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The relation between the atrial blood supply and the complexity of acute atrial fibrillation ☆

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ABSTRACT

Background: Patients with a history of myocardial infarction and coronary artery disease (CAD) have a higher risk of developing AF. Conversely, patients with atrial fibrillation (AF) have a higher risk of developing myocardial infarction, suggesting a link in underlying pathophysiology. The aim of this study was to assess whether coronary angiographic parameters are associated with a substrate for AF in patients without a history of AF.

Methods: During cardiac surgery in 62 patients (coronary artery bypass grafting (CABG;n = 47), aortic valve replacement (AVR;n = 9) or CABG + AVR (n = 6)) without a history of clinical AF (age 65.4 ± 8.5 years, 26.2% female), AF was induced by burst pacing. The preoperative coronary angiogram (CAG) was assessed for the severity of CAD, and the adequacy of atrial coronary blood supply as quantified by a novel scoring system including the location and severity of right coronary artery disease in relation to the right atrial branches. Epicardial mapping of the right atrium (256 unipolar electrodes) was used to assess the complexity of induced AF.

Results: There was no association between the adequacy of right atrial coronary blood supply on preoperative CAG and AF complexity parameters. Multivariable analysis revealed that only increasing age (B0.232 (0.030;0.433),p = 0.03) and the presence of 3VD (B3.602 (0.187;7.018),p = 0.04) were independently associated with an increased maximal activation time difference.

Conclusions: The adequacy of epicardial right atrial blood supply is not associated with increased complexity of induced atrial fibrillation in patients without a history of clinical AF, while age and the extent of ventricular coronary artery disease are.

1. Introduction

Coronary artery disease (CAD) is highly prevalent among patients with atrial fibrillation (AF) [1]. Even in patients with idiopathic AF, in which no other form of overt vascular disease is present, the prevalence of subclinical CAD is higher than in comparable patients in sinus rhythm [2]. Furthermore, patients with a history of myocardial infarction have a higher risk of developing AF [3]. Conversely, patients with AF have a higher risk of developing myocardial infarction [4], suggesting a link in underlying pathophysiology.

A direct association between atrial blood supply and AF can be deduced from several studies. Ligation of the blood supply to the left atrium in dogs [5,6] and sheep [7] leads to significant changes in the electrical properties of the atrium, resulting in increased AF inducibility and duration of induced AF. In humans, involvement of atrial branches during myocardial infarction was an independent predictor of new-onset AF [8–10].

In addition to a direct ischemic effect of reduced blood supply through specific atrial coronary arteries, a link between generalized atherosclerosis and AF has been proposed [11]. Firstly, ischemic heart disease is likely to affect the atrial myocardium directly [12].

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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In addition, CAD may directly cause abnormalities in ventricular structure and function that eventually lead to increased left atrial filling pressure, stretch and fibrosis, creating a substrate for AF [13]. In this study, we aimed to study the direct effects of coronary artery disease and potentially reduced tissue perfusion on the formation of an AF substrate. Therefore, we focused on the right atrium, as the left atrium is more likely to experience the confounding effects of increased atrial filling pressures due to left ventricular dysfunction caused by reduction in the left ventricular coronary blood supply.

We hypothesized that reduced coronary supply to the atria results in the formation of a substrate for AF. We focused on the right atrium, as the right atrium more adequately reflects the presence of structural substrate, rather than triggers and spontaneous episodes which may predominantly be found in the left atrium. We expected that the impact of a right coronary artery (RCA) stenosis on the right atrium would depend both on the degree of narrowing and on the location, with more proximal stenoses having a larger effect. To this end, we assessed the association between a scoring system for the adequacy of atrial coronary blood supply, and the extent of ventricular coronary artery disease on coronary angiogram, and the complexity of AF induced in patients without a history of AF undergoing cardiac surgery.

2. Methods

2.1. Patient selection

Patients undergoing elective cardiac surgery, without a known history of AF and with normal sinus rhythm on the screening electrocardiogram, were asked to participate in this study. Patients with insufficient right ventricular function and those deemed unsuitable for induction of AF during surgery were excluded. This study was approved by the institutional review board of the Maastricht Academic Hospital/Maastricht University, the Netherlands, and complied with the ethical principles of the Declaration of Helsinki. All patients gave written informed consent.

2.2. Coronary angiogram analysis

As part of the standard of care, coronary angiography was performed preoperatively in all patients. The presence and severity of coronary atherosclerosis was assessed by the cardiologist who performed the angiography. Patients were classified as having zero, one, two or three vessel disease; due to low prevalence, single vessel disease (n = 2) was combined with zero vessel disease. In addition, two cardiologists assessed atrial vascularization independently. In case of discrepancies, angiograms were reassessed to reach a consensus. The adequacy of atrial vascularization was categorized as follows, with the expected lowest adequacy of atrial vascularization in category 1 and the highest in category 5 (Fig. 1):

(1) Total occlusion of the proximal right coronary artery, before branching of right atrial branches, collateral filling is not sufficient to provide the right atrium with blood (Rentrop grade < 3; Panel A)
(2) Stenosis > 50% (visual estimation) in the right coronary artery (vessels > 1 mm Ø), leading to impaired perfusion of more than two thirds of the right atrial branches (Panel B)
(3) Stenosis > 50% (visual estimation) in the right coronary artery (vessels > 1 mm Ø), leading to impaired perfusion of less than two thirds of the right atrial branches (Panel C)
(4) Stenosis < 50% in the right coronary artery (vessels > 1 mm Ø; Panel D)
(5) No signs of stenosis of the right coronary arteries and right atrial branches (Panel E)

2.3. Characterization of the AF substrate

During open heart surgery, prior to right atrial cannulation, acute AF was induced by rapid atrial pacing (incremental 300–800 bpm or decremental 800–300 bpm, for 10 min). Epicardial high-density activation mapping of the right atrial wall was performed using a 256 unipolar electrode plaque (25 × 25 mm). The average length of the recording was 20 ± 9 s. The methods for characterization of the atrial substrate by high-density activation mapping were described in detail previously [14]. Examples of AF patterns in a patient with relatively low and relatively high complexity are shown in Fig. 2. In short, an established wave-mapping technique based on unipolar local activation time was used to compute the following substrate complexity measures (as described in detail previously [15]): AF wave conduction velocity, number of waves per AF cycle, number of breakthrough waves per AF cycle and maximal activation time difference, defined as the median of the maximal local activation time differences between adjacent electrodes, forming a measure for conduction heterogeneity and electrical dissociation. The automated deflection detection algorithm differentiates dominant from subsidiary activations, whereby the steepest negative deflection of a unipolar electrogram represents the dominant local activation [16], and any additional deflections are due to fractionation. Therefore, the unipolar fractionation index (FI) was defined as the ratio of subsidiary to dominant deflections.

2.4. Echocardiogram analysis

In patients (n = 39) in whom preoperative echocardiography was of sufficient quality, minimum and maximum right atrial area were assessed, and fractional area change of the right atrium by color kinesis on the apical 4-chamber view was determined in QLab 10 (Philips Healthcare, Best, the Netherlands). The diameter and degree of collapse of the inferior caval vein (ICV) were measured on the subcostal view during inspiration. In patients with tricuspid regurgitation, right ventricular systolic pressure was estimated.

2.5. Statistical analysis

Statistical analyses were performed using SPSS statistical software (IBM SPSS statistics version 23.0, IBM Corporation, Armonk, NY). Continuous variables are presented as mean ± standard deviation (SD) and were compared using an independent Student's *t*-test (two-tailed) or one-way ANOVA for normally distributed variables and as median [interquartile range] and compared using Mann–Whitney test (two-tailed) or Kruskal-Wallis test for non-normally distributed variables. Categorical variables are reported as number of patients and percentage and compared using Chi square testing, or two-tailed Fisher's Exact in case of an expected count below 5. All baseline characteristics were tested for a relation with the maximal activation time using univariable linear regression. All significant covariates were included in multivariable linear regression. Results were checked for collinearity and interaction among covariates. Manual backwards elimination was used to construct the final models (retention level set at 0.10). Odds ratios and 95% confidence intervals were calculated.

3. Results

3.1. Baseline characteristics

A total of 62 patients (65.1 ± 8.3 years, 21.0% female) undergoing coronary artery bypass grafting (CABG; n = 47, 75.8%), aortic

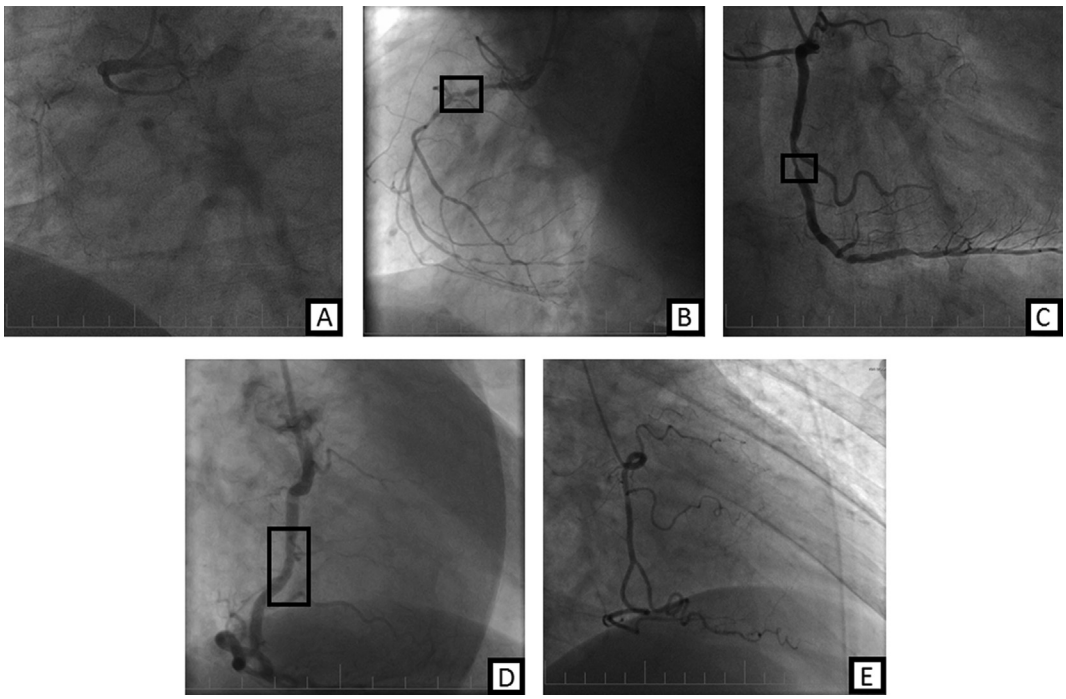

Fig. 1. Scoring of the right atrial blood supply: (1) Total occlusion of the right coronary artery (RCA; Panel A), (2) impaired perfusion of more than two thirds of the right atrial branches (Panel B), (3) impaired perfusion of less than two thirds of the right atrial branches (Panel C), (4) Stenosis < 50% in the RCA (Panel D), (5) no signs of stenosis in the RCA (Panel E).

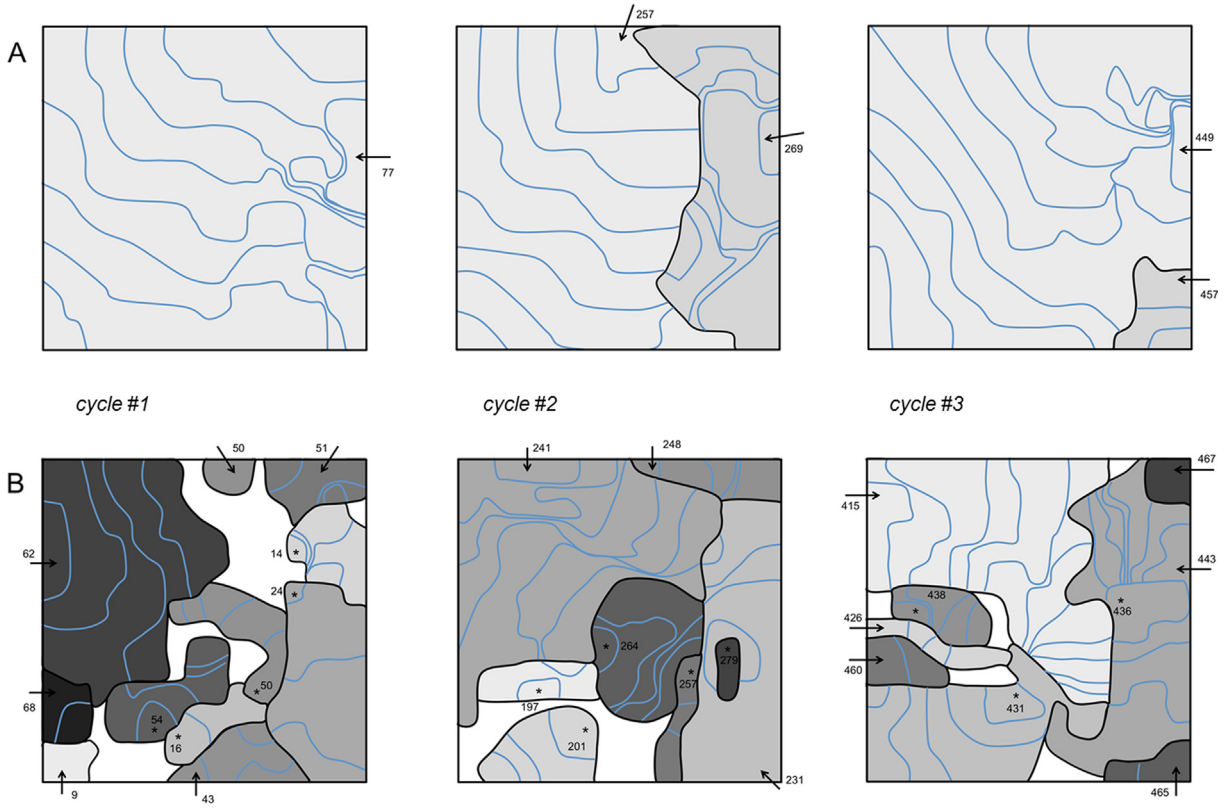

Fig. 2. Epicardial activation patterns during induced AF in a patient with low complexity (A) and high complexity (B) for three consecutive activation cycles. Blue lines are isochrones, black lines indicate lines of block, arrows indicate peripheral waves, asterisks indicate breakthrough. Numbers indicate time in milliseconds. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

valve replacement (AVR; n = 9, 14.5%) or CABG + AVR (n = 6, 9.7%), were included. Baseline characteristics are shown in Table 1.

3.2. Complexity of induced AF

Fig. 2 shows examples of a relatively simple and a relatively complex fibrillation pattern in the right atrium found in this cohort. None of the complexity parameters differed significantly between any of the atrial blood supply score categories (Table 2). There was a trend towards a decrease in wave size (mean number of electrodes allocated to each AF wave within the recording: 64.3 ± 27.6, 52.2 ± 22.1, and 47.3 ± 18.1 for 0VD, 2VD and 3VD respectively; p = 0.10), conduction velocity of AF waves (0.59 [0.12], 0.56 [0.09], and 0.53 [0.08] m/s; p = 0.12) and an increase in maximal activation time difference with increasing extent of CAD (16.5 ± 6.2, 18.1 ± 5.7, and 21.2 ± 8.1 ms; p = 0.11).

3.3. Echo parameters

As relative ischemia in the right atrium and ventricle may lead to a decrease in right atrial or ventricular function - which may both influence AF substrate formation – the right atrial function and pressures were assessed on the pre-operative echocardiogram. For the atrial blood supply score, there were no differences in maximal and minimal right atrial area, while there was a significant difference in the right atrial fractional area change (Table 3: 30.6 [13.4], 52.1 [14.4], 31.3 [23.8], 40.9 [15.5], 38.6 [17.1]; p = 0.03). The extent of CAD only was associated with a significant – yet clinically irrelevant – difference in right ventricular systolic pressure (33 [11], 25 [4], 25 [3]; p = 0.02).

3.4. Multivariable regression analysis

To identify factors associated with AF complexity, multivariable regression analysis was performed. As maximal activation time difference most sensitively reflects the AF substrate [17], parameters associated with this factor were assessed in regression analysis. Using univariable linear regression analysis it was shown that age, 3VD (versus 0VD), LDL cholesterol, total cholesterol and right atrial volume showed a significant (P < 0.10) univariable association with the maximal activation time difference (Table 4). Multivariable linear regression analysis revealed that only increasing age and the presence of 3VD (vs 0VD) were independently associated with an increase in the maximal activation time difference.

Table 1
Baseline characteristics of the study population. Shown are mean ± standard deviation or number (percentage). ACE = Angiotensin Converting Enzyme, AT II = Angiotensin 2, CABG = Coronary Artery Bypass Grafting.

Demographics and medical history	
Age (years)	65.1 ± 8.3
Sex (female)	13 (21.0)
Systolic blood pressure (mmHg)	146 ± 21
Diastolic blood pressure (mmHg)	80 ± 11
Hypertension	37 (59.7)
Diabetes Mellitus Type 2	16 (25.8)
Hypercholesterolemia	20 (32.3)
Medication (before surgery)	
Statin	47 (75.8)
Beta blocker	44 (71.0)
ACE inhibitor	17 (27.4)
AT II receptor blocker	14 (22.6)
Calcium channel blocker	12 (19.4)
Diuretics	17 (27.4)
Acetyl salicylic acid	47 (75.8)
P2Y12 receptor antagonist	8 (12.9)
Vitamin K antagonist	1 (1.6)
Surgery	
CABG	47 (75.8)
Valve surgery	9 (14.5)
CABG + Valve surgery	6 (9.7)

4. Discussion

Using direct contact epicardial mapping of electrically induced AF during cardiac surgery in patients without a history of AF, we found no association between the adequacy of the epicardial blood supply and the complexity of induced atrial fibrillation in the right atrium. However, advanced age and the extent of CAD were independently associated with complex fibrillatory conduction and may therefore contribute to a substrate for AF.

Despite previous reports describing a relationship between right atrial infarction and new-onset AF, we did not observe a relationship between blood supply to the right atrium and AF complexity. In dog models, both acute [5] and chronic [6] ligation of a right atrial artery produced a substrate for AF. The absence of such an association in our study may be explained by the gradual development of the impairment in atrial perfusion, potentially allowing both adaptation (e.g. through hibernation [18]) of the myocardium and formation of collaterals from the left atrium, or even from extra-coronary sources, which may have compensated for the reduced blood supply through the RCA [19–21].

Previous studies have shown that AF complexity increases with increasing AF duration, both in a goat model [22] and in patients [23,24]. To our knowledge, this is the first study to investigate the determinants of the complexity of acute, induced AF in patients that are prone to develop AF, yet without clinical history of AF. In our study, low complexity parameters were found as compared to other studies, which may be explained by the absence of AF-induced remodeling. This is consistent with the notion that atrial cardiomyopathy may have started to form before the clinical occurrence of AF [25], while the subsequent occurrence of the arrhythmia causes a further development of the substrate into more complex forms [26].

The direct association between extent of CAD and AF complexity has – to our best knowledge – not been described before. In this study, the extent of CAD was not associated with hemodynamic effects on the right atrium and ventricle – as there were no differences in echo parameters reflecting right atrial and ventricular size, function and pressure – pointing towards a more direct link between CAD and AF vulnerability. We can however not discriminate between direct effects of atherosclerosis on the atrial vascular wall, or modification by subsequent ischemia.

The association between age and AF complexity is in line with the clinical observations that the incidence of AF rises with age [27]. Furthermore, age is associated with the progression of paroxysmal to more persistent forms of AF [28]. In addition, PA-TDI - an echocardiographic parameter of total atrial conduction time - increases with age [29].

Both rising age and the extent of ventricular coronary artery disease reflect a myriad of cumulating risk factors, which are associated with underlying pathophysiological processes such as chronic inflammation and a hypercoagulable state. These processes – through cellular hypertrophy, fibroblast proliferation, tissue fibrosis [30], and decreased nitric oxide production [31] - are also thought to be involved in the pathophysiology of AF [17]. Several animal models have demonstrated the effects of morbidities associated with chronic inflammation and a hypercoagulable state, such as hypertension [32] and obesity [33] on AF substrate development, yet these morbidities also are associated with increased atrial pressure and volumes. The results from this study extend these observations to human atrial substrate formation and

Table 2
Complexity parameters vs atrial blood supply score and 0VD/2VD/3VD. Shown are mean ± SD or median [IQR].

Parameter	Atrial blood supply score					p	Extent of CAD			p
	1 (n = 9)	2 (n = 9)	3 (n = 13)	4 (n = 20)	5 (n = 11)		0VD (n = 13)	2VD (n = 26)	3VD (n = 23)	
Waves per cycle	5.5 ± 2.2	4.7 ± 1.5	5.2 ± 2.2	5.4 ± 2.3	5.1 ± 2.0	0.79	4.2 ± 1.7	5.3 ± 1.9	5.3 ± 2.2	0.28
Breakthrough waves per cycle	1.2 [1.1]	1.3 [0.7]	1.4 [0.9]	1.1 [1.6]	1.1 [0.8]	0.82	0.9 [1.1]	1.2 [1.2]	1.2 [0.6]	0.32
Wave size (number of electrodes)	48.2 ± 31.2	55.9 ± 18.4	47.0 ± 14.7	53.1 ± 24.1	57.5 ± 23.8	0.77	64.3 ± 27.6	52.2 ± 22.1	47.3 ± 18.1	0.10
AF Cycle length (ms)	161 [4]	179 [4]	170 [3]	176 [3]	178 [4]	0.63	177 [8]	176 [3]	178 [3]	0.72
Conduction velocity (m/s)	0.55 [0.12]	0.59 [0.18]	0.52 [0.06]	0.58 [0.13]	0.58 [0.06]	0.08	0.59 [0.12]	0.56 [0.09]	0.53 [0.08]	0.12
Fractionation index	1.2 [1.0]	1.1 [1.5]	1.8 [1.6]	1.5 [1.0]	1.3 [1.0]	0.99	1.6 [0.9]	1.4 [1.1]	1.4 [1.2]	0.80
Maximal activation time difference (ms)	21.3 ± 7.9	16.5 ± 6.2	19.8 ± 5.1	19.5 ± 8.5	15.5 ± 7.0	0.33	16.5 ± 6.2	18.1 ± 5.7	21.2 ± 8.1	0.11

Table 3
Measurements of right atrial and ventricular function vs atrial blood supply score and 0VD/2VD/3VD. Shown are mean ± SD or median [IQR]. BSA = body surface area, RAAmax = maximal right atrial area, RAAmin = minimal right atrial area, RAFAC = right atrial fractional area change, RVSP = right ventricular systolic pressure, ICV = inferior caval vein.

Parameter	Atrial blood supply score					p	Extent of CAD			p
	1 (n = 7)	2 (n = 4)	3 (n = 11)	4 (n = 10)	5 (n = 7)		0VD (n = 7)	2VD (n = 16)	3VD (n = 16)	
RAAmax/BSA (cm^2/m^2)	6.0 [1.3]	6.9 [1.7]	6.8 [4.8]	7.9 [3.8]	8.9 [5.4]	0.32	9.4 ± 2.1	7.1 ± 1.9	7.2 ± 2.6	0.10
RAAmin/BSA (cm^2/m^2)	4.1 [1.0]	3.3 [0.7]	4.0 [3.9]	4.7 [1.5]	4.1 [2.5]	0.10	5.1 ± 1.6	4.5 ± 1.3	4.6 ± 1.8	0.70
RAFAC (%)	30.6 [13.4]	52.1 [14.4]	31.3 [23.8]	40.9 [15.5]	38.6 [17.1]	**0.03**	45.8 ± 11.7	36.5 ± 13.0	34.3 ± 15.7	0.24
ICV diameter (mm)	16 [3]	17 [7]	15 [5]	17 [7]	16 [7]	0.72	16.0 ± 2.4	14.6 ± 4.3	17.9 ± 4.0	0.07
ICV collapse (%)	71 [15]	62 [41]	76 [14]	72 [19]	77 [18]	0.59	71.8 ± 11.8	70.8 ± 17.8	70.9 ± 11.2	0.99
RVSP (mmHg)	25 [5]	25 [4]	25 [5]	25 [11]	25 [5]	0.30	33 [11]	25 [4]	25 [3]	**0.02**

Table 4
Results from linear regression analysis: factors associated with the maximum dissociation.

Univariable			Multivariable	
Factor	B	p	B	p
Age (per year)	0.232 (−0.025;0.439)	**0.03**	0.232 (0.030;0.433)	**0.03**
2VD (vs 0VD)	1.387 (−3.207;5.980)	0.55		
3VD (vs 0VD)	3.339 (−0.165;9.219)	**0.06**	3.602 (0.187;7.018)	**0.04**
LDL (per mmol / L)	−1.730 (−3.556;0.095)	**0.06**		
Total cholesterol (per mmol / L)	−1.474 (−3.099;0.150)	**0.07**		

propagation properties without any signs of increased volumes or filling pressures.

The results of this study underline, with complexity of induced AF as a precursor of clinical AF [22–24,34,35], that substrate formation may have started to form before the occurrence of clinical AF. Therefore, as progression of the extent of CAD can be prevented through adequate life style and risk factor management, this study supports the recent clinical focus on early risk factor management to prevent the initiation or progression of AF [36,37].

4.1. Limitations

Patients in this study were clinically free of AF, yet we cannot be completely certain patients did not have any asymptomatic episodes before surgery, which – through supply/demand mismatch [38,39], AF induced microvascular dysfunction [40] and other forms and AF-induced remodeling – may have contributed to a substrate for AF. Furthermore, we do not know whether even physiological sinus tachycardia may increase demand enough to exceed supply in patients with compromised coronary blood supply.

In the current study, only standard coronary angiograms were available; hence we were limited to assessing the association between atherosclerosis and complexity rather than tissue perfusion and complexity. For this paper, we focused on the right atrium, and the findings cannot necessarily be extrapolated to the left atrium. Furthermore, the scoring system for 'adequacy of coronary perfusion' is clinically unvalidated. Lastly, all patients were under general anesthesia during mapping, and we do not know the influence of anesthesia on atrial complexity. However, as all patients received the same anesthesia, we expect the circumstances for patients within this study to be comparable.

4.2. Conclusion

The adequacy of epicardial right atrial blood supply is not associated with increased complexity of induced atrial fibrillation in the right atrium in patients without a history of clinical AF, while age and the extent of ventricular coronary artery disease are.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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