity of LGE-MRI regarding the detection of PV reconnection, but a rather low specificity and thus only moderate agreement with invasive assessment of PVI according to Cohen's kappa coefficient for inter-rater reliability (*Table 4*). While durable PVI was encountered in 22% of the patients according to invasive assessment, only 11% of the patients displayed complete LGE lesion sets encircling all four PVs. Of note, only one patient with a complete LGE lesion set showed electrical PV reconnection in the invasive repeat procedure, corresponding to a negative predictive value of 94.4%.

Discussion

This retrospective study investigated the accuracy of LGE-MRI to non-invasively determine PVI durability in 152 patients and 304 PV pairs, respectively, using subsequent invasive repeat procedures as a reference.

Late gadolinium enhancement-magnetic resonance imaging can rule out pulmonary vein reconnection with a high negative predictive value

These data demonstrate that the absence of LGE discontinuities is highly predictive of durable PVI, and patients with complete LGE lesions encircling the PVs are unlikely to present PV reconnection (negative predictive value 94.4%). In those patients the potential benefit of a repeat invasive procedure might be questionable and should be carefully reconsidered, taking a personalized approach with non-PV targets into account.

This is of increasing relevance as indeed, with recent technical advances, it is becoming increasingly common to find all PVs isolated in repeat procedures.[11] Thus, as ablation of extra-PV targets has failed to show benefit in large randomized trials, more and more often these highly invasive procedures are being performed only to confirm durable PVI—or even worse, investigators might feel obliged to target extra-PV structures, only to justify the invasive procedure.[23]

Standardized post-processing method

A particular strength of this study is the standardized post-processing method to define ablation lesions, which is investigator-independent and therefore readily reproducible.[24] As T_1-weighted imaging is based on signal intensity contrast rather than directly measured absolute values, for standardization LGE must be defined by a signal intensity threshold relative to an internal reference. Obviously, different internal references and/or thresholds applied to the same images will inevitably yield different sensitivities and specificities in the detection of fibrotic tissue.[25,26] One of the limitations that hampered the widespread use of LGE-MRI for atrial fibrosis and lesion assessment in the past has been the lack of standardization and thus reproducibility.

Against this background, our group has recently established a method quantifying local signal intensity ratios using the mean signal intensity of the blood pool as a reference for normalization (signal intensity of each given voxel/mean signal intensity of the blood).[21] Thresholds to define fibrotic tissue (signal intensity ratio >1.2) or dense scar (signal intensity ratio >1.32) in the atrium were derived from comparisons of distinct cohorts of young healthy individuals and post-AF ablation patients, and subsequently validated in numerous clinical studies with respect to electroanatomical voltage mapping, as well as procedural and clinical endpoints.[12,19,22,27] These uniform definitions for signal intensity thresholds and internal references render this method universally

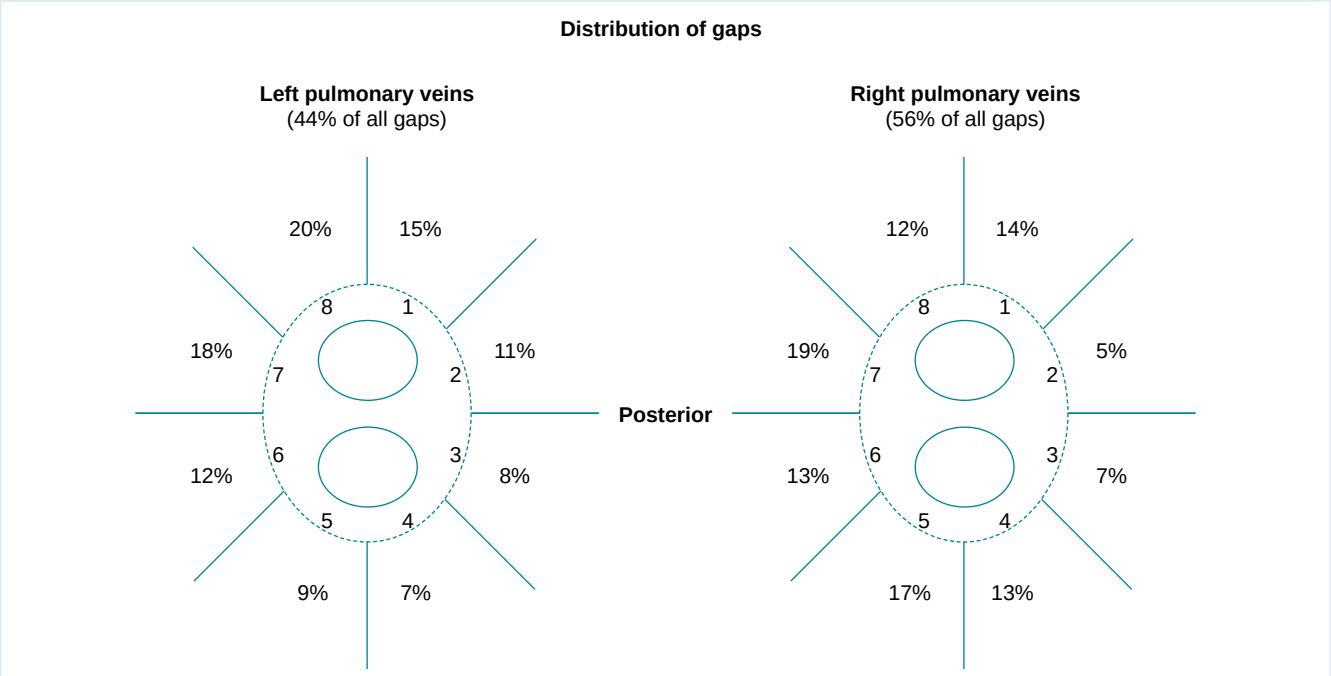

Figure 1 Distribution of LGE gaps. Proportion of LGE discontinuities in left vs. right PV pairs and according to PV segments.

Table 3 Predictive value regarding PV reconnection—per-PV pair analysis

	Left PVs	Right PVs	Left and right PVs
Sensitivity	98.8 (83/84)	99.0 (104/105)	98.9 (187/189)
Specificity	60.3 (41/68)	48.9 (23/47)	55.6 (64/115)
Positive predictive value	75.5 (83/110)	81.3 (104/128)	78.6 (187/238)
Negative predictive value	97.6 (41/42)	95.8 (23/24)	96.9 (64/66)
Agreement (kappa)	0.61*	0.56*	0.59*

Percentages (*n*-numbers); *$P < 0.0001$.

applicable irrespective of the centre and independent of the investigator, allowing for a widespread clinical use. However, it shall be emphasized that various other methods using distinct internal references and thresholds have been validated by other groups.[14,16,28,29] Moreover, it shall be stressed that sufficient image quality is an important prerequisite. Of note, image acquisition during AF is challenging and may result in insufficient image quality. Therefore image acquisition during sinus rhythm is recommended.

Proportion of complete late gadolinium enhancement lesions

In line with previous reports, the proportion of patients with complete LGE lesions encircling the PVs was rather low in this study.[13,30] However, it has to be considered that the selection of patients based on clinically indicated invasive repeat procedures introduces a substantial bias in this regard. It is also noteworthy that the majority of the index PVI procedures in this cohort were performed before the introduction of index-guided ablation following the CLOSE-protocol, and the proportion of repeat procedures showing complete isolation of all four PVs (22%) is also consistent with previous reports of comparable cohorts.[11] In fact, the recent advent of standardized index-guided ablation approaches has raised this proportion substantially with durable PVI being encountered in up to 60% of the repeat procedures.[11] However, to some extent, limitations in the detection of ablation-induced fibrosis are likely to contribute to the low proportion of complete LGE lesion sets.

False positive late gadolinium enhancement-predicted pulmonary vein reconnections

The fact that a substantial proportion of PV pairs with LGE discontinuities showed no electrical reconnection based on invasive mapping, likely reflects a partial failure of LGE-MRI to detect local ablation-induced scarring. Of note, this was despite application of a relatively low threshold defining LGE. In fact, in a recent study using electroanatomical mapping as a reference, we found that application of this lower of the two previously established and validated thresholds (signal intensity ratio >1.2) augmented sensitivity in the detection of ablation lesions while preserving specificity.[12] This was confirmed in the current study, where specificity in the detection of lesions (and thus sensitivity in the detection of PV reconnections) was extremly high despite using this lower threshold.

Previous data indicate that detectability of ablation lesions also depends on the timing of the image acquisition and can be improved accordingly. In fact, detectability of definite ablation lesions appears to be better and more accurate at 3 months post-ablation than at chronic stages (>12 months post-ablation).[12] However, it is important to note that acute and subacute LGE lesions (<2 months post-ablation), at least in part reflect a transient inflammatory response, which usually

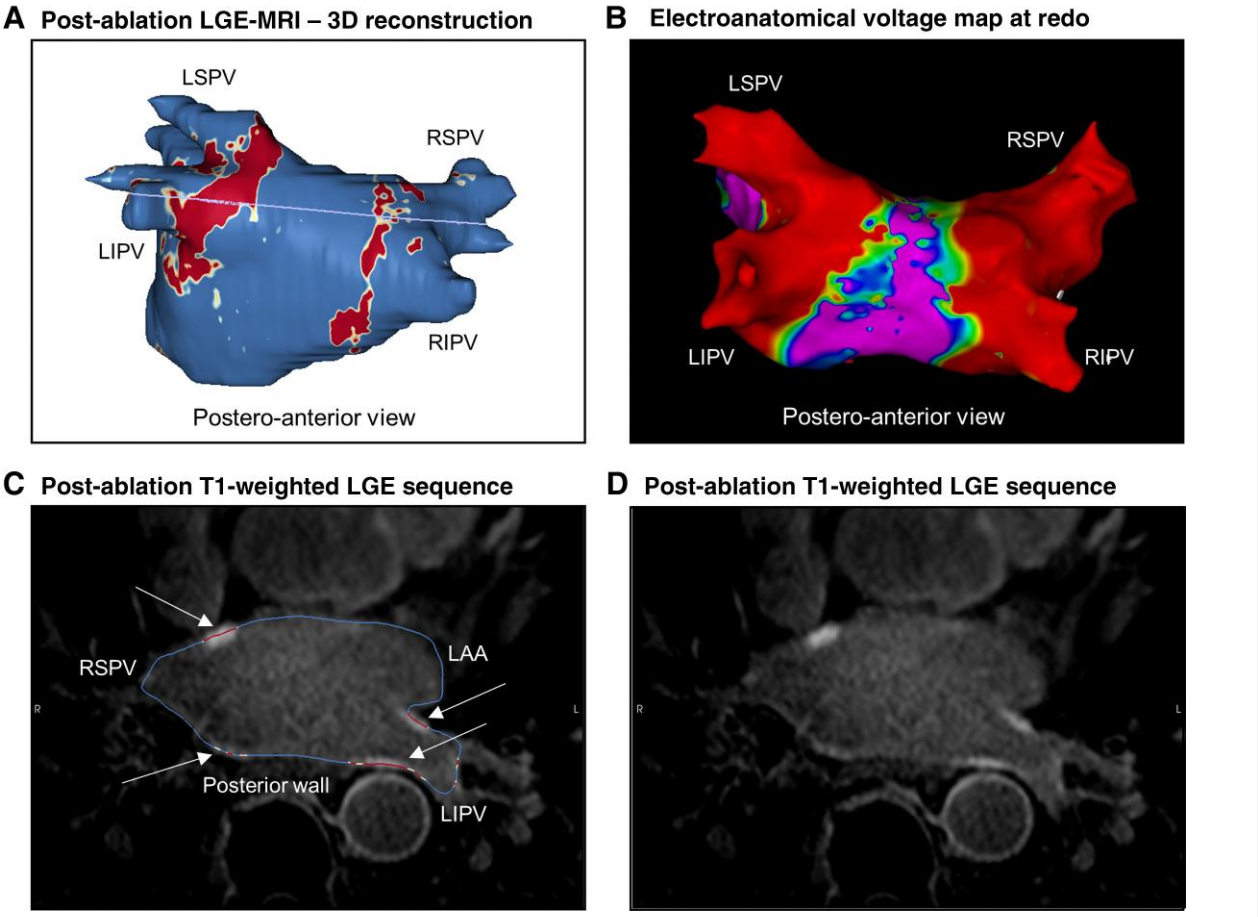

Figure 2 Complete LGE lesion set and durable PVI—representative case. (*A*) 3D reconstruction of left atrium and PVs 3 months after index PVI with colour coding based on signal intensity ratios applying thresholds for fibrotic tissue (yellow ≥1.2; red >1.32) using ADAS 3D software (Adas3D Medical Barcelona, Spain). The purple line indicates the plane of the LA slices in the lower panel (C&D). (*B*) Postero-anterior view of electroanatomical voltage map of the same left atrium and PVs in a subsequent repeat invasive procedure (24 months after index PVI) applying voltage thresholds of 0.1 and 0.5 mV, respectively. (*C*) Overlay of the T_1-weighted image with the LGE colour coding described previously. White arrows point to local ablation-induced LGE lesions at the PV ostial walls. (*D*) T_1-weighted raw image without overlay. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LAA, left atrial appendage.

Table 4 Predictive value regarding PV reconnection—per-patient analysis

Sensitivity	99.1% (116/117)
Specificity	48.6% (17/35)
Positive predictive value	86.6% (116/134)
Negative predictive value	94.4% (17/18)
Agreement (kappa)	0.58*

Percentages (*n*-numbers); *$P < 0.0001$.

resolves within the first 1–2 months following ablation, rather than definite scar formation.[31,32]

Finally, it also has to be taken into account that 'false positive' LGE discontinuities, may indicate true anatomical gaps in the ablation lesion that coincide with sites of dormant conduction or non-conductive tissue and therefore do not result in evident electrical PV reconnection.

Conclusion

Taken together, non-invasive ablation lesion assessment by LGE-MRI can rule out PV reconnection with a high negative predictive value. Therefore, it has the potential to guide selection of appropriate candidates and planning of the ablation strategy for repeat procedures, and may help to improve success rates and to avoid unnecessary procedures with all their associated risks and costs.

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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