


BMJ Open Does left atrial epicardial conduction time reflect atrial fibrosis and the risk of atrial fibrillation recurrence after thoracoscopic ablation? Post hoc analysis of the AFACT trial

R Wesselink , J Neefs, N W E van den Berg, E R Meulendijks, M M Terpstra, M Kawasaki, F A Nariswari, F R Piersma, W J P van Boven, A H G Driessen, J R de Groot

To cite: Wesselink R, Neefs J, van den Berg NWE, *et al.* Does left atrial epicardial conduction time reflect atrial fibrosis and the risk of atrial fibrillation recurrence after thoracoscopic ablation? Post hoc analysis of the AFACT trial. *BMJ Open* 2022;**12**:e056829. doi:10.1136/bmjopen-2021-056829

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056829>).

Received 06 September 2021
Accepted 10 February 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Heart Center, Department of Clinical and Experimental Cardiology and Cardiothoracic Surgery, Amsterdam Cardiovascular Sciences, Amsterdam UMC Location AMC, Amsterdam, Noord-Holland, The Netherlands

Correspondence to

R Wesselink;
r.wesselink@amsterdamumc.nl and
Professor J R de Groot;
j.r.degroot@amsterdamumc.nl

ABSTRACT

Objectives To determine the association between left atrial epicardial conduction time (LAECT), fibrosis and atrial fibrillation (AF) recurrence after thoracoscopic surgical ablation of persistent AF.

Setting Single tertiary care centre in the Netherlands.

Participants Patients with persistent AF from the randomised Atrial Fibrillation Ablation and Autonomic Modulation via Thoracoscopic Surgery (AFACT)-trial were included. Patients eligible for thoracoscopic AF ablation were included, full inclusion and exclusion criteria were previously published. All patients underwent thoracoscopic ablation, encompassing pulmonary vein isolation with an additional roof and trigone lesion. In patients with conduction block across the roof and trigone lesion, LAECT was measured. LAECT was defined as the time to local activation at one side of the roofline on pacing from the opposite side. Collagen fibre density was quantified from left atrial appendage histology.

Outcome measures Primary outcome: AF recurrence during 2 years of follow-up.

Results 121 patients were included, of whom 35(29%) were women, age was 60.4±7.8 and 51% (62) had at least one AF recurrence during 2 years of follow-up. LAECT was longer in patients with versus without AF recurrence (182±43 ms vs 147±29 ms, p<0.001). LAECT was longer in older patients, in patients with a higher body mass index (BMI) and in patients using class IC antiarrhythmic drugs. LAECT was shorter in patients with higher collagen fibre density. A previously failed catheter ablation, LAECT and BMI were independently associated with AF recurrence.

Conclusion LAECT is correlated with collagen fibre density and BMI and is independently associated with AF recurrence in patients with persistent AF. In these patients, LAECT appears to reflect substrate characteristics beyond clinical AF type and left atrial volume.

Trial registration number NCT01091389.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 2–4% of

Strengths and limitations of this study

- Unique combination of demographic, electrophysiological and histological data from a randomised controlled trial with standardised 2-year follow-up.
- Conclusions are based on differences in activation time rather than conduction velocity, as distance and fibre direction are not available.
- Per study design, left atrial epicardial conduction time measurement was only possible in patients with conduction block over the roofline.
- Short asymptomatic atrial fibrillation episodes may have been missed with 24-hour holter monitoring follow-up.

adults worldwide.^{1 2} Patients with AF have an increased risk of stroke, heart failure, dementia and a reduced quality of life.^{2 3} While the prevalence of AF increases, mainly due to ageing of the population,⁴ the effectiveness of AF treatment is still suboptimal. Especially persistent AF, that is not self-terminating and lasting longer than 7 days, is hard to treat and recurrences are common.⁵ When symptoms of AF recur despite antiarrhythmic drug (AAD) therapy, thoracoscopic ablation may be indicated.⁶ In this sub study of the AFACT trial, the indication for undergoing thoracoscopic ablation was advanced AF (usually persistent AF with enlarged left atrium or previously failed catheter ablation).⁷ The cornerstone of AF ablation is pulmonary vein isolation (PVI). Additional ablation targets have been pursued to reduce AF recurrences after ablation, but the optimal treatment strategy remains unclear.

Recurrence of AF after ablation is a multifactorial process. Individual and AF characteristics such as age, body mass index (BMI),

left atrial volume and duration of persistent AF may affect outcome after the procedure.⁸ Inflammation,⁹ abnormal calcium handling,¹⁰ possibly affected by sarco(endo)plasmic reticulum ATPase expression¹⁰ and autonomic dysfunction¹¹ may play a role in recurrence of AF as well as the quality of the procedure. Several ablation targets have been pursued to improve outcome after ablation.

Linear left atrial lesions in addition to PVI have been suggested to increase the efficacy of AF ablation.^{12 13} Left atrial lesions such as a posterior box or mitral isthmus line may preclude macroreentrant circuits after isolation of the pulmonary veins (PV's) and may thereby decrease the risk of arrhythmia recurrences.¹⁴ Moreover, left atrial lesions may compartmentalise the left atrium reducing the volume of left atrium available for fibrillation. However, in 2015, Verma *et al* showed in a large randomised controlled trial in patients with persistent AF that PVI alone was equally effective to additional left atrial lesions or additional ablation of complex fractionated atrial electrograms.¹⁵ More insight in the nature and extent of the arrhythmogenic left atrial substrate may increase our understanding of the mechanism of disease and contribute to improved selection of patients for invasive therapeutic strategies in AF.

Atrial fibrosis is the hallmark of atrial arrhythmogenic remodelling. Inflammation, fatty infiltration and fibroblast activity affect the distribution of extracellular matrix and thereby the electrical and mechanical function of the atria. Such structural remodelling leads to electrical dissociation of myocyte fibres and conduction inhomogeneity within the atrial wall.¹⁶ While locally longitudinal conduction velocity may increase due to fibrosis,¹⁷ slow conduction within low-voltage areas and heterogeneous rather than homogeneous activation patterns may increase total activation time of the atrium. Most attention regarding the clinical electrophysiological characteristics of electrical remodelling has been given to electrogram characteristics: low voltage of fragmented local atrial electrograms.^{18 19} However, the conduction velocity of the activation wave front is an important determinant for arrhythmogenesis and may be independent of local electrogram characteristics. Indeed, increased P-wave duration as a measure of prolonged atrial conduction time has been associated with AF recurrence in patients undergoing cryoablation.²⁰ Intra-atrial conduction time, however, can only be measured invasively. Despite that limitation, left atrial conduction time may provide additional insight into disease severity and prognosis beyond clinically relevant risk factors such as left atrial volume and AF type, and may carry important prognostic information regarding the arrhythmogenic substrate and the recurrence of AF.

We, therefore, performed a proof of principle study assessing left atrial conduction times as a measure for conduction velocity and hypothesised that periprocedurally measured left atrial conduction characteristics reflect atrial remodelling and are associated with AF recurrence after thoracoscopic ablation. Left atrial epicardial

conduction time (LAECT) was defined as the time to local activation at one side of the roofline on pacing from the opposite side with proven conduction block, the roofline forces the activation front to detour around the left atrium. We investigated the relation between LAECT and AF recurrence. In the same patients, we assessed the relation between LAECT and atrial fibrosis in the excised left atrial appendage (LAA). As a secondary outcome, we investigated the effects of incomplete conduction block across one of the ablation lines on AF recurrence.

METHODS

Patient selection and procedure

The AFACT trial was a single centre, prospective, randomised controlled trial in which patients with advanced AF (usually persistent AF, with enlarged left atria or previously failed catheter ablation) were randomised to ganglion plexus (GP) ablation versus no GP ablation in addition to thoracoscopic ablation. The atrial lesion set consisted of PVI, and a roof line and trigone line (Dallas lesion set)²¹ in patients with persistent AF. The LAA was excised in all patients. The study was approved by the institutional review board of the Amsterdam University Medical Centers. All patients provided written informed consent. The inclusion and exclusion criteria have been published previously.⁷ In short, the study included 240 patients (38–76 year old) with advanced (paroxysmal and persistent) AF undergoing thoracoscopic surgical ablation. Main exclusion criteria were prior catheter ablation within the preceding 4 months, New York Heart Association (NYHA) class IV heart failure symptoms, a history of radiation therapy on the thorax, longstanding persistent AF and a left ventricular ejection fraction (LVEF) of <35%. In the current analysis, we selected patients with persistent AF in whom a roofline and a trigone line was constructed. Conduction block across all lesions was evaluated through differential pacing by an electrophysiologist during surgery as described previously.²²

The surgical procedure has been described in detail previously.^{7 23} In short, bilateral video-assisted thoracoscopic surgery was used with unilateral ventilation of the contralateral lung. Trans-oesophageal echocardiography was used to exclude presence of a thrombus in the left atrium and LAA. After opening of the pericardium, the GPs were located with high-frequency stimulation and based on anatomical landmarks.²³ If the patient was randomised to the additional GP ablation arm, GPs were subsequently ablated and ablation was validated with high-frequency stimulation. The right PVs were isolated using a bidirectional bipolar radiofrequency clamp (Atricure, Mason, Ohio). During the right-sided thoracoscopy, the right side of the roof line (connecting the right and left isolated PV antrum) and the trigone line (connecting the roofline with the left fibrous trigone at the level of the sinus of Valsalva) were ablated (Atricure Isolator Transpolar pen or Coolrail). Conduction block across these lines (see below) was assessed. During the left-sided

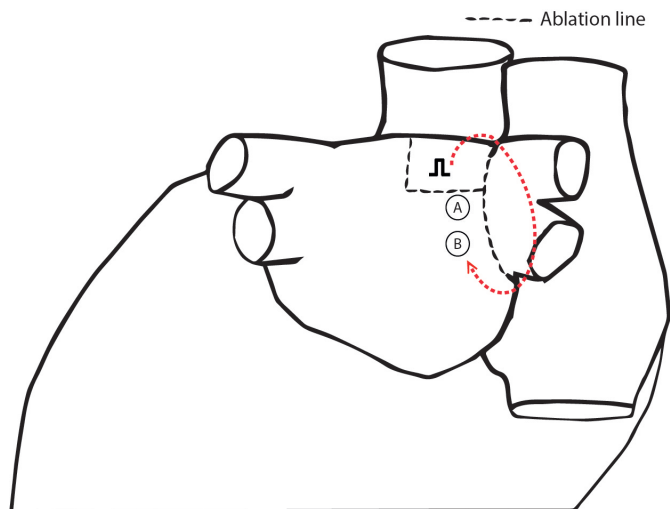


Figure 1 Schematic image of the posterior left atrium. A partial roofline is constructed, connected to the trigone line. The trigone line is connected to the left fibrous trigone. Evaluation of conduction block by the roofline by determining conduction time close to the roofline (position A), and further downward (position B) from the roofline. Red dotted line represents the direction of the activation front in case of conduction block by the roof- and trigone line. LAECT was defined as the conduction time at position A, close to the roofline, in case of proven conduction block by the roof- and trigone line. LAECT, left atrial epicardial conduction time.

thoracoscopy, the left PVs were isolated and the roofline was connected to the left PV antrum. PV isolation and conduction block of the left part of the roofline were assessed and the LAA was excised with a stapling device (Endo Gia stapler, Tyco Healthcare Group).

Assessment of conduction block

All mapping of the PVs and additional left atrial lines were performed with a custom-made bipolar electrode with seven (0.2 mm diameter) electrodes with an interelectrode distance of 1 mm. The signals were fed into a mobile electrophysiological workstation (Bard LabSystem PRO 2.4A, C. R. Bard, Murray Hill, New Jersey).

During the right-sided thoracoscopy, conduction block across the partial roofline and the trigone line was assessed with differential pacing manoeuvres.²² The left atrium was paced unipolarly at a fixed position anterior of the roofline and rightward of the trigone line with a fixed temporary pacing wire (figure 1). The indifferent electrode was connected to the skin. Activation time was defined as the time between the pacing artefact and local atrial activation at the opposite side of the line: the first maximally negative downslope in the unipolar signal. Activation time was measured at two positions, one closest to (figure 1, position A) and one further away from the ablation line (figure 1, position B). The measurement was repeated at a position laterally along the roofline.

Consequently, with an intact roofline, the activation propagates around the PVs, from inferior to superior over the left atrial posterior wall towards the ablation line. Similarly, activation propagates through the intra-atrial

septum around the aortic and mitral valve towards the intact trigone line. With intact lines, the activation time close to the line is longer than away from the line. Conversely, when the ablation line is not complete, activation propagates through the line and the area close to the line is activated earlier than the area away from the line (figure 1). In case of persistent conduction, additional ablation was applied to the area with the shortest activation time until conduction block was achieved or until surgical circumstances precluded further attempts to achieve conduction block. The initial construction of the roofline and trigone line typically lasted 30–45 min. This may have lasted for up to 1 hour in case of persistent conduction through one of the lines.

Left atrial epicardial conduction time

LAECT was defined as the time between the pacing artefact and the local activation time, measured closest to the roofline (position A in figure 1). LAECT was (per definition) only assessed in patients with confirmed conduction block of both the roofline and the trigone line. If activation time measurements were performed at two parallel positions closest to the roofline, the longest activation time of the two was selected for analysis of LAECT.

Interstitial atrial fibrosis quantification

In 65 patients with intact roofline and trigone line, part of the excised LAA was fixed in 4% formalin and embedded in paraffin. Sections of 5 µm thickness were prepared and stained with Picrosirius red for interstitial collagen quantification. Sections were digitized at 40× magnification (Philips IntelliSite Ultra Fast Scanner, 0.25 µm / pixel) and 20 non-overlapping fields (maximal 5000 by 5000 pixels) from each patient were randomly selected for collagen quantification. Endocardial, epicardial and perivascular fibrosis were manually excluded. An automated image analysis using Image J Software colour deconvolution was used to determine the area fraction of collagen of the combined area of cardiomyocytes and collagens with exclusion of white background in the images.

All individual interstitial collagen fibres were quantified using a custom matlab-based algorithm. A typical example is shown in figure 2. Images were binarised to a black-and-white image after colour deconvolution, preprocessed and filtered. First, all white pixels (representing collagen) were dilated and eroded using a 5 pixel (1.25 µm) radius stamp to smooth the image. Holes of maximal 2000 pixels were filled. Large collagen patches (>1250 µm²) were identified, quantified and removed from the image. The length of every fibre was determined by morphological skeletonisation. This technique creates a skeleton of a two-dimensional shape. The fibre length of each skeleton ≥4 pixels was defined as the length between the two end points that are farthest apart. The number of pixels determined the fibre area. We quantified the number of individual fibres, and the fibre density, defined as the total number of fibres divided by the total area of myocardium and interstitial collagen combined.

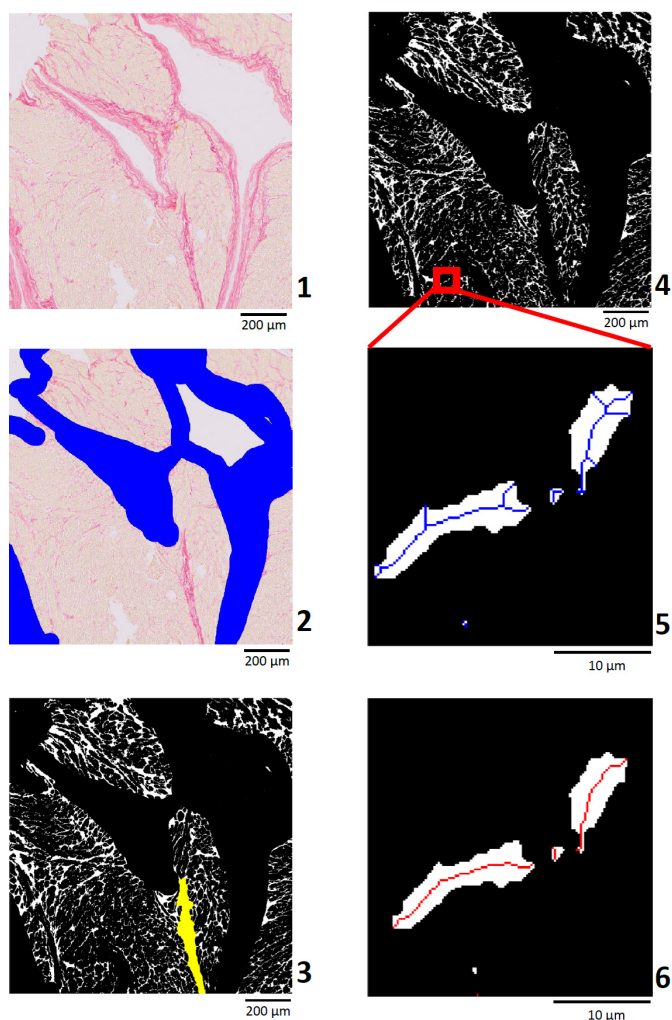


Figure 2 Typical example of collagen fibre analysis in six screens. (1) Selection of ± 4600 by 4600 pixels. (2) Manual removal of endocardial, epicardial and perivascular fibrosis (blue=excluded area). (3) Binarized (black and white) image, identification and removal of large interconnected areas of collagen (yellow). (4) Final input for fibre analysis algorithm. 5 and 6 are a magnification of the red aligned section of image 4. (5) Result of skeletonization, (6) fibres with a red centreline, reflecting the length of the fibre.

Follow-up and outcome

The primary outcome of this study was recurrence of AF during 2-year follow-up. Recurrence of AF was defined according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society/Latin American Society of Electrophysiology and Cardiac Stimulation (HRS/EHRA/ECAS/SOLAECE) consensus as any atrial tachyarrhythmia documented by ECG or lasting longer than 30s on continuous monitoring without AAD therapy.²⁴ Patients were followed for 2 years with outpatient visits, ECG and 24-hour Holters at 3, 6, 9, 12, 15, 18 and 24 months. Patients were encouraged to make extra ECG recordings when symptomatic. A blanking period of 3 months was used during which recurrence of AF was not considered a failure of the procedure. Three months after the procedure, all

antiarrhythmic drugs were discontinued. A blinded and independent clinical end point committee adjudicated all outcomes.

Statistical analysis

Baseline characteristics were presented as mean \pm standard deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for not normally distributed variables. Association of variables with recurrence of AF was determined using univariate and multivariable Cox proportional hazard modelling. Results of the Cox proportional hazard model were presented as hazard ratio (HR) with 95% confidence interval (CI). Cross correlation of variables used in the Cox proportional hazard model was determined with logistic regression for binomial variables and linear regression for continuous variables. Association of binary variables with recurrence of AF was performed using Pearson χ^2 test or Fisher's exact test if expected values were under 5. Correlation analysis of variables with LAECT was performed using linear regression. Analysis was conducted in R (R Core Team, 2020, R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

Patient and public involvement

No patient involved.

RESULTS

Patients

At baseline, 142 patients had persistent AF. In 127 (89%) of those, differential pacing for confirmation of conduction block across the roofline and trigone line was recorded. Six (4.7%) patients were excluded from the current analysis because of periprocedural bleeding, or because (continuation of) linear ablation was deemed unsafe. Consequently, 121 patients were included in the current analysis.

Baseline characteristics

Baseline characteristics are described in [table 1](#). Mean age was 60.4 ± 7.8 years, 29% were women, BMI was 27.5 ± 3.9 and left atrial volume index (LAVI) was 41.4 ± 13.1 mL/m². Sixty-two patients (51%) were randomised to additional GP ablation and treated accordingly. The median CHA₂DS₂VASc (Score to predict risk of thrombo-embolic events: Congestive heart failure or left ventricular dysfunction Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category) score was 1 (1 to 2). Medication use at baseline is shown in online supplemental table 1.

Conduction block of linear lesions

After various attempts, conduction block could not be confirmed across a linear lesion in 47 (39%) out of 121 patients, mainly due to persistent conduction across the trigone line (43 patients). Patients in whom conduction block across one or more lines could not be achieved had a higher BMI (28.4 ± 4.3 vs 26.9 ± 3.5 kg/m², $p=0.04$) and

Table 1 Baseline characteristics

Parameter	n=121
Females (%)	35 (28.9)
Age (y)	60.4 ± 7.8
BMI(kg/m ²)	27.5 ± 3.9
LVEF (%)	52.7 ± 10
LAVI (mL/m ²)	41.4 ± 13.1
RAVI (mL/m ²)	29.8 ± 10.0
AF duration (y)	4 (2–9)
Persistent AF (%)	121 (100)
Previous catheter ablation (%)	22 (18.2)
Myocardial infarction (%)	7 (5.8)
PCI (%)	10 (8.3)
GP ablation (%)	62 (51.2)
CHD (%)	10 (8.3)
Hypertension (%)	58 (47.9)
Diabetes mellitus (%)	12 (9.9)
Stroke (%)	12 (9.9)
Vascular disease (%)	17 (14.1)
Age≥65 y (%)	40 (33.1)
Age≥75 (%)	1 (0.8)
CHA ₂ DS ₂ VASc	1 (1–2)
Serum creatinin (μmol/L)	84 (76–95)
Serum NT-ProBNP (ng/L)	422 (214–856)

Values shown as mean±SD, median (IQR) or n(%).

AF, atrial fibrillation; BMI, body mass index; CHD, congestive heart disease; GP, ganglion plexus; L, litre; L, liter; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; m, meter; ml, milliliter; NT-ProBNP, n-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention; RAVI, right atrial volume index; y, year.

tended to have a higher CHA₂DS₂VASc score (2 (1 to 2) vs 1 (0 to 2) p=0.057), which was driven by patients aged 65 years and older (32 (43%) vs 8 (17%), p=0.005). Twenty-four (51%) out of 47 patients with incomplete conduction block were free of AF recurrences during 2-year follow-up, compared with 31 (42%) of the 74 patients with proven conduction block (HR 1.32 (0.78 to 2.21) p=0.30).

Risk of AF recurrence

In the 74 subjects with confirmed conduction block over the linear lesions, regression analysis demonstrated that a previous unsuccessful catheter ablation (HR 2.30; 95% CI 1.15 to 4.61), LAECT (HR 1.11; 95% CI 1.04 to 1.18, per 10 ms) and BMI (HR 1.12; 95% CI 1.02 to 1.23 per kg/m² increase) were significantly associated with AF recurrence (figure 3). In multivariable Cox proportional hazard regression analysis (figure 3), a previous unsuccessful catheter ablation (HR 2.48; 95% CI 1.08 to 5.7) and LAECT (HR 1.08; 95% CI 1.01 to 1.15) but not LAVI were independently associated with AF recurrence. Correction of the multivariate analysis for fibrosis variables in those

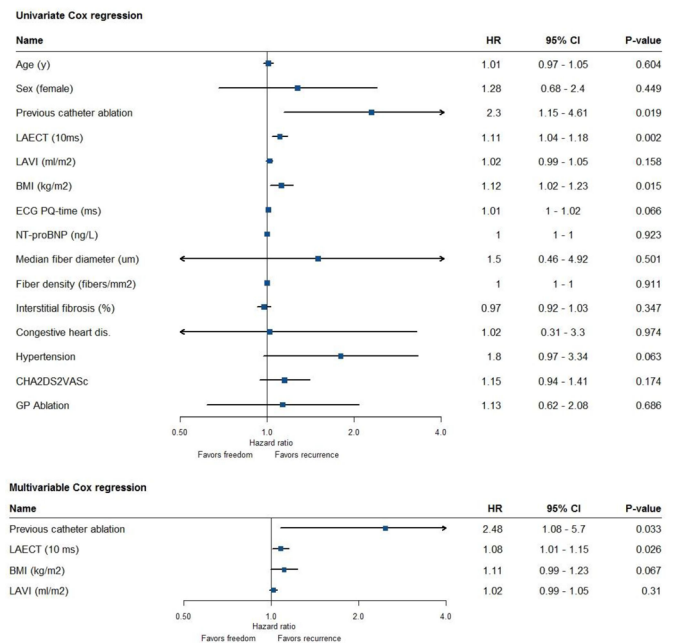


Figure 3 Univariate and multivariable Cox regression analysis of LAECT and other preselected risk factors for AF recurrence. AF, atrial fibrillation; BMI, body mass index; GP, ganglion plexus; LAECT, left atrial epicardial conduction time; LAVI, left atrial volume index; NT-proBNP, n-terminal pro natriuretic peptide; y, years.

patients in whom these were available did not affect the association between LAECT and AF recurrence.

Interstitial collagen fibres

The median interstitial collagen fibre length was 3.2 (1.5 to 7.9) μm, median fibre area was 2.31 (0.75 to 9.50) μm². Average fibre diameter was 0.76 (0.52 to 1.27) μm. A high-collagen fibre density (absolute number of fibres/area) was significantly correlated with a higher percentage of interstitial collagen (R=0.36, p=0.004) and with a higher proportion of larger collagen patches (>1250 μm) (R=0.28, p=0.028). Also high fibre density was correlated with an on average smaller median fibre diameter (R=-0.35, p=0.006). None of the collagen fibre characteristics was independently associated with AF recurrence.

Left atrial epicardial conduction time

A short LAECT was independently associated with more freedom of AF. LAECT was significantly longer in patients with AF recurrence compared with patients without AF recurrence during 2-year follow-up (182±43 ms vs 147±29 ms respectively, p<0.001).

Age (p=0.006), CHA₂DS₂VASc score (p=0.044) and AAD class 1 use at baseline (p=0.034) were significantly and positively correlated with LAECT. On the other hand, LAECT was shorter in patients with a higher collagen fibre density (R=-0.46, p=0.034). In this analysis, an increase of 1 fibre per mm² corresponded to 5 ms shorter LAECT. Sex, previous catheter ablation, LAVI, BMI, PR interval on the ECG and percentage of interstitial fibrosis were not significantly correlated with LAECT. Figure 4

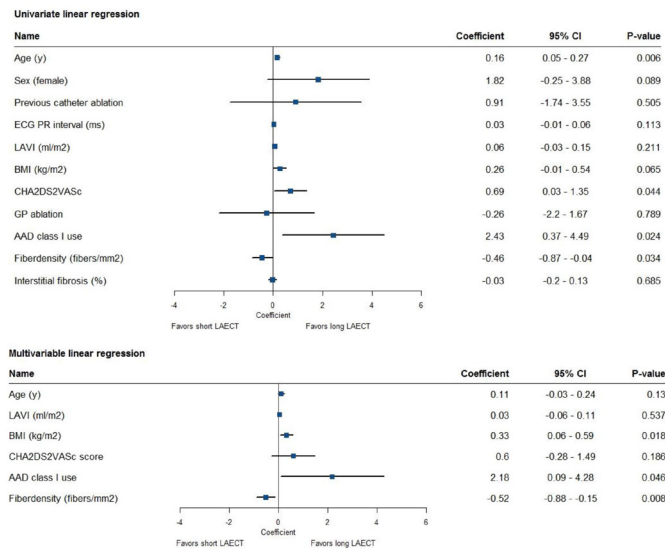


Figure 4 Univariate and multivariable linear regression of patient characteristics and LAECT. AAD, antiarrhythmic drugs; BMI, body mass index; GP, ganglion plexus; LAECT, left atrial epicardial conduction time; LAVI, left atrial volume index; RL, roof line; y, years.

demonstrates the correlation of patient characteristics with LAECT. In multivariable linear regression, BMI ($R=0.33$ (0.06 to 0.59), $p=0.018$), AAD class 1 use ($R=2.18$ (0.09 to 4.28], $p=0.046$) and fibrosis fibre density (-0.52 (-0.88 to -0.15), $p=0.008$) were independently associated with LAECT.

DISCUSSION

We performed a proof-of-principle study on the prognostic role of characteristics of conduction of activation in the left atrium in relation to AF recurrence. We investigated LAECT as an invasive marker for structural remodelling and associated electrophysiological characteristics of the left atrium with atrial collagen content and AF recurrence. We found that a longer LAECT is associated with more AF recurrences of any atrial tachyarrhythmia during two year after thoracoscopic surgery for persistent AF. In multivariable analysis, a short LAECT was independently associated with freedom of AF. LAECT across the intact roofline represents left atrial activation time and was used as a proxy for conduction velocity. LAECT may reflect the extent and electrophysiological implications of fibrosis in the left atrium.

Left atrial epicardial conduction time

LAECT may be determined by tissue properties for conduction and the pathway of conduction. Tissue properties that may impair conduction can be reduced atrial wall thickness, low voltage zones and heterogeneous patterns of conduction.²⁵ LAECT may, therefore, reflect electrophysiological as well as structural characteristics of the left atrium. The exact distance travelled by the activation front could not be determined from the current data, which precluded actual calculation of conduction velocity.

A large LAECT can result from an increased trajectory of conduction or a decreased conduction velocity. As we found no longer LAECT in patients with enlarged left atria (long trajectory of conduction), we suggest that increased LAECT results from decreased conduction velocity. On the other hand, we cannot exclude that atrial fibre orientation or zig-zag activation patterns may have resulted in apparently slowed conduction, where, in fact, the pathway of conduction is long.²⁶ Our finding that LAECT significantly correlated with BMI supports the notion that atrial tissue composition determines LAECT since BMI is a well-known determinant of atrial structural and electrical remodelling.²⁷ Moreover, our findings underscore the concept of decreased conduction velocity as an important determinant of arrhythmogenesis,²⁸ and a predictor of AF recurrence, independent of clinical characteristics or voltage criteria of local electrograms. Interestingly, collagen fibre density also correlated with LAECT. A higher fibre density corresponded to a shorter LAECT. This seemingly contradictory finding may be the result of more preferential conduction along, compared with parallel to the fibres in more fibrotically remodelled atria, that is, of more anisotropy.¹⁷ In another study performed in patients undergoing catheter ablation, right atrial conduction time was significantly associated with the occurrence of recurrent AF.²⁹ That study confirms our finding of increased conduction time as a robust, single point measurement, associated with the risk of recurrent AF. Moreover, we demonstrated that LAECT provides additional information on the arrhythmogenic substrate, beyond clinical characteristics and left atrial size, with prognostic implications for AF recurrence.

Collagen fibre density

Collagen fibre density indicates the total number of collagen fibres per mm², irrespective of the fibre size. An increased fibre density was associated with a smaller median fibre diameter, which may indicate active fibrosis formation. The extent of fibrosis in LAA tissue was previously correlated to the extent of fibrosis in the posterior LA.³⁰ Moreover, the proportion of collagen in the LAA and posterior wall have been associated with left atrial volume and AF duration.^{31 32} The architecture and distribution of collagen fibres in the LAA may, thus, reflect the duration or burden of AF. However, this reaches beyond the scope of this study.

Conduction block across ablation lines

Gaps in linear ablation lines may be pro-arrhythmogenic and enable the formation of macro re-entry circuits. Our data did not show more arrhythmia recurrence in patients in whom conduction block was not achieved. This may in part relate to the utmost importance of isolation of the PVs, which was accomplished in all patients. Acute conduction block may not correspond to long-term conduction block. Damaged myocardial cells may recover, and a gap of merely one millimetre is enough for propagation of the activation front.³³ Additionally,

even after the creation of transmural and complete scars during the surgical cut-and-sew Cox Maze procedure, cases of reconnection have been reported.³⁴ How linear lesions affect the substrate for arrhythmia is, therefore, not completely clear. Part of the antiarrhythmic effect of linear lesions may rely solely on exclusion of atrial tissue, regardless of conduction block,³⁵ in line with the critical mass theory.³⁶ Some advocate exclusion of the posterior wall with a roof and floor lesion to improve outcome.¹⁴ Finally, and maybe most importantly, aside from conjectures on optimal lesion sets, clinically there may be no advantage of additional lesions over PV isolation alone in patients with persistent AF.¹⁵

Previous catheter ablation

We found that a higher proportion of patients with persistent AF and a previously failed catheter ablation suffered from AF recurrence after thoracoscopic AF ablation compared with ablation naïve patients. To our knowledge, the paper by Driessen *et al* is the only study that suggested this association before.³⁷ The number of patients with a previous catheter ablation was limited in the current analysis (n=22). Therefore, studies in a larger patient cohorts should be performed to determine if a previously failed catheter ablation is indeed associated with worse clinical characteristics, or that failure of catheter ablation is merely an indicator of patients with a more advanced form of AF.

LAECT was measured in a subset of patients with persistent AF, with confirmed conduction block across both roofline and trigone line. It was not possible to quantify the exact distances between the measurement locations, which precluded calculation of (an estimate of) conduction velocity. Detection of recurrent AF with 24-hour holter monitoring may have resulted in an underestimation of the number of asymptomatic recurrences. This is a systematic error, and, therefore, we expect little to no effect on our outcome variables.

Strengths and limitations

In this study, we combined demographic, electrophysiological and histological data from a previously published RCT with standardised 2-year follow-up. During follow-up, rhythm monitoring was performed with 24-hour Holter monitoring, by which short asymptomatic episodes of AF may have been missed. Due to the study design, LAECT was only measured in patients with conduction block over the roofline, thereby limiting the number of patients included in this study. Conclusions are based on differences in activation time rather than conduction velocity, as distance travelled by the activation front and myocardial fibre orientation were not available.

CONCLUSION

In patients with persistent AF, a longer LAECT was independently associated with more AF recurrences after thoracoscopic AF ablation. A higher BMI and use of class

I AAD were associated with prolongation of LAECT, whereas a higher interstitial collagen fibre density was associated with a shorter LAECT. Our data supply evidence for the notion that conduction characteristics may provide additional insight into the arrhythmogenic substrate, and prognostic information beyond established clinical factors, left atrial dilatation or voltage characteristic of the electrogram. Clinical application of our invasive findings may require the study of non-invasive alternatives for LAECT, which may improve patient selection for invasive treatment of persistent AF.

Contributors RW, JN, NWEvdB, ERM, MMT, MK, FAN, FRP, WJPvB, AHGD, JRdG have contributed to the data acquisition and interpretation of the data. RW, JN, NWEvdB, JRdG have contributed to the conceptualisation of the study and drafted the manuscript. All authors (RW, JN, NWEvdB, ERM, MMT, MK, FN, FRP, WJPvB, AHGD, JRdG) have contributed significantly to the study, critically reviewed the manuscript and approved the final version of the manuscript. RW and JRdG were responsible for the overall content of the manuscript. All authors take full responsibility for all aspects of the reliability of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the AFACT trial was registered at clinicaltrials.gov with the number NCT01091389. The AFACT trial was approved by the METC AMC and was assigned project number METC 09 10/002. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

R Wesselink <http://orcid.org/0000-0001-5671-2531>

REFERENCES

- 1 Benjamin EJ, Muntner P, *et al*, American Heart Association Council on E. Prevention statistics C and stroke statistics S. heart disease and stroke Statistics-2019 update: a report from the American heart association. *Circulation* 2019;139:e56–28.
- 2 January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;74:104–32.
- 3 Virani SS, Alonso A, *et al*, American Heart Association Council on E. Prevention statistics C and stroke statistics S. heart disease and stroke Statistics-2021 update: a report from the American heart association. *Circulation* 2021;143:e254–743.
- 4 Krijthe BP, Kunst A, Benjamin EJ, *et al*. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746–51.

- 5 Berger WR, Meulendijks ER, Limpens J, *et al.* Persistent atrial fibrillation: a systematic review and meta-analysis of invasive strategies. *Int J Cardiol* 2019;278:137–43.
- 6 Hindricks G, Potpara T, *et al.*, Watkins CL and Group ESCSD. Esc guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for Cardio-Thoracic surgery (EACTS). *Eur Heart J* 2020;2021:373–498.
- 7 Driessen AHG, Berger WR, Krul SPJ, *et al.* Ganglion plexus ablation in advanced atrial fibrillation: the AFACT study. *J Am Coll Cardiol* 2016;68:1155–65.
- 8 Calkins H, Hindricks G, Cappato R. HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Europace* 2017;2018:e1–160.
- 9 Sardu C, Santulli G, Santamaria M, *et al.* Effects of alpha lipoic acid on multiple cytokines and biomarkers and recurrence of atrial fibrillation within 1 year of catheter ablation. *Am J Cardiol* 2017;119:1382–6.
- 10 Sardu C, Santulli G, Guerra G, *et al.* Modulation of SERCA in patients with persistent atrial fibrillation treated by epicardial thoracoscopic ablation: the CAMAF study. *J Clin Med* 2020;9:544. doi:10.3390/jcm9020544
- 11 Rizzo MR, Sasso FC, Marfella R, *et al.* Autonomic dysfunction is associated with brief episodes of atrial fibrillation in type 2 diabetes. *J Diabetes Complications* 2015;29:88–92.
- 12 Hocini M, Jaïs P, Sanders P, *et al.* Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. *Circulation* 2005;112:3688–96.
- 13 Jaïs P, Hocini M, Hsu L-F, *et al.* Technique and results of linear ablation at the mitral isthmus. *Circulation* 2004;110:2996–3002.
- 14 Henn MC, Lancaster TS, Miller JR, *et al.* Late outcomes after the COX maze IV procedure for atrial fibrillation. *J Thorac Cardiovasc Surg* 2015;150:1168–78.
- 15 Verma A, Jiang C-yang, Betts TR, *et al.* Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;372:1812–22.
- 16 Alessie MA, de Groot NMS, Houben RPM, *et al.* Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. *Circ Arrhythm Electrophysiol* 2010;3:606–15.
- 17 Krul SPJ, Berger WR, Smit NW, *et al.* Atrial fibrosis and conduction slowing in the left atrial appendage of patients undergoing thoracoscopic surgical pulmonary vein isolation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2015;8:288–95.
- 18 Marcus GM, Yang Y, Varosy PD, *et al.* Regional left atrial voltage in patients with atrial fibrillation. *Heart Rhythm* 2007;4:138–44.
- 19 Blandino A, Bianchi F, Grossi S, *et al.* Left atrial substrate modification targeting low-voltage areas for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Pacing Clin Electrophysiol* 2017;40:199–212.
- 20 Kaypakli O, Koca H, Şahin DY, *et al.* Association of P wave duration index with atrial fibrillation recurrence after cryoballoon catheter ablation. *J Electrocardiol* 2018;51:182–7.
- 21 Edgerton JR, Jackman WM, Mack MJ. A new epicardial lesion set for minimal access left atrial maze: the Dallas lesion set. *Ann Thorac Surg* 2009;88:1655–7.
- 22 de Groot JR, Driessen AHG, Van Boven WJ, *et al.* Epicardial confirmation of conduction block during thoracoscopic surgery for atrial fibrillation—a hybrid surgical-electrophysiological approach. *Minim Invasive Ther Allied Technol* 2012;21:293–301.
- 23 Krul SPJ, Driessen AHG, van Boven WJ, *et al.* Thoracoscopic video-assisted pulmonary vein antrum isolation, ganglionated plexus ablation, and periprocedural confirmation of ablation lesions: first results of a hybrid surgical-electrophysiological approach for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2011;4:262–70.
- 24 Calkins H, Hindricks G, Cappato R. HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm* 2017;2017:e275–444.
- 25 Rossi S, Gaeta S, Griffith BE, *et al.* Muscle thickness and curvature influence atrial conduction velocities. *Front Physiol* 2018;9:1344.
- 26 de Bakker JM, van Capelle FJ, Janse MJ, *et al.* Slow conduction in the infarcted human heart. 'Zigzag' course of activation. *Circulation* 1993;88:915–26.
- 27 Mahajan R, Nelson A, Pathak RK, *et al.* Electroanatomical Remodeling of the Atria in Obesity: Impact of Adjacent Epicardial Fat. *JACC Clin Electrophysiol* 2018;4:1529–40.
- 28 King JH, Huang CL-H, Fraser JA. Determinants of myocardial conduction velocity: implications for arrhythmogenesis. *Front Physiol* 2013;4:154.
- 29 Kanemaru Y, Arima Y, Kaikita K, *et al.* Elongation of the high right atrium to coronary sinus conduction time predicts the recurrence of atrial fibrillation after radiofrequency catheter ablation. *Int J Cardiol* 2020;300:147–53.
- 30 Corradi D, Callegari S, Benussi S, *et al.* Regional left atrial interstitial remodeling in patients with chronic atrial fibrillation undergoing mitral-valve surgery. *Virchows Arch* 2004;445:498–505.
- 31 Geuzebroek GSC, van Amersfoort SCM, Hoogendijk MG, *et al.* Increased amount of atrial fibrosis in patients with atrial fibrillation secondary to mitral valve disease. *J Thorac Cardiovasc Surg* 2012;144:327–33.
- 32 Callegari S, Macchi E, Monaco R, *et al.* Clinicopathological bird's-eye view of left atrial myocardial fibrosis in 121 patients with persistent atrial fibrillation: developing architecture and main cellular players. *Circ Arrhythm Electrophysiol* 2020;13:e007588.
- 33 Melby SJ, Lee AM, Zierer A, *et al.* Atrial fibrillation propagates through gaps in ablation lines: implications for ablative treatment of atrial fibrillation. *Heart Rhythm* 2008;5:1296–301.
- 34 Wazni OM, Saliba W, Fahmy T, *et al.* Atrial arrhythmias after surgical maze: findings during catheter ablation. *J Am Coll Cardiol* 2006;48:1405–9.
- 35 Byrd GD, Prasad SM, Ripplinger CM, *et al.* Importance of geometry and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *Circulation* 2005;112:17–13.
- 36 Lee AM, Aziz A, Didesch J, *et al.* Importance of atrial surface area and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *J Thorac Cardiovasc Surg* 2013;146:593–8.
- 37 Driessen AHG, Berger WR, Chan Pin Yin DRPP, *et al.* Electrophysiologically guided thoracoscopic surgery for advanced atrial fibrillation: 5-year follow-up. *J Am Coll Cardiol* 2017;69:1753–4.