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Angiographic characterization and clinical implications of specific anatomical features in human coronary arteries

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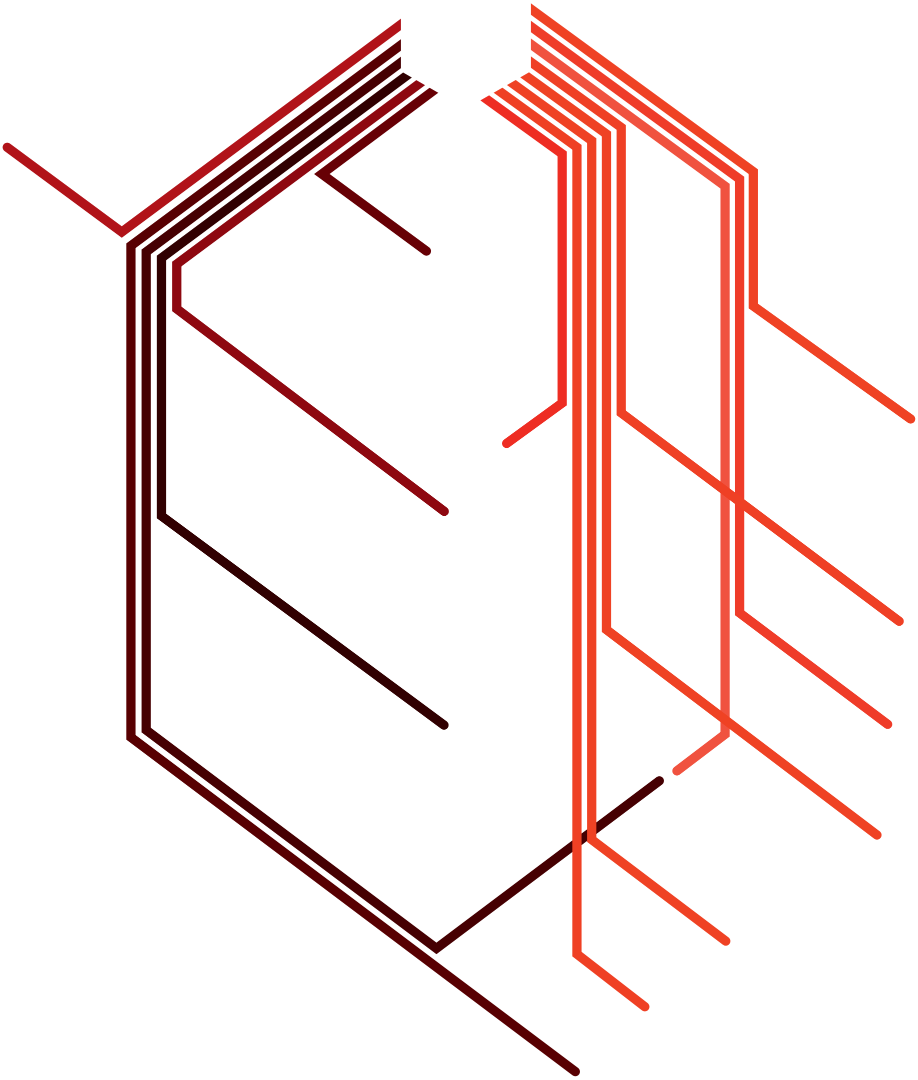

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J.M. Montero Cabezas

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Angiographic characterization and clinical implications of specific anatomical features in human coronary arteries

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus Prof.dr.ir. H. Bijl,
volgens besluit van het College voor Promoties
te verdedigen op 30 mei 2023
klokke 15:00 uur

door

José Manuel Montero Cabezas
geboren te Badajoz
in 1983

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Dr. N. Ajmone Marsan
Dr. M. Bootsma

Para Bernardo, mi amigo.

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General Introduction and Outline of Thesis

Like many other great advancements in the history of medicine, the story of coronary angiography began as result of pure chance. When in 1958, Mason Sones inadvertently injected contrast in a right coronary artery while performing a ventriculography[1], he started and amazing journey which evolved into the development of life-saving invasive techniques for the treatment of coronary artery disease (CAD), impacting the lives of millions of human beings in the next decades.

Shortly after its introduction, coronary angiography was broadly accepted and became soon the gold standard for assessing CAD. In 1977, the ground-breaking introduction of the percutaneous transluminal coronary angioplasty (PTCA) technique by Andreas Gruntzig changed forever the natural history of ischemic heart disease[2.3.4]. This major contribution was the starting point of the spectacular evolution of the field , with the subsequent introduction and refinement of novel techniques and technologies, together with expansion of the clinical indications (acute myocardial infarction, chronic coronary total occlusions, calcific disease, etc). All these innovations resulted in the creation of an entirely new sub-specialty, interventional cardiology, which continues today expanding its horizons towards new modalities of percutaneous treatments for coronary and structural heart disease[5,6,7]. Only four decades later, an annual median of 5131 diagnostic coronary angiographies and 2478 percutaneous coronary interventions per million people were reported in 2016 in Europe[8], which illustrates the major impact of these techniques in current clinical practice.

Diagnostic coronary angiography remains the core of cardiac catheterization. The goal of the procedure is to thoroughly characterize the coronary tree by injecting contrast is a number of pre-specified angiographic projections, aiming to evaluate all coronary segments and relevant pathological findings. With current use of high-resolution fluoroscopy, vessels up to 0.3 mm of diameter can be visualized[9]. Despite of the very well-known limitations of the technique and the development and improvement of non-invasive coronary imaging modalities such as computed tomography coronary angiography, invasive coronary angiography still remains as the cornerstone for risk stratification assessment in CAD[9]. Countless clinical decisions are taken on a daily basis based on angiographic findings. Angiography-derived tools, such as the SYNTAX score, have helped to standardize the evaluation of CAD complexity and have becoming a basic tool in helping clinicians in decision-making processes in coronary artery revascularization[10,11]. Needless to say, in patients undergoing percutaneous coronary artery revascularization, understanding angiographic coronary anatomy is indispensable to define the technical approach and the potential challenges derived from the procedure[9]. In addition, there are several angiographic anatomical or procedural related features that have been linked to patients prognosis, both immediate and long-term. For instance, in patients presenting with ST-segment elevation myocardial infarction, the presence of coronary no-reflow phenomenon complicating primary PCI has been linked to an increased mortality both at 1- and 5-years, independent of infarct size[12,13].

The standardization of coronary angiography interpretation, focused mostly on the ventricular coronary branches, has paid little attention to the coronary arterial branches supplying the atrial myocardium. The lack of consensus in the characterization of the angiographic anatomy of the atrial coronary branches has resulted is a confusing and heterogeneous mix of definitions, illustrating an evident gap of knowledge that remains nowadays[14]. Important clinical implications may be intimately related with the integrity of the atrial coronary circulation, such as the development of atrial arrythmias[15] or atrial structural and functional damage[16]. Likewise, the presence of coronary atrial branches in the vicinity of anatomical targets in atrial fibrillation ablation may impact negatively the effect of the procedure, highlighting the importance of a correct characterization of the coronary atrial branches anatomy in this clinical scenario[17].

Coronary ectasia was firstly described in 1812 by Bougon, and was considered many years as a rare pathological finding[18]. The advent and posterior universalization of coronary angiography made possible the diagnosis of this condition in living individuals[19]. Coronary angiography made possible the anatomic characterization and distribution of the abnormally dilated coronary segments, resulting in the identification of several phenotypes based on morphologic features (focal, diffuse) and extension, which important prognostic value[20,21,22]. In addition, coronary artery ectasia has been linked to particular diseases of clinical scenarios, such as inflammatory diseases, infections, trauma or atherosclerotic coronary artery disease[23]. The presence of coronary ectasia in patients requiring percutaneous coronary artery revascularization, particularly in acute coronary syndromes, is often a technical challenge with an important impact on procedural success and clinical prognosis. Despite of the existing evidence, a standardized, homogeneous, universal nomenclature and angiographic classification of coronary artery ectasia are lacking[24].

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated to cardiovascular complications, which are currently well known[25,26,27,28]. In early phases of the pandemic, little was known about the cardiovascular effects of COVID-19. The first data suggesting a hypercoagulable status in severely ill patients, with both venous and arterial thrombotic events[28], was rapidly followed by a number of reports of patients presenting with acute myocardial infarction due to coronary thrombosis with large thrombus burden[29,30,31]. Elevated cardiac biomarkers due to alternative cause of myocardial injury (myocarditis, Takotsubo cardiomyopathy, etc) were also described, requiring often the exclusion of acute coronary syndrome by coronary angiography[26]. Coronary angiography was therefore key in establishing the diagnosis, characterizing the pathological coronary findings and determining the percutaneous therapeutical strategy when indicated.

Coronary angiography is facing new challenges. As the burden of cardiovascular disease continues to increase globally[32], an increase of the number of diagnostic and therapeutic coronary procedures is expected. The impact of healthcare structures from an economic and a logistic perspective, may compromise both quality and timely access to care. In the past years, non-invasive computed tomographic coronary angiography has emerged as a valid alternative to invasive coronary angiography[33]. With a high negative predictive value, coronary computed tomography angiography allows to safely rule out coronary artery disease, decreasing significantly the number of patients referred for invasive evaluation. Despite of the refinements of the technique, poor image quality studies are not infrequent due to low resolution, motion, artifacts or suboptimal image acquisition to irregular or increased heart rate. These limitations compromise the diagnostic accuracy of CCTA, requiring diagnostic evaluation with invasive coronary angiography in all cases deemed positive[33]. Technical improvements in the next few years are warranted. For the moment, the announced downfall of invasive CAD is not yet effective. The promising development of technology based on artificial intelligence, with applications not only on image interpretation but also in other areas such as cath-lab logistics[34], may set the grounds for the next revolution in the field.

The journey still continues.

AIM AND OUTLINE OF THE THESIS

The objective of this thesis was to evaluate the role of invasive coronary angiography for risk stratification in patients presenting with myocardial infarction in specific clinical scenarios.

In **Part I**, we focused on the clinical impact of coronary flow impairment in coronary atrial branches. **Chapter 2** evaluated the impact of coronary atrial branch occlusion complicating a primary percutaneous coronary intervention in patients presenting with acute myocardial infarction. We defined the rate of this complication and its potential role in the occurrence of atrial arrythmias. In **Chapter 3**, we evaluated the impact of coronary flow limitation in the most developed coronary atrial branch, introducing the term of "atrial coronary dominance", and evaluating its potential role in the development of atrial arrythmias. **Chapter 4** studied the effects of atrial ischemia in both functional and structural remodelling of the left atrium in patients with acute myocardial infarction, by using serial advanced echocardiography techniques. Part II evaluated the prognostic value of coronary angiography in acute myocardial infarction in specific scenarios. **Chapter 5** focused in patients with coronary artery ectasia presenting with acute coronary syndromes, providing a systematic angiographic phenotypical classification and evaluating its impact in the occurrence of major cardiovascular events. Finally, in **Chapter 6** we evaluated the angiographic and clinical profile of patients with COVID-19 referred for invasive coronary angiography from an international registry, analysing as well the prognosis of this specific population.

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I

Coronary atrial circulation and atrial ischemia

2

Procedural-related coronary atrial branch occlusion during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction and atrial arrhythmias at follow-up.

Montero-Cabezas JM, Abou R, Goedemans L, Agüero J, Schalij MJ, Ajmone Marsan N, Fuster V, Ibáñez B, Bax JJ, Delgado V.

Catheter Cardiovasc Interv. 2020;95:686-693.

ABSTRACT

Objectives

To evaluate the frequency of procedural-related atrial branch occlusion in ST-segment elevation myocardial infarction (STEMI) patients and its association with atrial arrhythmias at 1-year follow-up.

Background

Atrial ischemia due to procedural-related coronary atrial branch occlusion in elective percutaneous coronary intervention (PCI) has been associated with atrial arrhythmias. Its role in a STEMI scenario is unknown.

Methods

STEMI patients treated with primary PCI were classified according to the loss or patency of an atrial branch at the end of the procedure. The occurrence of atrial arrhythmias was documented on 24-hour Holter-ECG at 3 and 6 months or on ECG during 1-year follow-up visits.

Results

Of 900 patients, 355 (age 61±12 years,79% male) underwent primary PCI involving the origin of an atrial branch. Procedural-related coronary atrial branch occlusion was observed in 18 (5%) individuals). During 1-year follow-up, 33% of patients with procedural-related atrial branch occlusion presented atrial arrhythmias, as compared with 55% in those with a patent atrial branch (P=0.088). Age, no previous history of myocardial infarction and a reduced flow in the culprit vessel were the only independent correlates of atrial arrhythmias.

Conclusions

The frequency of procedural-related atrial branch occlusion during primary PCI is low (5%) and is not associated with increased frequency of atrial arrhythmias at 1-year follow-up.

INTRODUCTION

Atrial arrhythmias (AA) occur frequently in patients with ST-segment elevation myocardial infarction (STEMI) and have been associated with poor prognosis[1]. Atrial fibrillation (AF), the most common AA, is diagnosed in 6 to 21% of patients with STEMI and is associated with increased risk of stroke and mortality at short- and long-term follow-up[1]. The onset of AA in STEMI results from a complex interaction of various pathophysiological mechanisms. Left ventricular myocardial ischemia leads to hemodynamic and neurohormonal changes that contribute to modify the atrial substrate[2]. Likewise, atrial ischemia has been demonstrated to induce electrophysiological modifications leading to an increased risk of AF[2]. A reduced atrial blood perfusion may result from a compromised integrity of the coronary atrial branches. In patients with STEMI, the presence of lesions in the atrial branches has been related to a higher rate of AF[3]. In addition, an atrial branch occlusion complicating an elective percutaneous coronary intervention (PCI) was detected in 21% of patients with stable coronary artery disease[4] and it has been associated with increased incidence of AA at short-term follow-up[5]. However, in patients with STEMI treated with primary PCI (a context in which procedural thrombotic complications are more frequent), the frequency of procedural-related atrial branch occlusion and its impact on the occurrence of AA at follow-up remains unknown. The present study aimed at describing the rate of procedural-related atrial branch occlusion in patients with STEMI treated with primary PCI. In addition, the association between procedural-related atrial branch loss and the occurrence of AA at 1-year follow-up was evaluated.

MATERIALS AND METHODS

Patients with STEMI with a right (RCA) or left circumflex coronary artery (LCx) as culprit vessels treated with primary PCI at the Leiden University Medical Center between February 2004 and May 2013 were included. Patients were treated according to the institutional protocol for STEMI[6]. Digitalized coronary angiograms were analysed to identify the patients in whom an atrial branch emerged from the treated coronary segment. Patients were admitted for at least 48 hours, remaining under continuous electrocardiographic (ECG) monitoring. Blood levels of creatinekinase and troponin-T were determined at admission and every 6 hours. Echocardiography was performed within 48 hours of admission. At discharge, patients received guideline-based medical therapy according to current recommendations[7]. Exclusion criteria were prior documented AA, prior coronary artery bypass grafting, conservative medical treatment after performing diagnostic coronary angiography or missing data during follow-up.

Study flowchart is shown in Figure 1. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

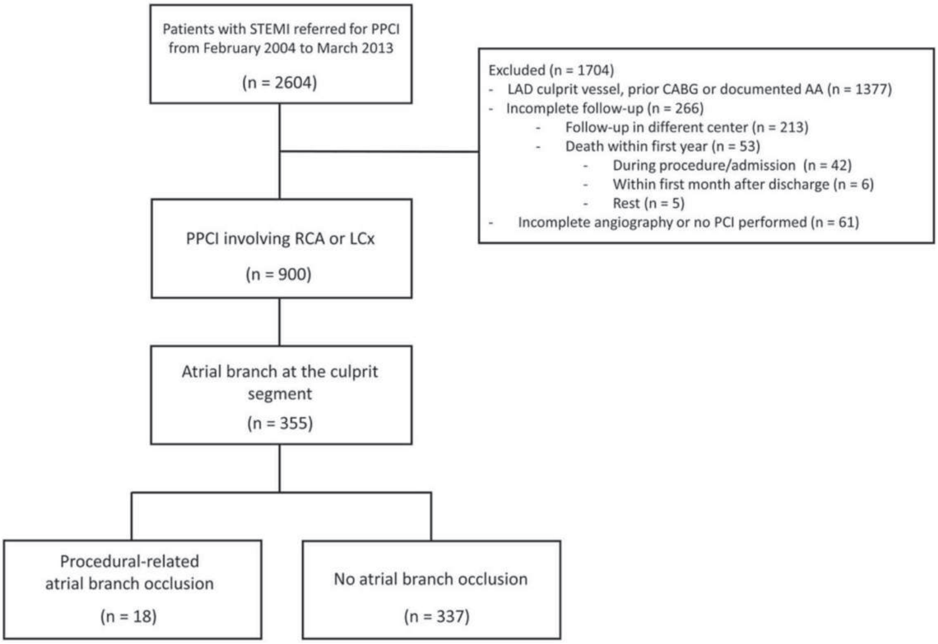

Figure 1. Study flowchart. AA=atrial arrhythmias; CABG=coronary artery bypass grafting; LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; PPCI=primary percutaneous coronary intervention; RCA=right coronary artery.

Coronary angiograms were analysed by an experienced interventional cardiologist blinded to the clinical outcomes. Culprit lesions were categorized according to the American College of Cardiology/American Heart Association lesion classification[8]. Coronary artery flow was evaluated by using the Thrombolysis In Myocardial Infarction (TIMI) frame count method[9]. The presence of intracoronary thrombus was assessed and thrombus burden was graded from 0 to 5[10]. Multi-vessel disease was defined as the presence >1 vessel with luminal narrowing ≥50%.

The angiographic anatomy of the coronary atrial branches was analysed (Figure 2 and Supplementary Figure). The following atrial branches were considered: sinus node artery, defined as the artery supplying the sinoatrial node (irrespective of its origin); atrioventricular node artery, defined as the branch supplying the atrioventricular node area; minor RCA atrial branches, defined as branches emerging from the RCA along the atrioventricular groove supplying the right atrial wall[11]; left anterior atrial branch, defined as the artery arising from the proximal LCx coursing upward along the left atrium; s-shaped atrial branch, an artery arising from the LCx coursing along the posterolateral wall of the left atrium[12] and left circumflex atrial branch, artery arising from the LCx or other atrial branch coursing along the lower margin of the left atrium[11]. The patency of the atrial branches arising from the treated coronary segment was determined both before and after the intervention. Coronary atrial branch occlusion was defined as the presence of TIMI flow 0 or a reduction ≥2 TIMI score grades at the end of the procedure. We considered those atrial branches with TIMI 0 or reduced flow at the end of the intervention, meaning that they were visible at any moment during the procedure.

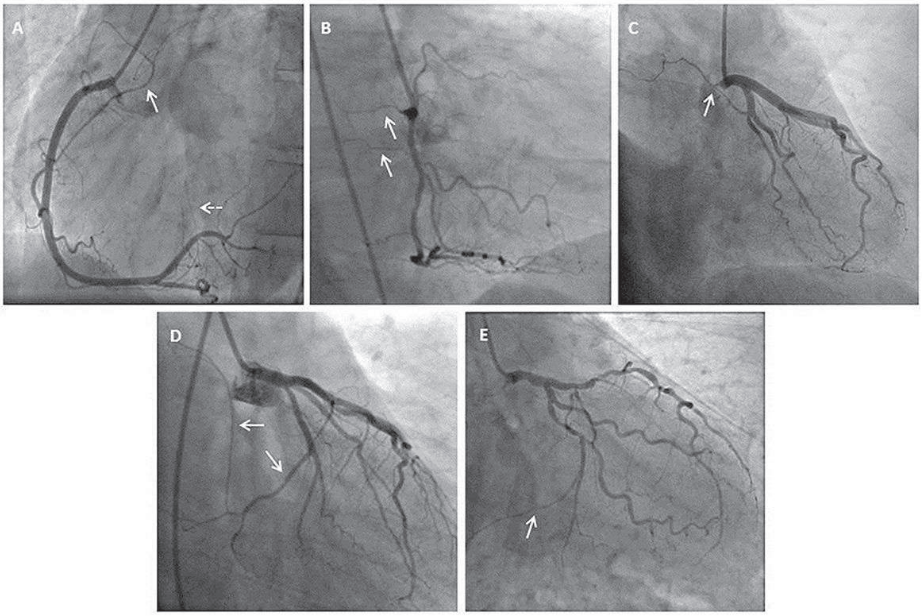

Figure 2. Angiographic examples of coronary atrial branches. Panel A: sinus node branch (arrow) and atrioventricular node branch (dotted arrow) arising from the RCA. Panel B: minor right atrial branches (arrows). Panel C: left anterior atrial branch arising from the proximal LCx (arrow). Panel D: s-shaped atrial branch emerging from the LCx (arrows). Panel E: left circumflex atrial branch (arrow).

When available, follow-up coronary angiograms performed within 1 year after index PCI were evaluated to determine the patency of the atrial branch in patients with procedural-related atrial branch occlusion. A patent atrial branch was defined as a TIMI 3 flow or an increase of ≥2 TIMI score grades with respect to the atrial branch flow at the end of the index procedure.

Clinical and ECG data during hospitalization were obtained. Patients were followed-up during 1 year according to the institutional protocol which includes 24-h Holter ECG monitoring at 3 and 6 months. All documented AA, both on 12-lead ECG and on

24-h Holter ECG, were collected during this period. The following AA were considered: AF, defined as any supraventricular tachyarrhythmia with irregular R-R intervals, absence of defined P waves and irregular atrial activity[13]; premature atrial complexes[14]; atrial tachycardia, defined as runs of ≥3 premature atrial complexes and excessive supraventricular ectopic activity, defined as ≥30 premature atrial complexes per hour or any episode of runs of ≥20 premature atrial complexes[14]. The diagnosis of AF extracted from medical records during follow-up was confirmed by ECG.

The primary endpoint was the frequency of procedural-related coronary atrial branch occlusion during primary PCI. The secondary endpoint was to assess the association between procedural-related atrial branch occlusion and occurrence of AA (comprising AF, atrial tachycardia and excessive supraventricular ectopic activity)during 1 year of follow-up. Furthermore, in patients with procedural-related atrial branch occlusion during primary PCI, the status of the lost atrial branch at follow-up coronary angiography (patency vs. permanent occlusion) was determined.

Continuous variables are presented as mean ± standard deviation or as median and interquartile range as appropriate. Differences between groups were analysed using the unpaired Student t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables are expressed as frequencies and percentages and were analysed using the $\chi 2$ or Fischer exact test. Uni- and multivariable binary logistic regression analyses were performed. Variables with a P-value <0.2 on univariable analysis were included in the multivariate analysis. Statistical analysis was performed with SPSS v23.0 (IBM, Armonk, New York). A 2-tailed P-value <0.05 was considered statistically significant.

RESULTS

Of 900 patients with STEMI involving the RCA or the LCx, 355 (age 61±12 years-old, 79% male) underwent PCI in a coronary segment comprising the origin of an atrial branch (visible anytime during the procedure) and were included in the analysis. Procedural-related atrial branch occlusion was detected in 18/355 patients (5%). Baseline characteristics and angiographic findings of patients with and without procedural-related atrial branch occlusion are summarized in Table 1 and 2 respectively. In both groups, the sinus node artery was the atrial branch emerging from the treated coronary segment most frequently detected (61%). The sinus node artery was as well the most frequently atrial branch lost during PCI (13 out of 18 atrial branch losses,72%) (Figure 3), of which 9 originated from the RCA and 4 emerged from the LCx. There were no differences between groups regarding the complexity of the treated coronary lesion, the extension of the coronary artery disease, the presence of thrombus or the existence of a reduced TIMI flow at the culprit vessel. Only the presence of significant ostial stenosis of the atrial branch was more frequently observed among patients with procedural-related coronary atrial branch occlusion (39% vs. 7%, P<0.001). The procedural characteristics were similar between both groups (Supplementary Table).

Table 1. Baseline clinical characteristics

	Overall (n=355)	Procedural-related atrial branch occlusion (n=18)	No atrial branch occlusion (n=337)	P-value
Age. years	61±12	56±10	61±12	0.083
Male sex, n(%)	282 (79)	17 (94)	265 (79)	0.138
Hypertension, n(%)	128 (36)	7 (35)	121 (36)	0.805
Hypercholesterolemia, n(%)	77 (22)	5 (29)	72 (21)	0.558
Family history of coronary artery disease, n(%)	147 (41)	8 (40)	139 (40)	1.000
Diabetes, n(%)	46 (13)	1 (6)	45 (13)	0.488
Smoking history, n(%)	226 (63)	12 (71)	214 (63)	1.000
Previous myocardial infarction, n(%)	33 (9)	1 (6)	32 (9)	1.000
Killip class≥2, n(%)	21 (6)	1 (6)	20 (6)	1.000
Heart rate at admission (beats/min)	71±19	73±18	71±19	0.733
Systolic pressure at admission (mmHg)	132±26	141±20	132±26	0.172
Diastolic pressure at admission (mmHg)	79±17	90±12	79±16	**0.008**
Severe hypotension (mean pressure <65 mmHg) at admission (%)	17	0	17 (5)	**0.331**
Left ventricle ejection fraction (%)	48±9	47±12	48±9	0.887
Peak creatinekinase (U/L)	1416 (661-2398)	1477 (843-1477)	1417 (657-2396)	0.594
Peak troponin T (μg/L)	3.6 (1.45-6.5)	3.8 (2.6-10)	3.6 (1.4-6.5)	0.559
Clearance creatinine (mL/min)	97±35	108±39	97±35	0.316

Electrocardiographic findings are shown in Table 3. During 1-year follow-up, 193 (54%) patients developed AA. There was no association between intervention-related atrial branch occlusion and AA during follow-up: the incidence of AA was 33% and 55% in patients with and without intervention-related atrial branch occlusion respectively (p=0.088). Similarly, there was no association between intervention-related atrial branch occlusion and AF during follow-up: 6% vs. 55% (p=0.135). In addition, there were no differences in the frequency of atrial tachycardia or number of premature

Table 2. Angiographic findings

	Overall (n=355)	Procedural-related atrial branch occlusion (n=18)	No atrial branch occlusion (n=337)	P-value
Atrial branches at the treated coronary segment, n(%)				
Sinus node branch	216 (61)	12 (67)	204 (61)	
Atrioventricular node branch	15 (4)	0 (0)	15 (4)	
Minor atrial branches	44 (12)	2 (11)	44 (13)	
Left anterior atrial branch	10 (3)	0	10 (3)	0.782
S-shaped branch	6 (2)	1 (6)	5 (1)	
Left circumflex atrial branch	63 (18)	3 (17)	60 (19)	
Others	1 (0.5)	0 (0)	1 (0.5)	
Atrial branch ostial lesion, n(%)	31 (9)	7 (39)	24 (7)	**<0.001**
Multivessel coronary artery disease, n(%)	153 (43)	8 (44)	143 (42)	0.331
Culprit vessel RCA, n(%)	232 (65)	12 (67)	220 (65)	1.000
ACC/AHA type B2/C , n(%)	259 (73)	13 (72)	246 (73)	1.000
Culprit vessel TIMI 0-1 pre-PCI, n(%)	237 (67)	11 (61)	226 (67)	0.613
Culprit vessel TIMI 0-1 post-PCI, n(%)	6 (2)	1 (6)	5 (1)	0.270
Thrombus grade	2±1.3	2±1.4	2±1.3	0.908

PCI = percutaneous coronary intervention ; RCA = right coronary artery

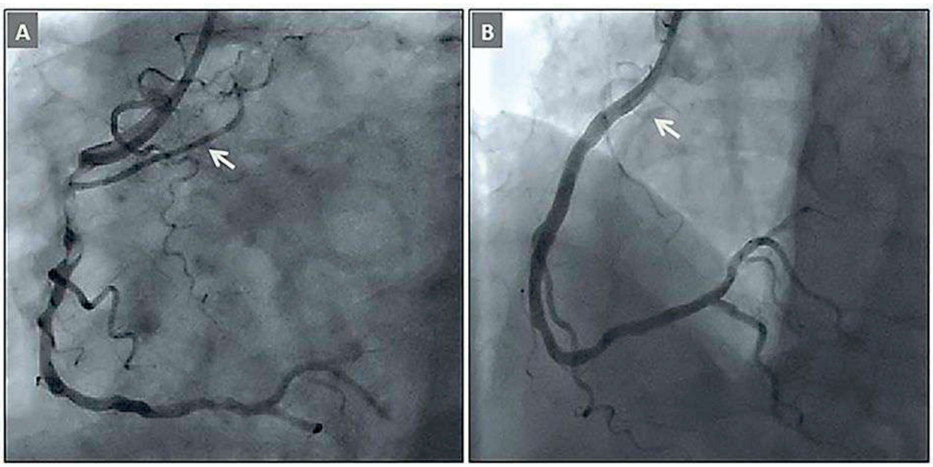

Figure 3. Occlusion of a sinus node branch (white arrows) after primary percutaneous intervention of the proximal RCA.

atrial complexes between groups. Patients with coronary atrial branch loss during primary PCI did not show a significantly higher rate of excessive supraventricular ectopic activity neither at 3 nor at 6 months of follow-up as compared to their counterparts (18% vs. 9%, P=0.057 at 3 months; 20% vs. 9% P=0.159 at 6 months).

Table 3. Electrocardiographic findings

	Overall (n=355)	Procedural-related atrial branch occlusion (n=18)	No atrial branch occlusion (n=337)	P-value
New onset atrial fibrillation within 48 hours, n(%)	22 (6)	1 (6)	21 (6)	1.000
ECG within 48 hours				
PR-interval admission (ms)	171±50	167±22	172±51	0.719
PR-interval discharge (ms)	161±25	155±26	161 ± 25	0.340
24-hour Holter ECG at 3 months, n(%)	330 (93)	16 (89)	314 (94)	
Atrial fibrillation, n(%)	4 (1)	0 (0)	4 (1)	1.000
Atrial tachycardia, n(%)	139 (42)	3 (18)	136 (43)	0.068
Excessive supraventricular ectopic activity, n(%)	30 (9)	3 (18)	27 (9)	0.057
Premature atrial complexes, n(%)	41 (13-130)	18 (6-49)	43 (13-133)	0.141
24-hour Holter ECG at 6 months, n(%)	296 (83)	15 (75)	281 (84)	
Atrial fibrillation, n(%)	3 (1)	0 (0)	3 (1)	1.000
Atrial tachycardia, n(%)	130 (44)	6 (40)	124 (44)	1.000
Excessive supraventricular ectopic activity, n(%)	30 (10)	3 (20)	27 (9)	0.159
Premature atrial complexes, n(%)	35 (13-116)	22 (9-22)	36 (13-116)	0.717
Atrial arrhythmias at 1 year follow-up, n(%)	193 (54)	7 (33)	187 (55)	0.088

ECG = electrocardiogram

To determine the impact of procedural-related coronary atrial branch occlusion and other variables potentially related with the development of AA after STEMI, univariable and multivariable analysis were performed (Table 4). On multivariable analysis, age and a reduced TIMI flow at the culprit vessel before the primary PCI were independently associated with new onset of atrial arrhythmias, whereas the history of a previous myocardial infarction was found to be protective.

Coronary angiography was performed within 1 year of follow-up in 234 (66%) patients, at the discretion of the treating physician. Follow-up coronary angiography was performed in 15/18(83%) patients with atrial branch loss during primary PCI. Patency of the occluded atrial branch with TIMI 3 flow was demonstrated in 14/15(93%) patients. Significant in-stent restenosis, defined as >50% in-stent lumen reduction, was observed in 20 patients (9%) of the overall population. Revascularization of the affected vessel was performed in 18/20 (90%). None of the patients with atrial branch loss during primary PCI presented significant in-stent restenosis. The presence of significant in-stent restenosis was not associated with the occurrence of atrial arrhythmias at 1-year of follow-up (P=0.508).

Table 4. Uni- and multivariate logistic regression analyses of the variables associated with the development of atrial arrhythmias

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age (years)	1.085	1.061-1.110	<0.001	1.098	1.070-1.127	<0.001
Gender (male)	1.261	0.749-2.125	0.383			
Hypertension	0.925	0.599-1.428	0.724			
Diabetes	0.904	0.486-1.681	0.749			
Previous myocardial infarction	0.445	0.212-0.935	0.033	0.395	0.163-0.958	0.040
Heart rate admission (beats/min)	0.998	0.987-1.009	0.690			
Systolic blood pressure admission (mmHg)	1.007	0.998-1.015	0.132	1.008	0.998-1.018	0.104
Diastolic blood pressure admission (mmHg)	0.998	0.985-1.012	0.803			
Killip class≥2	1.120	0.459-2.729	0.804			
TIMI flow<3 pre-PCI	0.844	0.721-0.988	0.035	2.268	1.286-4.002	0.005
Procedural-related atrial branch occlusion	0.401	0.147-1.094	0.074	0.530	0.169-1.664	0.277
Multivessel disease	0.957	0.577-1.588	0.865			
Peak troponin T	0.988	0.957-1.020	0.466			
Peak creatinekinase	1.000	1.000-1.0000	0.355			
Left ventricle ejection fraction (%)	0.988	0.963-1.013	0.348			
Heart rate at discharge	0.991	0.975-1.008	0.302			
Betablockers at discharge	0.989	0.683-1.432	0.955			
ACEi/ARB at discharge	1.017	0.631-1.672	0.914			

ACEi/ARB = Angiotensin-converting-enzyme inhibitors/ angiotensin receptor blocker; PCI = percutaneous coronary intervention.

Additionally, of the 545 patients with STEMI involving the RCA or the LCx who did not show an atrial branch at the treated segment, 62% underwent coronary angiography at follow-up and were analysed to eventually detect an atrial branch arising from the stented segment that was not visible during the index procedure (i.e., due to ostial occlusion). There were no new atrial branches detected, suggesting a low likelihood that occluded atrial branches could have been overlooked during the index procedure.

DISCUSSION

In this study comprising a cohort of STEMI patients, the frequency of procedural-related occlusion of an atrial branch coronary artery during a primary PCI was low (5%). Coronary atrial branch loss during primary PCI was not associated with increased frequency of AA at 1-year follow-up. Importantly, the majority of the atrial branches lost during primary PCI were patent on follow-up coronary angiography.

Previous studies have reported the prevalence of PCI-related coronary atrial branch occlusion in stable coronary artery disease patients(4,15). Alvarez-Garcia et al[4]. described a frequency of 21% in 200 patients who underwent elective PCI in a segment involving the origin of these vessels. In contrast, the frequency of primary PCI-related atrial branch loss in the present study was only 5%. In a study evaluating 80 STEMI patients who underwent primary PCI comprising the origin of a side branch, only 10 (12.5%) presented procedural-related coronary side branch loss[16], significantly less than the 21% rate of coronary atrial branch occlusion reported by Alvarez-García et al. in elective PCI patients[4]. There are several possible explanations for this discrepancy. In elective PCI in stable coronary artery disease, procedural-related side branch occlusion (such as an atrial branch) after main vessel stenting is related to the presence of ostial stenosis of the side branch, small side branch diameter, use of post-dilatation and high-pressure balloon inflation[4]. In this scenario, side branch occlusion probably results from plaque shift and/or embolization. In contrast, in STEMI, ruptured vulnerable atherosclerotic plaques lead to thrombus formation resulting in a partial or complete vessel occlusion due to thrombus displacement most likely[17]. Aggressive use of antiplatelet and anticoagulant therapy in STEMI reduces thrombus burden and might therefore decrease the risk of coronary atrial branch occlusion. Moreover, patients with STEMI present less severe angiographic phenotype of coronary artery disease when compared with patients with stable coronary artery disease which may result in lower risk of side branch occlusion[18]. In addition, a significant proportion of plaque ruptures occur at lesion sites with <50% diameter stenosis[19].

Several mechanisms leading to the development of AA in STEMI patients have been proposed[2,20]. Atrial branch occlusion causes ischemia of the atrial myocardium, left atrial dilation and dysfunction which further modify the arrhythmogenic substrate[21]. In a pig model, the occlusion of the proximal LCx involving the origin of an atrial branch caused left atrial infarction and led to larger left atrial volumes, more impaired reservoir function and more atrial fibrosis accumulation over time as compared to the changes observed after occlusion of the LCx distal to the atrial branch[22]. In addition, the association between spontaneous compromised flow thought the atrial branch and atrial arrhythmias in STEMI has been previously investigated. Hod et al[23]. analysed the coronary anatomy of 7 patients with STEMI who developed AF shortly after the onset of pain. All patients presented with impaired flow at the LCx atrial branch and the atrioventricular node artery. The authors hypothesized that the subsequent left atrial ischemia could have triggered AF. In a study evaluating 454 STEMI patients who underwent coronary angiograms after receiving thrombolysis, patients presenting with a culprit lesion proximal to the origin of an atrial branch presented more frequently AA and atrioventricular block shortly after the infusion of the thrombolytic agent compared to those without[24]. In addition, Kyriakidis et al[25]. described a compromised sinus node artery in 10 of 12 patients with STEMI who develop AA within the first 12 hours of admission. Of note, none of the abovementioned studies evaluated the effects of atrial ischemia at long-term follow-up. All these studies evaluated the impact of presenting with an occluded atrial branch, thus probably resulting in long-lasting atrial ischemia. Conversely, we focused on patients with procedural-related atrial branch occlusion. At one year, almost all atrial branches lost during primary PCI were patent. Due to the design of the study, we cannot determine when these arteries recovered flow. However, the use of antithrombotic and anticoagulation treatment in STEMI patients may lead to spontaneous reperfusion of the atrial branches.

The lack of association with AA at 1-year follow-up in the present study may be explained by several issues. Spontaneous reperfusion of the atrial branch lost during the primary PCI procedure occurs frequently after PCI, as shown on coronary angiography at follow-up (93% of the coronary atrial branches initially occluded were patent). In a study evaluating 185 patients (10% unstable) undergoing PCI, 26% showed side branch occlusion[15]. At follow-up coronary angiography performed 4 to 6 months after the index procedure, 82% of the procedural-related occluded branches were patent. Several explanations of this phenomenon have been proposed, such as negative remodeling of the plaque at the ostium of the side branch or resolution of side branch spasm[15]. As previously mentioned, reperfusion of an atrial branch lost during PCI in STEMI may result from the antiplatelet and antithrombotic treatment. A short ischemia time may therefore limit atrial damage, which may not increase the risk of AA at long-term follow-up.

Another explanation for the variable association between atrial branch occlusion and the occurrence of AA relates to the anatomical variability of atrial circulation[11]. This leads to a variable extent of myocardial ischemia depending on the supplied territory by a given atrial branch. In a study conducted in ovine hearts[26], perfusion patterns of the posterior wall of the left atrium (a key anatomical region for AF maintenance) were analysed. Three different atrial branches supplied this area. By selective dye injections, three anatomical perfusion variants were identified (triple, double and single vessel perfusion). The existence of complex vascular interconnections within the atria may justify this highly heterogeneous perfusion phenotype. Although it is unknown whether these findings can be extrapolated to humans, they suggest that the effect of the occlusion of a sole coronary atrial branch might vary among individuals, since atrial collateral blood supply may limit the ischemia-induced damage and prevent the occurrence of AA.

The absence of previous history of myocardial infarction was associated with a lower risk of AA. This finding might be explained by the highly selected population (patients with AA and prior infarction were excluded), the development of atrial coronary collaterals and the use of post-infarction medical treatment in this subset of patients.

This study has several limitations that should be acknowledged. This is a retrospective single center study, analysing a relatively small number of patients with procedural-related coronary atrial branch occlusion during primary PCI. Therefore, the results may not be generalizable to other clinical scenarios or populations. Moreover, patients with incomplete follow-up were excluded from the analysis. Thus, a potential selection bias cannot be excluded. Subclinical atrial arrhythmias may have been underreported. The presence of electrical right ventricular infarction was not systematically determined. Furthermore, the impact of left atrial dimensions and function on the occurrence of AA after STEMI involving one of the atrial branches was not assessed in this study. Additional studies investigating the interplay between left atrial remodeling and AA in this particular clinical scenario are warranted.

CONCLUSIONS

The frequency of procedural-related coronary atrial branch occlusion complicating a primary PCI is low (5% of primary PCIs involving a segment of atrial branch arise).

Procedural-related coronary atrial branch occlusion was not associated with an increased risk of atrial arrhythmias at 1 year of follow-up. Age, no previous history of myocardial infarction and a reduced flow in the culprit vessel at presentation were independently associated with development of atrial arrhythmias.

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DISCLOSURES

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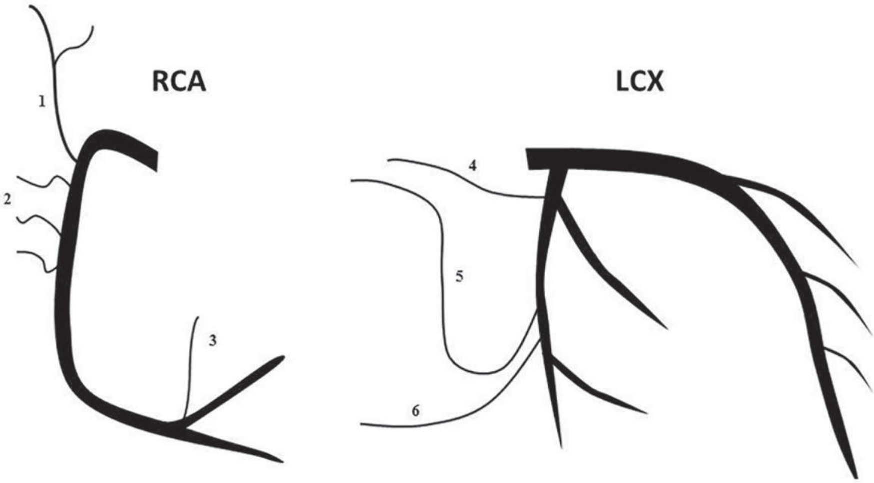

Supplementary Figure S1. Schematic representation of coronary atrial branches. LCx=left circumflex artery; RCA=right coronary artery. 1=sinus node branch; 2=minor right atrial branches; 3=atrioventricular node branch; 4=left anterior atrial branch; 5=s-shaped atrial branch; 6=left circumflex atrial branch.

Supplementary table. Procedural findings

	Overall (n=355)	Procedural-related atrial branch occlusion (n=18)	No atrial branch occlusion (n=337)	P-value
Pre-dilatation, n (%)	282 (79)	14 (78)	268 (80)	0.771
Post-dilatation, n (%)	48 (14)	3 (11)	46 (14)	1.000
Thrombo-suction, n (%)	66 (19)	2 (15)	64 (20)	0.544
Number stents	1.6±0.9	1.7±0.9	1.6±0.9	0.819
Index stent length (mm)	20.9±4.6	22±4.6	20.8±4.6	0.262
Index stent diameter (mm)	3.6±2.7	3.4±0.4	3.6±2.8	0.782
Drug-eluting stents, n (%)	222 (62)	11 (61)	210 (62)	0.590
Stent platform, n (%)				
Stainless steel	23 (7)	1 (6)	22 (6)	
Cobalt-chrome	180 (51)	10 (56)	170 (50)	0.971
Platinum-chrome	110 (31)	6 (33)	104 (31)	
Struts thickness (μm)	86±14	85±5.6	86±14	0.735
Maximum pressure (atm)	13±3	13±2.6	13±2.9	0.910

3

Association between flow impairment in dominant coronary atrial branches and atrial arrhythmias in patients with ST-segment elevation myocardial infarction

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ABSTRACT

Objectives

The impact of atrial ischemia in the occurrence of atrial arrhythmias may vary based on the amount of jeopardized myocardium. We sought to determine the association between coronary flow impairment in dominant coronary atrial branches (CAB) and atrial arrhythmias at 1-year follow-up in ST-segment elevation myocardial infarction (STEMI) patients.

Methods

Patients with STEMI involving the right or circumflex coronary artery were included. Dominant CAB was defined as the most developed CAB. Patients were followed-up during 1 year, including 24-hour Holter ECG at 3 and 6 months. Atrial arrhythmias were defined as atrial fibrillation/flutter, atrial tachycardia (≥3 consecutive supraventricular ectopic beats) and excessive supraventricular ectopic activity (>30 supraventricular beats/hour or runs ≥20 beats).

Results

A dominant CAB was identified in 897 of 900 patients STEMI (age 61±12 years,79% male). TIMI flow<3 at the dominant CAB was present in 69 (8%) patients. Compared to those with dominant CAB preserved flow, patients with dominant CAB flow impairment presented with higher levels of troponin T (3.9 [2.2-8.2] vs. 3.1 [1.3-5.8],P=0.008) and higher rates of atrial tachycardia at 3 months (68% vs. 37%, P=0.007) and more supraventricular ectopic beats both at 3 months (58 [21-235] vs. 33 [12-119], P=0.02) and at 6 months (62 [24-156] vs. 32 [12-115];P=0.04) on 24-hour Holter ECG. Age and an impaired coronary flow at the dominant CAB were independently related to a higher risk of developing atrial arrhythmias at 1-year follow-up.

Conclusion

Dominant CAB flow impairment is infrequent and is associated with the occurrence of atrial arrhythmias, in the form atrial tachycardia and supraventricular ectopic beats, at follow-up

INTRODUCTION

Atrial arrhythmias occur often in patients presenting with ST-segment elevation myocardial infarction (STEMI). The development of atrial fibrillation (the most frequent atrial arrhythmia) in patients with STEMI has been associated with an increase in morbidity and mortality[1]. It is known that atrial arrhythmias in this clinical scenario result from the interaction of complex pathophysiological mechanisms[2], being atrial ischemia one of them[3]. Atrial ischemia influences the electrophysiological remodeling of the atria, promoting the perpetuation of atrial arrhythmias[2, 4]. A compromised coronary flow in a coronary atrial branch (CAB) may occur in STEMI[2, 5], causing ischemia of the atrial myocardium. However, the variability of the anatomy of the CAB[6, 7] and the presumable existence of several atrial perfusion phenotypes[8] may prevent the correct evaluation of the real clinical impact of atrial ischemia in patients with STEMI. The amount of myocardial mass supplied by a given coronary artery is proportional to the anatomical and morphometric characteristics of the artery, such as vessel volume, length and diameter[9]. Hence, larger atrial myocardium territories will be perfused by larger atrial coronary arteries. We hypothesized that flow impairment in the largest CAB may consequently impact the integrity of a significant amount of atrial myocardium, leading to the occurrence of atrial arrhythmias. The present study aimed to evaluate the association between coronary flow impairment in the largest CAB (denominated as the dominant CAB) and atrial arrhythmias at 1-year follow-up in a cohort of patients with STEMI treated with primary percutaneous coronary intervention (PCI).

METHODS

The study population consisted of patients with STEMI treated with primary PCI at the Leiden University Medical Center between February 2004 and May 2013. The study flowchart is depicted in Figure 1. For the purpose of the study, patients with CAB originating from the right (RCA) or the left circumflex coronary artery (LCx) as culprit vessels, were selected and formed the study population. Patients were treated according to the institutional protocol for STEMI, as previously described[10, 11]. The procedure was performed in a standard fashion and revascularization of the culprit lesion was performed according to recommendations at that time. After the procedure, patients were admitted at the cardiac care unit and remained under continuous ECG-monitoring for at least 48 hours. Guideline-based medical treatment was prescribed in all patients at discharge[12].

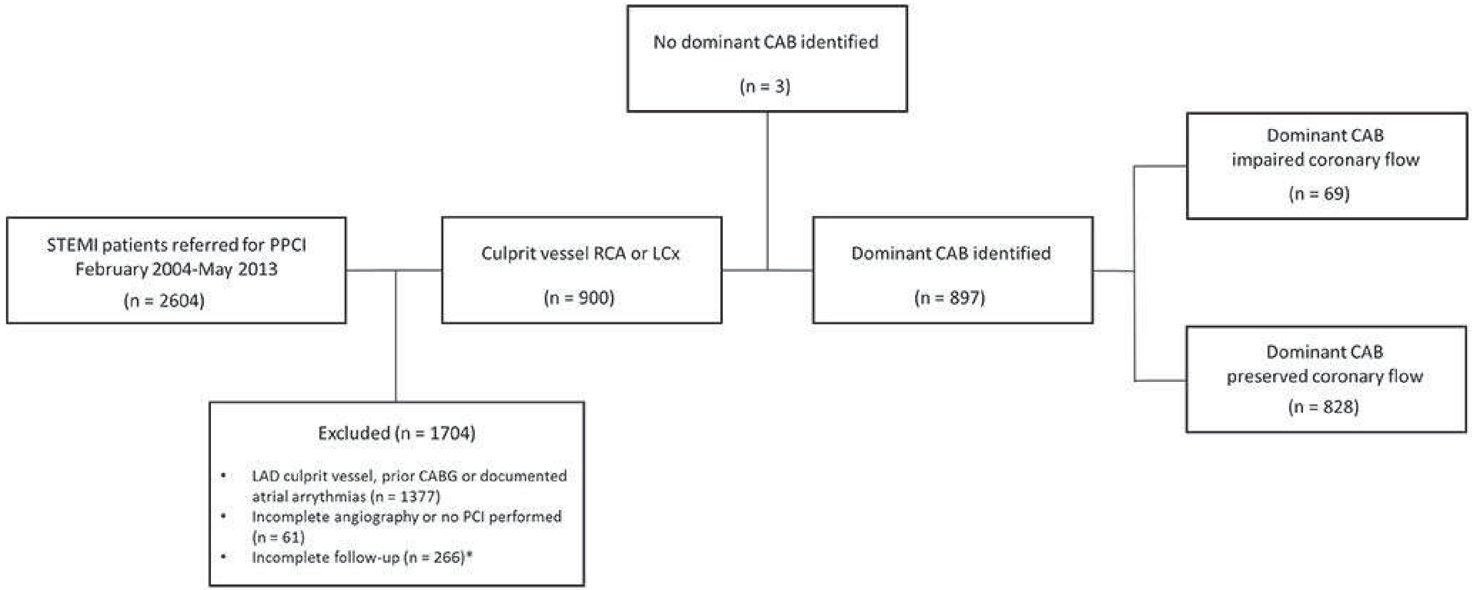

Figure 1. Study flowchart. *Incomplete follow-up comprises: follow-up in different center (n=218); death within first year (n=53) including death during procedure/admission (n=42), death within first month after discharge (n=6)

Exclusion criteria were prior documented atrial arrhythmias, coronary artery bypass grafting, conservative medical treatment after performing diagnostic coronary angiography or missing data during follow-up, as detailed in Figure 1. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Coronary angiograms obtained during the index procedure were retrospectively analyzed by an experienced interventional cardiologist blinded to the clinical outcomes. In general, the left coronary artery was assessed by at least 4 standard angiographic projections (left anterior oblique 30-45° - cranial 25-35°; left anterior oblique 40-50° - caudal 25-40°; right anterior oblique 30-45° - caudal 30-40° and right anterior oblique 30-40° - cranial 35-45°) and the RCA by at least 3 (left anterior oblique 45-60°; left anterior oblique 45-60° - cranial 35-45°and right anterior oblique 30-45°). Image intensification was used at discretion of the operator. Angiographic anatomy of all visible CAB was systematically evaluated following a stepwise method including: 1) type of CAB; 2) coronary artery of origin; 3) coronary segment of origin; 4) CAB development and course. Type of CAB was classified as follows: sinus node artery; atrioventricular node artery; minor RCA atrial branches[6]; left anterior atrial branch; s-shaped atrial branch[13] and LCx atrial branch[6]. The anatomical definitions and the schematic representation of the CAB are provided in the Supplementary material. The dominant CAB was defined as the most developed CAB, irrespectively of the type, based on visual estimation (Figure 2). Coronary atrial dominance was defined as right or left based of the coronary vessel which gives rise to the dominant CAB (either the RCA or LCx). Concordant dominance was considered when the dominant CAB emerged from the dominant coronary artery. Coronary artery flow at the dominant CAB was based on the Thrombolysis In Myocardial Infarction (TIMI) frame count method[14] at diagnostic coronary angiography and at the end of the primary PCI procedure. Dominant CAB flow impairment was defined as a TIMI flow score <3 at any of these two assessments (Figure 3).

In-hospital clinical and ECG data were collected. Patients were followed-up during 1 year according to the institutional protocol[10]. A 24-hour ECG Holter was systematically performed at 3 and 6 months irrespective of symptoms. Documented atrial arrhythmias during follow-up, either on 12-lead ECG or 24-hour ECG Holter, were collected. We considered the following atrial arrhythmias: atrial fibrillation/flutter; premature atrial complexes; atrial tachycardia, defined as ≥3 consecutive premature atrial complexes) and excessive supraventricular ectopic activity, defined as >30 premature atrial complexes per hour or any episode of runs ≥20 premature atrial complexes[15].

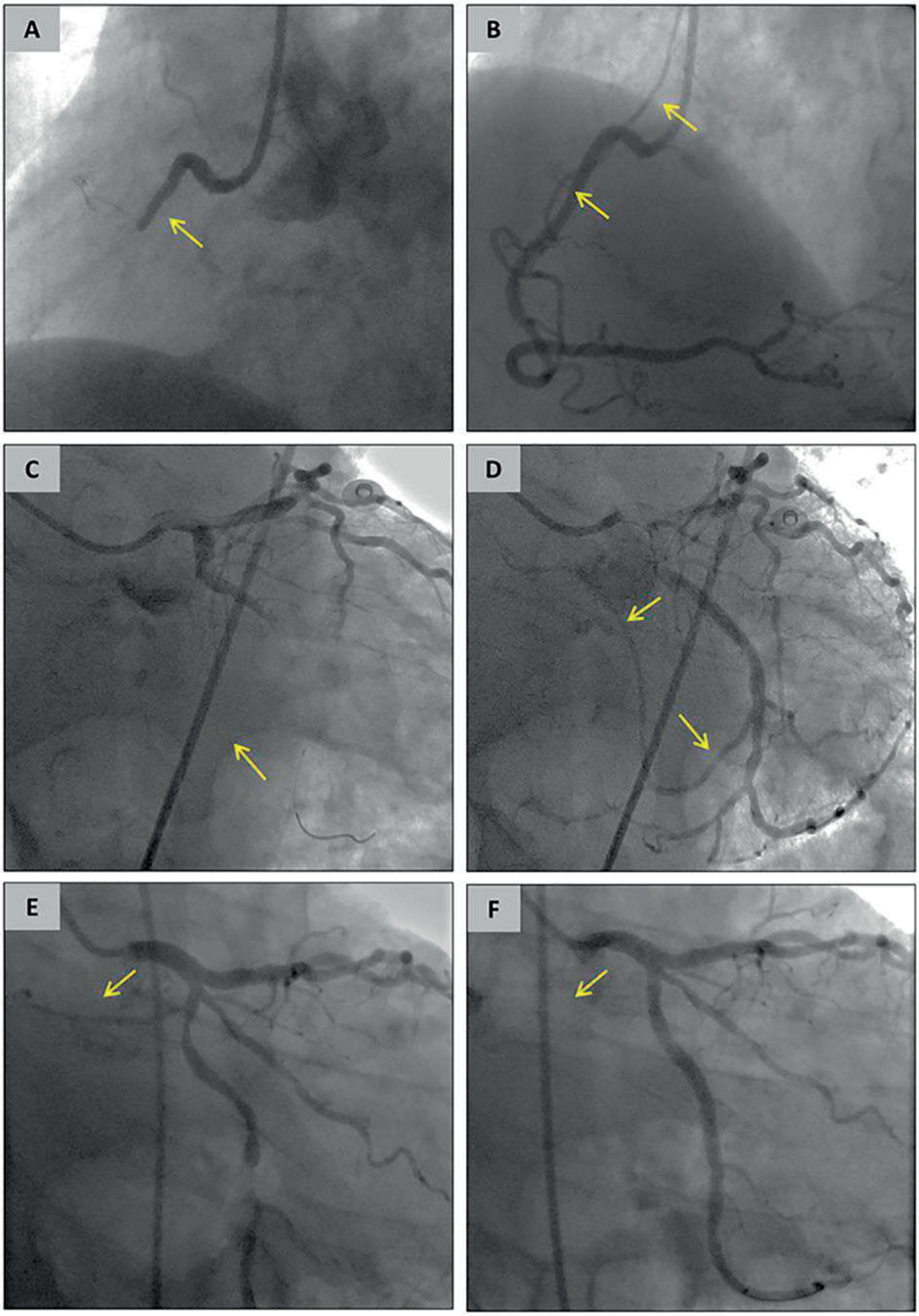

Figure 2. Examples of dominant coronary atrial branches (CAB, arrows) on coronary angiography. A: Dominant CAB corresponding to a sinus node artery arising from the proximal right coronary artery (RCA). B: Dominant CAB corresponding to a sinus node artery arising from the posterolateral branch of the RCA. C: dominant s-shaped sinus node branch arising from the left circumflex artery (LCx). D: left anterior atrial branch arising from the proximal LCx identified as the dominant CAB. E: Dominant CAB corresponding to a left circumflex atrial branch.

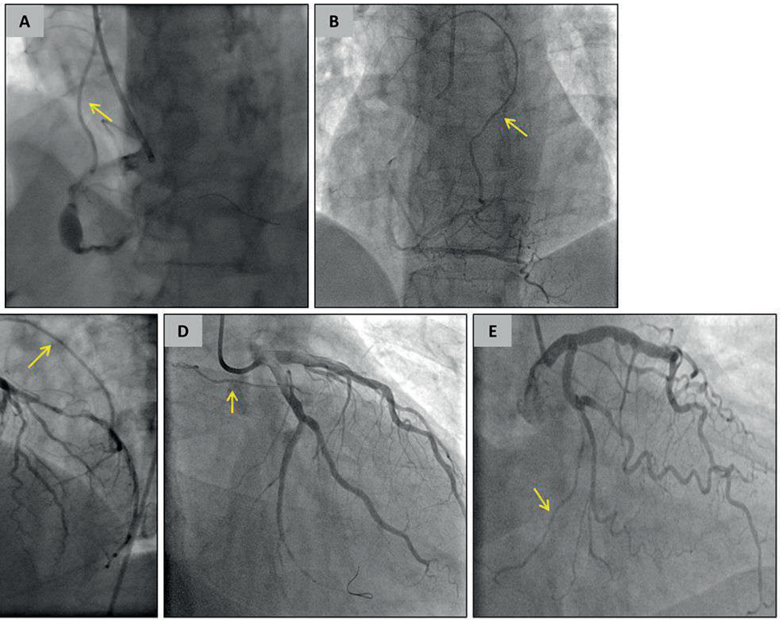

Figure 3. Impaired coronary flow at the dominant coronary atrial branch (CAB). A: occlusion of the right coronary artery (RCA) and subsequently the dominant CAB corresponding to a sinus node artery (arrow). B: reperfusion of both RCA and dominant CAB (arrows) after revascularization of the culprit lesion. C: occlusion of the proximal left circumflex coronary artery (LCx) and a dominant CAB corresponding to a s-shaped CAB (arrow). D: reperfusion of both LCx and dominant CAB (arrows) after LCx stenting. E: Dominant CAB corresponding to a left anterior atrial branch (arrow). The culprit lesion is located at the mid LCx. F: dominant CAB occlusion (arrow) resulting from proximal-mid LCx stenting.

The diagnosis of atrial arrhythmias extracted from medical records during follow-up was confirmed on evaluation of the by ECG.

Continuous variables are presented as either means ± standard deviation or medians with interquartile range, as appropriate. Differences between continuous variables were assessed with the use of the unpaired Student t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were reported as frequencies and percentages and were analyzed using the $\chi 2$ or Fischer exact test. Uni- and multivariable binary logistic regression analyses were performed. Variables with a P-value <0.2 on univariable analysis were included in the multivariate analysis. Statistical analysis was performed with SPSS v23.0 (IBM, Armonk, New York). All tests were two-sided, and a P<0.05 was considered statistically significant.

RESULTS

A total of 900 patients with STEMI (age 61±12 years, male 79%) with a culprit lesion located the RCA or the LCX were analyzed. A dominant CAB was identified in 897 patients (99%), who formed the study population. Impaired coronary flow at the dominant CAB was observed in 69 patients (8%) (TIMI 0 in 39 patients, TIMI 1 in 16 and TIMI 2 in 4). At the end of the procedure, the coronary flow at the dominant CAB was fully restored in 50 patients (72%) whereas 19 of them (28%) showed a persistent impaired coronary flow (TIMI 0 in 11 patients, TIMI 1 in 5 and TIMI 2 in 6). Baseline characteristics are presented in Table 1. Patients with dominant CAB impaired coronary flow presented with higher levels of troponin T when compared to those with preserved flow at the dominant CAB (3.9 [2.2-8.2] vs. 3.1 [1.3-5.8], P=0.008). Angiographic findings are shown in Table 2. The dominant CAB corresponded with the sinus node artery in the majority of patients in both groups. In the group of patients with impaired flow at the dominant CAB, the RCA was more frequently the origin of the dominant CAB (84% vs. 52%, P<0.001). A concordant dominance (dominant CAB originating from the dominant coronary artery) was observed in 54% patients. Interestingly, a concordant dominance was more frequently observed in the dominant CAB with impaired flow (85% vs. 51%, P<0.001). Furthermore, the RCA was the culprit vessel in the majority of patients with impaired flow at the dominant CAB (84% vs. 65%, P=0.001). Procedural complications were infrequent (15 patients, 1.6%). Coronary perforation was observed in 2 patients, one of them requiring pericardial drainage; occlusive dissection of the culprit vessel was observed in 3 patients, one of them treated with emergent coronary bypass grafting. Major vascular complications were present in 6 patients (5 of them required blood transfusions and 1 surgical repair). Four patients required cardiopulmonary resuscitation during the procedure. There were no procedural deaths. The distribution of procedural complications was similar between groups (p=0.10)

Electrocardiographic findings are summarized in Table 3. Patients with dominant CAB with impaired coronary flow presented higher rates of atrial tachycardia at 3 months (58% vs. 37%; P=0.004) and a higher burden of premature atrial complexes both at 3 months (58 [21-235] vs. 33 [12-119], P=0.02) and at 6 months (62 [24-156] vs. 32 [12-115]; P=0.04) on 24-hour Holter ECG when compared to patients with dominant CAB with preserved coronary flow. At 1-year follow-up, there were no differences in the rate of atrial arrhythmias in patients with dominant CAB with impaired flow when compared to their counterparts (64% vs. 52%; P=0.07).

Table 1. Baseline characteristics

	Overall (n=897)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=828)	P-value
Age, years	61±12	62±11	61±12	0.43
Male, n (%)	710 (79)	57 (83)	653 (79)	0.53
Hypertension, n (%)	301 (34)	25 (36)	276 (34)	0.69
Hypercholesterolemia, n (%)	180 (20)	10 (15)	170 (21)	0.27
Family history of CAD, n (%)	343 (39)	27 (40)	316 (39)	0.89
Diabetes, n (%)	93 (10)	8 (12)	85 (10)	0.68
Smoking history, n (%)	545 (62)	42 (63)	503 (62)	0.89
Previous MI, n (%)	89 (10)	6 (9)	83 (10)	0.83
Killip class ≥ 2, n (%)	42 (5)	6 (9)	36 (5)	0.12
Heart rate at admission (beats/min)	71±25	66±19	72±25	0.07
SBP at admission (mmHg)	133±27	127±27	134±27	**0.04**
DBP at admission (mmHg)	81±32	76±19	81±33	0.19
Peak CK (U/L)	1266 (627-2198)	1422 (822-2583)	1243 (619-2154)	0.18
Peak TnT (µg/L)	3.1 (1.3-6)	3.9 (2.2-8.2)	3.1 (1.3-5.8)	**0.008**
Medication at discharge				
Aspirin, n(%)	877 (98)	68 (98)	806 (97)	0.91
P2Y12 inhibitors, n(%)	890 (99)	68 (98)	822 (99)	0.27
Betablockers, n(%)	822 (92)	63 (91)	759 (92)	0.81
ACEI/ARBs, n(%)	851 (95)	67 (97)	784 (95)	0.76
Statins, n(%)	886 (99)	69 (100)	817 (99)	0.81
Medication 6-months				
Betablockers, n(%)	771/843 (91)	54/62 (87)	717/781 (92)	0.23
ACEI/ARBs, n(%)	804/843 (90)	61/62 (98)	743/781 (95)	0.35
Medication 12-months				
Betablockers, n(%)	774/835 (93)	54/61 (86)	715/774 (92)	0.31
ACEI/ARBs, n(%)	750/835 (90)	59/61 (97)	750/774 (97)	1.00
LVEF baseline (%)	49±9	47±11	49±8	0.69
LVEF 6-months (%)	51±7	52±7	51±7	0.50
LVEF 12-months (%)	52±8	51±6	52±8	0.80

ACEi/ARB = Angiotensin-converting-enzyme inhibitors/ angiotensin receptor blocker; CAB = coronary atrial branch; CK = creatininkinase; MI = myocardial infraction; DBP = diastolic blood pressure; LVEF = left ventricular jection fraction; SBP = systolic blood pressure; TnT = troponin T

Table 2. Angiographic and procedural findings

	Overall (n=897)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=828)	P-value
Dominant CAB type, n(%)				
Sinus node branch	840 (94)	62 (90)	778 (94)	0.19
Others	57 (6)	7 (10)	50 (6)	
Dominant CAB vessel of origin, n(%)				
Right coronary artery	485 (54)	58 (84)	427 (52)	**<0.001**
Left circumflex artery	412 (46)	11 (16)	401 (48)	
Right coronary dominancy, n(%)	857 (95)	66 (95)	791 (95)	1.00
Concordant coronary dominancy, n(%)	482 (54)	59 (85)	423 (51)	**<0.001**
Dominant CAB from culprit vessel, n (%)	462 (51)	67 (97)	395 (47)	**<0.001**
Multi-vessel coronary artery disease, n(%)	401 (455)	28 (41)	373 (45)	0.52
Culprit vessel right coronary artery, n(%)	594 (66)	58 (84)	536 (65)	**0.001**
Culprit lesion segment location				
Segment 1	149 (17)	34 (50)	114 (14)	**<0.001**
Segment 2	299 (33)	23 (33)	275 (33)	
Segment 3	118 (13)	1 (1)	117 (14)	
Segment 4	11 (1)	-	11 (1)	
Segment 11	101 (11)	7 (10)	93 (1)	
Segment 12	32 (4)	-	32 (4)	
Segment 12a	61 (7)	-	61 (7)	
Segment 13	94 (10)	4 (6)	90 (11)	
Segment 14	15 (2)	-	15 (2)	
Segment 16	20 (2)	-	20 (2)	
Culprit lesion ACC/AHA type B2/C, n(%)	620 (69)	60 (87)	560 (68)	**0.001**
Visible thrombus, n(%)	762 (85)	65 (94)	697 (84)	**0.02**
Thrombus grade	2±1.3	2.7±1.2	1.9±1.3	**<0.001**
Culprit vessel TIMI flow pre-PCI	1.1±1.3	0.6±1.2	1.1±1.3	0.85
Culprit vessel TIMI flow post-PCI	2.9±0.3	2.7±0.6	2.9±0.3	0.24
Culprit vessel TIMI 0-1 post-PCI, n(%)	13 (1)	1 (1)	12 (1)	1.00
Door-to-balloon time, minutes	49 [35-74]	50 [31-79]	48 [35-73.5]	0.21

CAB = coronary atrial branch; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

In order to define the impact of an impaired coronary flow at the dominant CAB on the occurrence of atrial arrhythmias at follow-up, uni- and multivariate analyses were performed. The results are displayed in Table 4. On multivariate analysis, age and an impaired coronary flow at the dominant CAB were independently related to a higher risk of developing atrial arrhythmias at 1-year follow-up, whereas history of myocardial infarction and heart rate at discharge showed a protective effect.

Table 3. Electrocardiographic findings

	Overall (n=897)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=828)	P-value
New onset atrial fibrillation within 48 hours, n (%)	51 (6)	4 (6)	47 (6)	1.00
ECG within 48 hours				
PR interval admission (ms)	172±44	167±30	173±44	0.27
PR interval discharge (ms)	162±26	161±25	162±26	0.65
24-hour Holter-ECG at 3 months, n (%)	827 (92)	60 (88)	767 (93)	0.09
Atrial fibrillation, n (%)	13 (2)	1 (2)	12 (2)	1.00
Atrial tachycardia, n (%)	320 (39)	35 (58)	285 (37)	**0.004**
Excessive supraventricular ectopic activity, n (%)	71 (9)	9 (15)	62 (7)	0.08
Premature atrial complexes, n	34 (13-122)	58 (21-235)	33 (12-119)	**0.03**
24-hour Holter-ECG at 6 months, n (%)	757 (85)	53 (77)	704 (85)	0.12
Atrial fibrillation, n (%)	10 (1)	1 (2)	9 (1)	0.55
Atrial tachycardia, n (%)	325 (43)	29 (55)	296 (36)	0.08
Excessive supraventricular ectopic activity, n (%)	67 (9)	7 (13)	60 (7)	0.31
Premature atrial complexes, n	33 (13-116)	59 (24-184)	32 (12-115)	**0.04**
Atrial arrhythmias at 1-year follow-up, n (%)	478 (53)	44 (64)	433 (52)	0.07

ECG = electrocardiogram

DISCUSSION

The main conclusions of the present study are: 1) the frequency of dominant CAB with impaired flow is relatively low among patients with STEMI treated with primary PCI (8%); 2) patients with dominant CAB and impaired flow present more often with atrial tachycardia at 3 months follow-up and atrial premature complexes both at 3 and 6 months follow-up as compared to patients with dominant CAB and preserved flow; 3) patients with dominant CAB and impaired flow showed a trend toward higher rates of atrial arrhythmias (in general) at 1-year follow-up; 4) age and impaired flow of the dominant CAB were independently associated with atrial arrhythmias at 1-year follow-up.

The relation between the size of a coronary artery and the volume of the perfused myocardium is well-known. As other branching systems in nature, the coronary tree follows a fractal pattern[16]. Hence, morphological (diameter, length, volume) and functional (flow) parameters of the coronary artery tree have shown a scaling relationship with the perfused myocardial mass[9]. Clinical applications of this experimentally-validated concept have been proposed[9, 17]. Kassab et al[17] developed a mathematical

Table 4. Uni- and multivariate logistic regression analyses of the variables associated with the development of atrial arrhythmias

Variable	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	1.072	1.058-1.087	<0.001	1.074	1.060-1.089	**<0.001**
Gender (male)	1.126	0.814-.1.556	0.47	-----	-----	-----
Hypertension	1.137	0.861-1.503	0.36	-----	-----	-----
Diabetes	0.973	0.633-1.496	0.90	-----	-----	-----
Previous myocardial infarction	0.592	0.380-0.923	0.02	0.476	0.293-0.775	**0.003**
Heart rate admission (beats/min)	1.000	0.995-1.006	0.96	-----	-----	-----
SBP admission (mmHg)	1.002	0.997-1.007	0.48	-----	-----	-----
DBP admission (mmHg)	0.995	0.988-1.003	0.20	0.998	0.993-1.003	0.47
Killip class≥2	2.017	1.034-3.933	0.04	1.371	0.618-3.051	0.43
Impaired flow at dominant CAB	1.598	0.960-2.659	0.07	1.774	1.012-3.111	**0.04**
Multi-vessel disease	0.870	0.668-1.133	0.30	-----	-----	-----
Peak troponin-T	1.000	0.975-1.025	0.99	-----	-----	-----
Peak creatine kinase	1.000	1.000-1.000	0.33	-----	-----	-----
LVEF (%)	0.990	0.974-1.006	0.21	-----	-----	-----
Heart rate at discharge	0.991	0.980-1.002	0.10	0.987	0.976-0.999	**0.03**
Betablockers at discharge	1.120	0.689-1.819	0.64	-----	-----	-----
ACEi/ARB at discharge	1.270	0.683-2.361	0.45	-----	-----	-----
Betablockers at 6-months	1.193	0.736-1.934	0.47	-----	-----	-----
Betablockers at 12-months	1.188	0.718-1.964	0.50	-----	-----	-----
Dominant CAB vessel of origin	1.027	0.789-1.336	0.84	-----	-----	-----

ACEi/ARB = Angiotensin-converting-enzyme inhibitors/ angiotensin receptor blocker; CAB = coronary atrial branch; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure

model to estimate the myocardial mass supplied by side branches in coronary bifurcations, derived from the cross sectional angiographic area of the side branch. The extension of injured myocardium due to ischemia may determine the occurrence of rhythm disturbances. Hence, larger ventricular infarcted areas have been related to a higher risk of developing ventricular arrhythmias[18]. The concept of dominant CAB arises from the translation of these concepts to the atria. The impact of atrial injury may be reflected by higher levels of troponin T observed in patients with dominant CAB and impaired flow as compared to patients with preserved flow in the dominant CAB.

The frequency of flow impairment at the dominant CAB in the present study is relatively low (8%) and was related with complex coronary artery lesions and high thrombus burden. Treatment of the culprit coronary artery lesion resulted in reperfusion of the majority of CAB, whereas 28% of the dominant CAB showed persistent impaired flow at the end of the procedure. No-reflow phenomenon and thrombus displacement may explain the absence of reperfusion in these vessels.

The association of atrial ischemia/infarction and the occurrence of atrial arrhythmias has been previously documented both in animal and human studies[3, 4]. Atrial fibrillation (the most common atrial arrhythmia) frequently complicates STEMI and is linked to a higher morbidity and mortality[19]. Atrial fibrillation may result from the interaction of several factors, including increased atrial pressures or atrial ischemia[2]. Direct ischemia resulting in atrial infarction in this context is not rare, since autopsy studies have shown atrial infarction in up to 17% of patients[20]. The ischemic atrial myocardium presents a pattern of patchy necrotic areas and viable myocytes, immature connective tissue and interstitial fibrosis. The occurrence of atrial fibrillation results from spontaneous focal discharges leading to reentry mostly at the border zone between the ischemic and the normal atrial myocardium[21].

We found a significant higher rate of atrial tachycardia and burden of atrial premature complexes in patients with dominant CAB and impaired flow. However, this did not translate in a significantly higher rate of atrial arrhythmias at 1-year follow-up. Lack of this association might be explained by the intrinsic configuration of the atrial coronary perfusion.

Atrial coronary perfusion territories are not well defined in the human heart. In a study conducted in isolated ovine hearts[8], dye injections in the CABs (defined as right sinus node artery, left sinus node artery and atrial branches of the circumflex) were performed to delineate the perfusion area of each branch at the left atrium. Surprisingly, three well-differentiated equally-distributed perfusion patterns were observed, indicating that the contribution of each CAB to the atrial perfusion may vary significantly among individuals. The impact of atrial ischemia/infarction on left atrial remodeling in a pig model was evaluated by Agüero et al[22]. Atrial ischemia was induced by occluding the LCx before the origin of the left circumflex CAB. Left atrial ischemia was associated with significant atrial remodeling and impaired atrial function. This suggest that the effects of atrial ischemia may be determined by the location of the CAB. In our study, we did not observe differences regarding rates of atrial arrhythmias based on the vessel of origin of the dominant CAB with impaired coronary flow (RCA vs. LCx). Whether this depends on a heterogeneous atrial perfusion pattern in humans is unknown.

Additionally, atrial arrhythmogenicity after STEMI may not depend solely on the left atrium. Autopsy studies in patients with myocardial infarction revealed the presence of right atrium infarction in 81-98% of patients[23]. Right atrial perfusion is mostly provided by the sinus node artery, which is frequently the dominant CAB (94% in our patient cohort). When arising from the LCx, dominant CABs reaching the sinus node area perfuse also large areas of the left atrium. Interestingly, in our population, the majority of the dominant CAB with impaired coronary flow emerged from the RCA (84%). In a study conducted in 24 human heart specimens, a sinus node artery arising from the RCA was found in 58%, which macroscopically did not reach the left atrium[7]. Our observations may suggest that, in a significant proportion of patients, atrial arrhythmias mainly resulted from right atrial ischemia secondary to coronary flow impairment dominant CABs originating from the RCA.

Successful reperfusion and restoration of coronary flow at the dominant CAB may not prevent the occurrence of atrial arrhythmias. Patients with final TIMI 0-1 flow at the dominant CAB did not show higher rates of events at follow-up. This suggests that transient reduction in coronary flow may be sufficient to induce structural atrial injury with subsequent atrial arrhythmias. Previous history of myocardial infraction showed a protective effect against the development of atrial arrhythmias. This observation might be explained by the use of post-infarction medical therapy (especially betablockers) in this population and the potential development of atrial coronary collaterals.

Several limitations should be acknowledged. This is a single-center, observational, retrospective study. A total of 266 patients were excluded from the analysis due to incomplete follow-up (transfer to a different center or death within the first year), which may introduce potential selection bias and influence the observed results The occurrence of subclinical atrial arrhythmias cannot be excluded. Only a residual number of patients (1%) presented pre-existent thyroid disorders. However, thyroid hormones determination was not performed systematically and, therefore, the potential influence of undetected thyroid dysfunction cannot be excluded. The present study does not provide insight into the interaction between age and ischemia on the left atrial remodeling after STEMI, which is an important factor in the pathophysiology of atrial arrhythmias. It is well known that aging is associated with impaired left atrial compliance[24].

CONCLUSIONS

In patients with STEMI treated with primary PCI , dominant CAB with coronary flow impairment is infrequent and is associated with higher rates of atrial arrhythmias, in the form of atrial tachycardia and supraventricular ectopic beats, when compared to those with preserved coronary flow at the dominant CAB. Age and the presence of an impaired coronary flow at the dominant CAB were independently associated with the occurrence of atrial arrhythmias at 1-year follow-up.

DISCLOSURES

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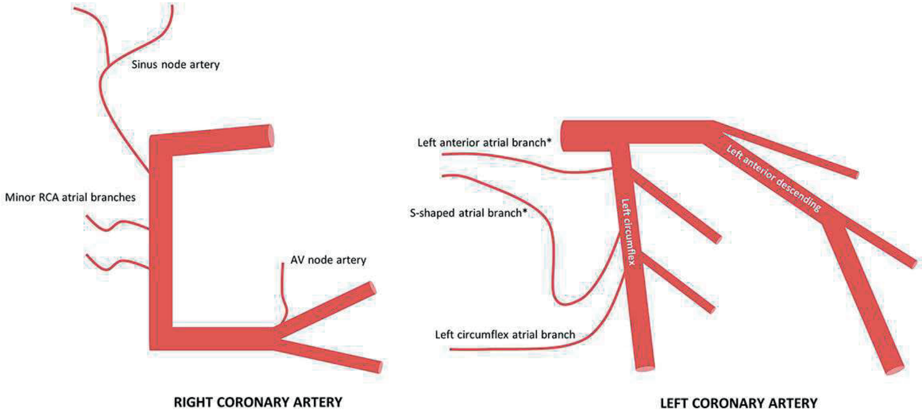

Figure 1 Supplementary material. Schematic representation of coronary atrial branches. *Sinus node artery when appropriate. AV=atrioventricular; RCA=right coronary artery.

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Effects of atrial ischemia on left atrial remodeling in patients with ST-segment elevation myocardial infarction.

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ABSTRACT

Aims Adverse left atrial (LA) remodeling after ST-segment elevation myocardial infarction (STEMI) has been associated with poor prognosis. Flow impairment in the dominant coronary atrial branch (CAB) may affect large areas of LA myocardium, potentially leading to adverse LA remodeling during follow-up. We assessed echocardiographic LA remodeling in STEMI patients with impaired coronary flow in the dominant CAB,

Methods. Of 897 STEMI patients, 69 patients (62±11 years,83% males) with impaired coronary flow in the dominant CAB (defined as TIMI flow<3) were retrospectively compared to an age- and sex-matched control group of 138 patients with normal dominant CAB coronary flow.

Results. Patients with dominant CAB-impaired flow had higher peak troponin T (3.9 μg/L[2.2-8.2] vs.3.2 μg/L[1.5-5.6];p=0.009). No differences in left ventricular ejection fraction or mitral regurgitation were observed between groups neither at baseline nor at follow-up. LA remodeling assessment included maximum LA volume, speckle tracking echocardiography-derived LA strain and total atrial conduction time assessed by tissue Doppler imaging (PA-TDI) at baseline, 6 and 12 months. Patients with dominant CAB-impaired flow presented larger LA maximal volumes (26.9±10.9 vs.18.1±7.1 ml/m2,p<0.001) and longer PA-TDI (150±23 vs.124±22 msec., p<0.001) at 6-months, remaining unchanged at 12-months.However, all LA strain parameters were significantly lower from baseline (reservoir 20.3±10.1% vs.27.1±14.5%,p<0.001;conduit 9.1±5.6% vs.12.8±8%,p<0.001; booster 9.1±5.6% vs.12.8±8%, p<0.001),being these differences sustained at 6- and 12-months follow-up.

Conclusion. Atrial ischemia resulting from an impaired coronary flow in the dominant CAB in patients with STEMI is associated with LA adverse anatomical and functional remodeling. Reduced LA strain preceded LA anatomical remodeling in early phases after STEMI.

INTRODUCTION

The left atrium (LA) may exhibit anatomical and functional remodeling after ST-segment elevation myocardial infarction (STEMI) and is a strong predictor of mortality and cardiovascular morbidity[1,2]. LA remodeling after STEMI results from the interaction of different pathophysiological mechanisms, such as increased left ventricular (LV) filling pressures, ischemic mitral regurgitation (MR) and atrial ischemia. Particularly, atrial ischemia resulting from coronary flow interruption in a coronary atrial branch (CAB) has been linked to anatomical and functional LA remodeling, with extensive fibrosis present from early phases after acute myocardial infarction[3]. Atrial infarction is not infrequent in STEMI patients, and has been detected in up to 17% of cases in postmortem studies[4]. However, the contribution of atrial ischemia/infarction to the LA remodeling after STEMI is still poorly understood. In addition, the anatomical variability of CABs in humans[5,6] may hamper the evaluation of the impact of atrial ischemia on LA remodeling, since this may vary based on the amount of jeopardized LA myocardium. Coronary flow impairment in the dominant CAB, defined as the largest CAB on coronary angiography, may affect large areas of LA myocardium, with important clinical consequences.

The present study analyzes the association of coronary flow impairment in the dominant CAB in patients presenting with STEMI and echocardiographic parameters of LA remodeling, both anatomical (LA volume and total atrial conduction time assessed by tissue Doppler imaging [PA-TDI], a surrogate marker of atrial fibrosis[7]) and functional (based on LA myocardial strain measurements), at baseline (<48h of admission), 6- and 12-months follow-up.

METHODS

Study population

Patients with STEMI referred to the Leiden University Medical Center for primary percutaneous coronary intervention (PCI) between February 2004 and May 2013 were considered for inclusion. Only patients presenting with culprit lesions located in the right coronary artery (RCA) or the left circumflex coronary artery (LCx) were included in the analysis since the CABs originate either from these vessels. During index hospitalization, patients underwent echocardiography within 48 hours of admission. At discharge, all patients were systematically followed-up for at least 1 year according to the institutional clinical care-track for patients with STEMI[8,9], which includes transthoracic echocardiograms at 6- and 12-months. Baseline clinical characteristics were obtained from the departmental electronic patient information system (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands). Exclusion criteria have been previously described[10], and included patients with incomplete coronary angiography data for analysis of CAB flow, prior coronary artery bypass grafting, conservative medical treatment during index coronary angiography or patients lost to follow-up. The control group consisted of 138 age- and sex-matched subjects with STEMI involving either the RCA or LCx with normal coronary flow at the dominant CAB in coronary angiograms performed pre-, during- and post-primary PCI. The control group was extracted from the same institutional STEMI database. This retrospective analysis of prospectively clinically acquired data was approved by the internal review board that waived the need for written informed consent.

Angiographic evaluation

Coronary angiograms were retrospectively assessed by an experienced interventional cardiologist. The angiographic anatomical definitions of the different CABs have been described[9]. As previously reported, the angiographic anatomy of all visible CAB branches was systematically evaluated and characterized based on the type of CAB, coronary artery and segment of origin and CAB course (Figure 1). The dominant CAB was defined as the largest CAB[10]. Coronary flow at the dominant CAB was evaluated both after the initial diagnostic angiography and at the end of the procedure and was graded based by the Thrombolysis In Myocardial Infarction (TIMI) frame count method. We defined coronary flow impairment in the dominant CAB as a TIMI flow score < 3 at any time of the index PCI[10].

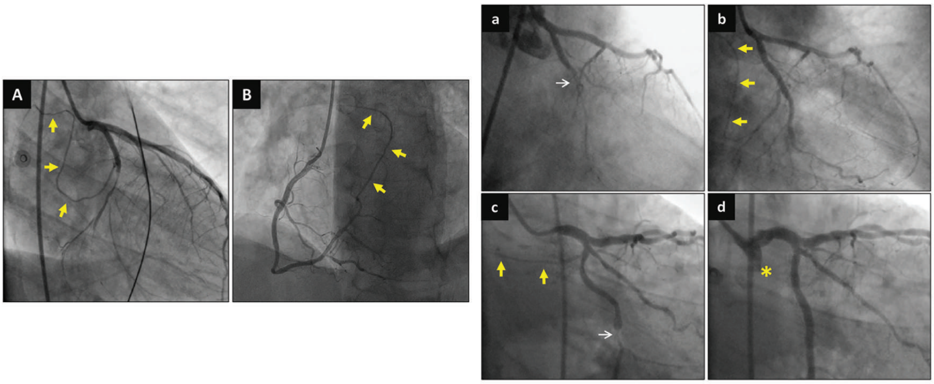

Figure 1. Panels A and B. Examples of dominant coronary atrial branches (CAB, arrows) corresponding to a sinus node artery arising from LCx (A) and to a sinus node artery arising from the posterolateral branch of the RCA (B). **Panels a-d**: impaired coronary flow at the dominant CAB. Occlusion of the mid-LCx (a, white arrow) and result after treatment of the culprit lesion showing reperfusion of a previously occluded dominant CAB (b, yellow arrows). Dominant CAB arising from the proximal LCx (c, yellow arrows) with culprit lesion located at mid-LCx (c, white arrow), and subsequent occlusion of the dominant CAB (d, asterisk) after the implantation of stents up to the proximal segment of the LCx.

Echocardiography evaluation

Transthoracic echocardiography was performed with patients in the left lateral decubitus position using commercially available systems. Parasternal, apical, and subcostal views were acquired using 3.5 MHz or M5S transducers. Standard two-dimensional, M-mode and Doppler data were digitally stored for offline analysis (EchoPAC 201.0.0, GE Vingmed Ultrasound, General Electric, Horten, Norway). Off-line analysis of echocardiographic images was blinded to angiographic findings. Left ventricular ejection fraction (LVEF) was calculated by the Simpson's biplane method[11]. Mitral regurgitation severity was evaluated according to current recommendations[12] and graded as mild, moderate and severe. Moderate and severe MR were considered as significant MR. LA maximal volume was measured at end-systole before mitral valve opening in the apical views according to the Simpson's method and indexed to body surface area[11]. LV diastolic function was assessed by measuring the early diastolic peak velocity (E) and late diastolic peak velocity (A) on pulsed wave Doppler of mitral inflow with subsequent calculation of the E/A ratio. Septal and lateral peak early diastolic mitral annular velocities were measured in the apical 4-chamber view on TDI[13]. Left ventricular filling pressures were assessed by the ratio of the early diastolic transmitral peak flow velocity to the early diastolic mitral annular tissue peak velocity.

Strain imaging

LA reservoir, conduit and booster pump functions were evaluated by using two-dimensional speckle tracking echocardiography on the apical 4-chamber view, with special attention to avoid images with LA foreshortening (Figure 2). The LA endocardial border was manually traced and the region of interest was adjusted to include the LA wall. Pulmonary veins and LA appendage were excluded. The electrocardiogram (ECG) was adjusted to the onset of the QRS complex (R-R gated). LA reservoir strain was defined as the peak positive longitudinal strain during ventricular systole. LA conduit and booster pump functions were obtained at early and late diastole respectively[14]. The intra- and interobserver variability for LA strain analysis in our institution has been previously reported[15].

Atrial tissue Doppler imaging

Color-coded TDI was used to calculate the total atrial conduction time. An atrial tissue Doppler tracing was obtained by placing the sample volume on the lateral wall of the LA above the mitral annulus in a 4-chamber apical view (Figure 2). The PA-TDI duration, an echocardiographic-derived parameter of total atrial electrical conduction time was defined as the time delay from the onset of the P wave on surface ECG to the peak of the A' wave on the TDI tracing[16].

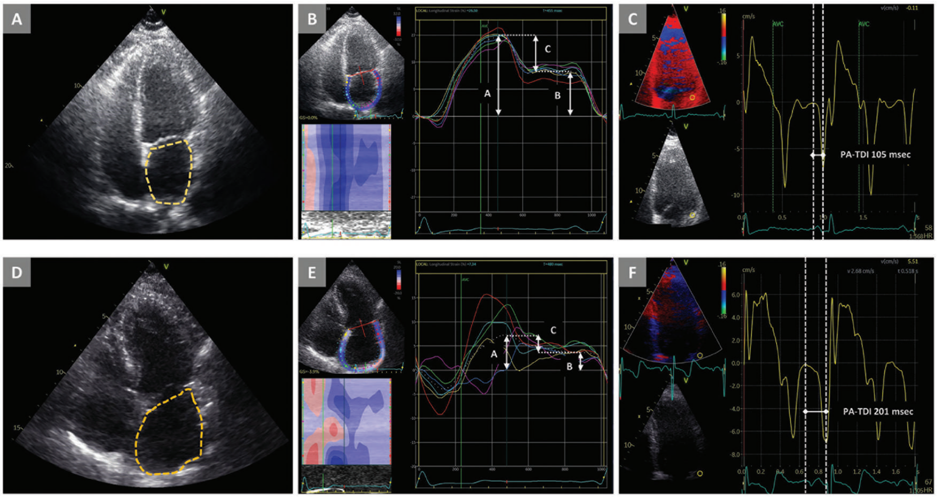

Figure 2. Example of measurement of left atrial (LA) maximal volume (panels A and D), strain (panels B and E) and PA-TDI (panels C and F) in two patients with ST-elevation myocardial infarction (STEMI) with normal coronary flow in the dominant CAB (upper row) and impaired coronary flow in the dominant CAB (lower row). In contrast to the patient with preserved coronary flow, the patient with impaired coronary flow in the dominant CAB shows an enlarged LA, a markedly reduced LA strain reservoir (Panels B and E, arrow A), booster pump function (Panels B and E, arrow B and conduit (Panels B and E, arrow C) and a prolonged PA-TDI (201 msec. vs. 105 msec., Panels C and F).

Follow-up and data collection

Patients were followed-up at 6 and 12 months and transthoracic echocardiography was performed at each follow-up. Changes in LA volume and PA-TDI (anatomical remodeling) and changes in reservoir, conduit and booster pump strain (functional remodeling) were assessed over time.

Statistical analysis

Continuous variables are presented as means ± standard deviation or medians with interquartile range, as appropriate. Continuous variables were compared with the unpaired Student t-test if normally distributed and with the Mann–Whitney U test if non-normally distributed. Categorical data are summarized as frequencies and percentages and compared using the $\chi 2$ or Fischer exact test, as appropriate. Changes in LA volume, LA strain parameters and PA-TDI during echocardiographic follow-up were compared using 2-way repeated-measure analysis of variance (ANOVA) with appropriate interaction terms. Post-hoc analysis (Bonferroni correction) was performed if statistical significance ($P \leq 0.05$) was achieved. Statistical analysis was performed with SPSS v23.0 (IBM, Armonk, New York). A two-tailed $P<0.05$ was considered statistically significant.

RESULTS

Of 897 STEMI patients, 69 STEMI patients (62±11 years, 83% males) with impaired coronary flow in the dominant CAB were matched and compared to 138 controls. Coronary flow impairment in the dominant CAB at the moment of the diagnostic coronary angiography was reported as follows: TIMI 0 in 39 patients, TIMI 1 in 16 and TIMI 2 in 4. At the end of the procedure, the coronary flow in the dominant CAB was fully restored in 50 patients (72%) whereas 19 of them (28%) showed a persistent impaired coronary flow (TIMI 0 in 11 patients, TIMI 1 in 5 and TIMI 2 in 6). Baseline clinical characteristics are summarized in Table 1. Of note, patients with impaired flow in the dominant CAB showed significantly higher troponin T peak values as compared to controls(3.9 [2.2-8.2] µg/L vs. 3.2 [1.5-5.6] µg/L; P=0.009).

Table 1. Baseline characteristics

	Overall Population (n=207)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=138)	P-value
Age, years	62±11	62±11	62±11	0.816
Male, n (%)	171 (82)	57 (83)	114 (83)	1.000
Hypertension, n (%)	75 (36)	25 (36)	50 (36)	1.000
Hypercholesterolemia, n (%)	48 (23)	10 (14)	38 (26)	0.037
Family history of CAD, n (%)	77 (37)	27 (39)	50 (36)	0.878
Diabetes, n (%)	22 (10)	8 (12)	14 (10)	0.812
Smoking history, n (%)	128 (62)	42 (61)	86 (62)	0.876
Previous MI, n (%)	21 (10)	6 (9)	15 (11)	0.808
Previous stroke, n(%)	9 (4)	3 (4)	6 (1)	1.000
Peripheral vascular disease, n(%)	11 (5)	1 (1)	10 (7)	0.104
BSA, kg/m2	2±0.2	1.9±0.2	2±0.2	0.275
SBP at admission (mmHg)	132.9±27.1	126.8±27.6	136.1±26.4	**0.025**
DBP at admission (mmHg)	79.3±17.5	75.6±18.7	81.3±16.6	**0.035**
Killip class ≥ 2, n (%)	12 (6)	6 (9)	6 (4)	0.220
Peak CK (U/L)	1329 [765-2179]	1422 [822-2583]	1217 [735-1694]	0.084
Peak TnT (µg/L)	3.4 [1.6-6.4]	3.9 [2.2-8.2]	3.2 [1.5-5.6]	**0.009**
eGFR, mL/min/1.73m2	100.3±36.6	91.3±35.1	105.1±36.8	0.051
Glucose, mmol/L	72.6±39.7	75.5±40.9	71.2±39.2	0.472
Aspirine at discharge, n (%)	203 (98)	68 (99)	135 (98)	0.778
P2Y12 inhibitor at discharge, n (%)	206 (99)	68 (98)	137 (99)	0.335
ACEi/ARB at discharge, n (%)	197 (95)	67 (98)	130 (95)	0.721
Betablockers at discharge, n (%)	192 (93)	63 (91)	129 (93)	0.558
Statins at discharge, n (%)	206 (99)	69 (100)	137 (99)	1.000

ACEi/ARBs=angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CAD=coronary artery disease; CK=creatine kinase; DBP=diastolic blood pressure; MI=myocardial infarction; SBP=systolic blood pressure; TnT=troponin-T.

Coronary angiography findings are summarized in Table 2. Compared to controls, patients with impaired flow in the dominant CAB had more often complex coronary culprit lesions (87% vs. 74% , P=0.033) and higher thrombus burden (2.6±1.2 vs. 2.1±1.2 TIMI-thrombus grades, P=0.010).

Table 2. Angiographic findings

	Overall population (n=207)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=138)	P-value
Dominant CAB type, n(%)				
Sinus node branch	194 (94)	62 (90)	132 (96)	0.131
Others	13 (66)	7 (10)	6 (4)	
Dominant CAB vessel of origin, n(%)				
Right coronary artery	125 (60)	58 (84)	67 (49)	**<0.001**
Left circumflex artery	82 (40)	11 (16)	71 (51)	
Right coronary dominancy, n(%)	198 (96)	66 (96)	132 (96)	1.000
Multi-vessel coronary artery disease, n(%)	92 (44)	28 (41)	64 (46)	0.461
Culprit vessel right coronary artery, n(%)	155 (75)	58 (84)	97 (70)	**0.041**
Culprit lesion ACC/AHA type B2/C, n(%)	162 (78)	60 (87)	102 (74)	**0.033**
Visible thrombus, n(%)	186 (90)	65 (94)	121 (88)	0.221
Thrombus grade	2.3±1.2	2.6±1.2	2.1±1.2	**0.010**
Culprit vessel TIMI flow pre-PCI	0.7±1.2	0.4±0.8	0.9±1.2	**0.002**
Culprit vessel TIMI 0-1 post-PCI, n(%)	5 (2)	1 (1)	4 (3)	0.667
Door-to-balloon time, minutes	51 [36-75]	50 [31-79]	50 [35-75]	0.478

CAB = coronary atrial branch; PC I= percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

Echocardiography was available in 192 patients (93%) at baseline, in 190 (92%) at 6-months follow-up, and in 191 (92%) at 12-months follow-up. Baseline echocardiographic characteristics are displayed in Table 3. There were no differences in LVEF and frequency of significant MR between groups throughout follow-up. LA maximal volume, PA-TDI and LA strain parameters are summarized in Table 3. LA maximal volume was similar in both groups at baseline. However, patients with impaired flow in the dominant CAB exhibited larger LA volumes at 6 months as compared to their counterparts, and the difference was sustained at 12 months follow-up. Similarly, mean PA-TDI times were similar in both groups at baseline, whereas significantly longer PA-TDI times were observed in patients with impaired flow in the dominant CAB both at 6- and 12-months follow-up. All LA strain parameters (LA reservoir, conduit and booster pump functions) were significantly lower in patients with impaired vs. normal flow in the dominant CAB at baseline, remaining significantly impaired during both at 6- and 12-months follow-up (Table 4).

Table 3. Baseline echocardiographic findings

	Overall population (n=207)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=138)	P-value
Baseline				
LV end-systolic diameter (mm)	32.5±6.7	31.6±6.6	32.8±6.7	0.266
LV end-diastolic diameter (mm)	48.2±6.4	47.2±7.3	48.6±6	0.183
LV interventricular septum diameter (mm)	11.5±2.1	11.9±2.4	11.3±2	0.096
LV posterior wall diameter (mm)	11.3±2.1	11.6±2.4	11.1±2	0.179
LV mass, indexed (g/m2)	105.1±28.3	107.5±32.8	104.1±26	0.457
LV end-systolic volume (mL)	54.6±21.7	53.9±24.9	55±19.9	0.758
LV end-diastolic volume (mL)	103.7±33	99.2±33.2	106±32.8	0.189
LVEF (%)	48.6±9.2	48.1±11.2	48.9±8	0.613
E/A ratio	2.1±11.4	4.5±19.7	0.9±0.3	0.167
E' (cm/sec)	6.1±2	6.5±2.3	5.8±1.8	0.043
E/E'	12.2±6.5	11.2±4.9	12.7±7.3	0.148
Significant MR n ≥2,n(%)	15 (7)	8 (12)	7 (5)	0.084
6-months				
LV end-systolic volume (mL)	48.1±19.9	45.4±18.3	49.3±20.6	0.257
LV end-diastolic volume (mL)	104±31.3	98.1±30	106.7±31.7	0.114
LVEF (%)	50.8±6.9	51.5±7.1	50.5±6.8	0.370
E/A ratio	0.8±0.2	0.8±0.2	0.8±0.3	0.549
E' (cm/sec)	5.9±1.8	5.9±2	5.9±1.7	0.879
E/E'	11.7±5.1	11.9±6.8	11.5±4.2	0.686
Significant MR n ≥2,n(%)	8 (4)	5 (7)	3 (2)	0.052
12-months				
LV end-systolic volume (mL)	46.7±19.7	43.9±16.1	47.9±21.1	0.245
LV end-diastolic volume (mL)	102.1±34.1	95.8±27	104.9±36.6	0.127
LVEF (%)	51.7±7.1	51.8±6.5	51.7±7.3	0.869
E/A ratio	0.9±0.2	0.8±0.2	0.9±0.3	0.147
E' (cm/sec)	5.8±1.8	5.7±1.8	5.9±1.8	0.615
E/E'	14±26	12.5±5.2	14.7±31.8	0.647
Significant MR n ≥2,n(%)	8 (4)	3 (4)	5 (4)	0.694

LV=left ventricle; LVEF=left ventricular ejection fraction; MR=mitral regurgitation. Echocardiograms available in 192/207 patients at baseline; 190/207 at 6- and 191/207 at 12-months follow-up

Repeated measures ANOVA showed a statistically significant effect of time on LA maximal volume ($F_{1.8,267}$=41,3, P<0.001), PA-TDI ($F_{1.7,275}$=17.1, P<0.001), LA strain reservoir ($F_{1.5,253}$=12.7, P<0.001), LA strain conduit ($F_{1.7,278}$=8.2, P<0.001) and LA strain booster pump function ($F_{1.7,273}$=9.1, P<0.001) (Figure 3). Post-hoc testing revealed significant differences between patients with impaired vs. normal flow in the dominant CAB in all the evaluated parameters: LA maximal index volume $F_{1,145}$=23.7, P<0.001 (corrected by LVEF and E/E' ratio), PA-TDI $F_{1,156}$=21.7, P<0.001, LA strain reservoir $F_{1,160}$=80.7, P<0.001, LA strain conduit $F_{1,160}$=45.8, P<0.001 and LA strain booster pump function $F_{1,160}$=63.8, P<0.001 (Figure 3).

Table 4. Left atrium echocardiographic findings*

	Overall population (n=207)	Impaired flow dominant atrial branch (n=69)	Normal flow dominant atrial branch (n=138)	P-value
LA maximal indexed volume (mL/m2)				
Baseline	20.82±6.2	20.5±5.3	20.9±6.7	0.639
6-months	20.7±9.2	26.9±10.9	18.1±7.02	**<0.001**
12-months	20.9±8.6	27.7±9.1	18±6.6	**<0.001**
LA strain-reservoir (%)				
Baseline	24.9±13.6	20.3±10.1	27.1±14.5	**0.001**
6-months	33.3±15.4	19.1±6.8	39±14.2	**<0.001**
12-months	31.7±15	20±7.6	36.8±14.6	**<0.001**
LA strain-conduit (%)				
Baseline	13.3±9	11.4±7.6	14.3±9.4	**0.036**
6-months	16±9.5	8.8±4.4	19±9.5	**<0.001**
12-months	15±9.5	9±4.8	17.6±10	**<0.001**
LA strain-booster (%)				
Baseline	11.6±7.6	9.1±5.6	12.8±8	**0.001**
6-months	17.2±8.3	10.3±4	20±8	**<0.001**
12-months	16.7±8.1	11±5.1	19.2±7.9	**<0.001**
PA-TDI (msec)				
Baseline	125.9±28	125±30.7	126.3±26.7	0.781
6-months	131.5±25.3	150.1±23.3	124±22.1	**<0.001**
12-months	131.1±25.7	144.8±24.9	124.9±23.6	**<0.001**

Echocardiograms available in 192/207 patients at baseline; 190/207 at 6- and 191/207 at 12-months follow-up

DISCUSSION

The main conclusions of the study are: 1) atrial ischemia resulting from coronary flow impairment in the dominant CAB in STEMI patients was associated with significant LA anatomical remodeling, expressed as a larger LA maximal volume and a longer PA-TDI, present at 6 months follow-up and maintained at 12-months; 2) LA functional remodeling, expressed as impaired LA strain parameters, resulting from coronary flow limitation in the dominant CAB was observed at baseline and remained impaired both at 6- and 12-months follow-up; 3) there were no significant differences in LVEF, significant MR or LV diastolic dysfunction parameters between groups at any time point of the evaluation.

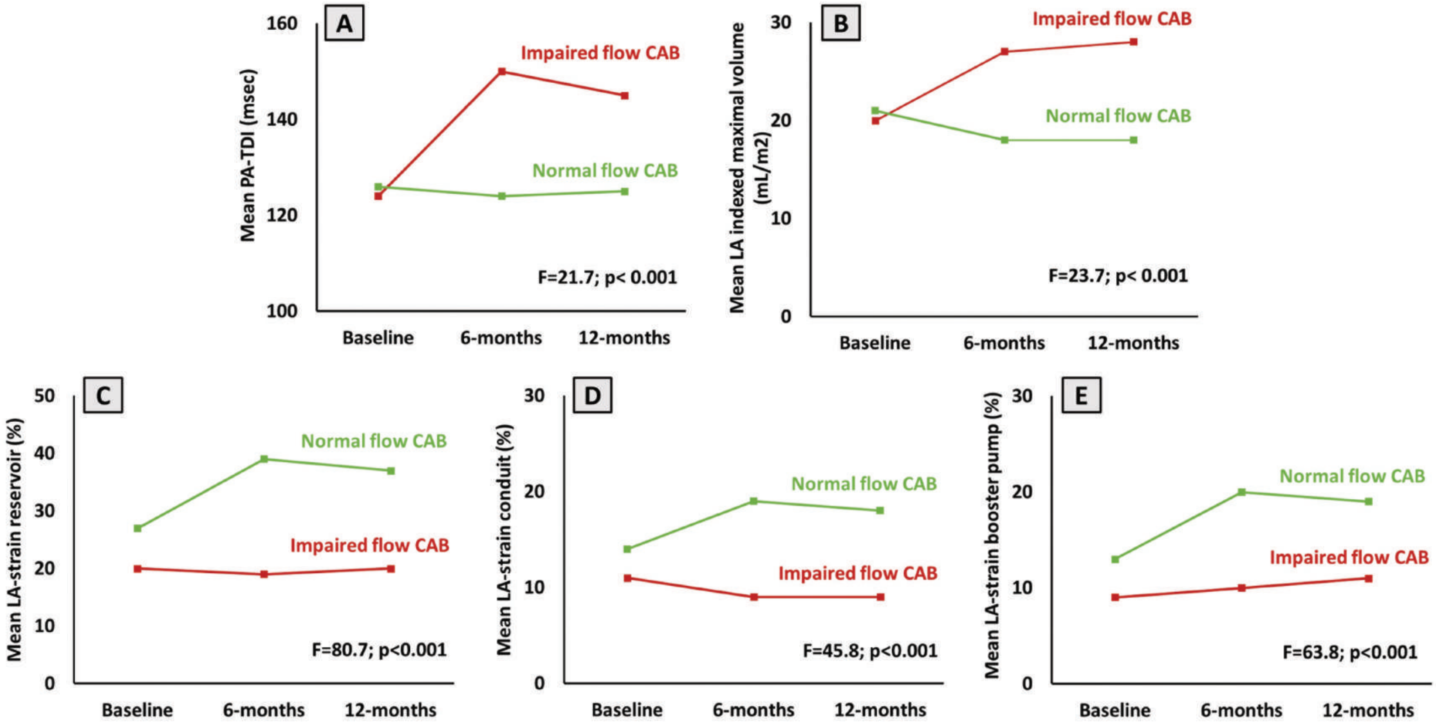

Figure 3. Two-way repeated-measures ANOVA analysis performed on left atrium (LA) echocardiographic variables assessed at baseline, 6- and 12-months follow-up, evaluating differences between patients with impaired (red) vs. normal (green) coronary flow in the dominant coronary atrial branch (CAB). The results (change at each time point) are plotted as mean values. Patients with impaired flow in the dominant CAB showed larger LA maximal index volumes (Panel A) and longer PA-TDI (Panel B) at 6-months and 12-months. Additionally, they showed a lower LA strain reservoir (Panel C), conduit (Panel D) and pump booster function (Panel E) in all measurements when compared with patients with preserved flow at the dominant CAB.

Atrial coronary anatomy, LA coronary perfusion phenotype and atrial ischemia

It has been postulated that coronary perfusion of the LA relies solely on CABs arising from the LCx. In a study conducted by Aguero et al[3]. in a swine model, an LA infarction was induced by occluding a CAB arising from the proximal LCx, which lead to structural and functional LA remodeling. Similarly, the occlusion of the proximal LCx artery in a sheep model lead to significant electrophysiological changes in the LA compared to individuals with left anterior descending coronary artery infarctions[17]. However, it has been shown that LA coronary perfusion is complex and results from a variable contribution of the left and right CAB. In a sheep model, Yamazaki et al[18]. described three well-differentiated LA perfusion patterns: left dominant (relying on the left proximal CAB); balanced double vessel (left proximal and right CAB) and triple vessel perfusion (right CAB, left proximal and distal CAB). In most of the specimens, a double vessel LA perfusion pattern was identified. Due to the similar distribution of CAB in sheep and human hearts[19], it can be speculated that similar inter-specimen variability of LA perfusion may also exist in the human heart. The same conclusions might be extracted from our observations: in 84% of the cases with impaired flow, the dominant CAB emerged from the RCA and yet presented LA remodeling. In addition, flow limitation in dominant CABs emerging from the LCx did not determined a greater LA structural and functional impairment. These findings highly suggest the existence of, at least, a double vessel LA perfusion pattern in a high proportion of patients.

Atrial ischemia and LA anatomical and functional remodeling

Atrial remodeling, defined as a permanent change in LA size and function, is a complex pathophysiological process, especially after myocardial infarction[20]. However, isolated atrial infarction has been recently recognized as a trigger of atrial fibrosis. Extensive atrial scarring with diffuse interstitial accumulation of collagen was observed 2 months after ischemic injury in an animal model[3]. Due to the thin myocardial wall of the atrium (2-3 mm), even limited ischemic injury may lead to significant structural impairment[21,22]. In clinical practice, non-invasive quantification of atrial fibrosis remains challenging. However, several echocardiography-based techniques have proven to be a reliable surrogate of atrial fibrosis. Prolongation of the PA-TDI, which measures the total atrial conduction time, shows a linear relationship with the degree of atrial fibrosis[7]. Likewise, atrial fibrosis may result in a reduced LA compliance, represented by impaired LA reservoir strain[23]. A distorted structural and functional atrial substrate ultimately results in dilatation of the atria[20]. As demonstrated in other clinical scenarios, LA functional impairment often precedes LA anatomical changes[24,25]. In the present study, a marked impairment of atrial function was evident shortly after ischemia. Far from transient, this effect remained unchanged throughout follow-up.

However, significant changes in atrial structure, expressed as longer PA-TDI (surrogate of atrial fibrosis) and larger LA volume, were observed from 6-months onwards. Our observations are in line with experimental swine models of atrial ischemia[3], in which a markedly reduced LA reservoir and booster pump function were present shortly after LA ischemia and remained depressed at 2 months. In addition, specimens with atrial infarction presented with larger LA dilatation at 2 months as a result of extensive post-ischemic fibrosis. The maintenance of these structural changes over time, despite of optimal medical therapy after STEMI, indicate the presence of extensive ischemia-related injury. Importantly, these findings were independent from LVEF or the presence of significant MR.

In the past years, the term "atrial cardiomyopathy" has been introduced to define any structural and/or functional change in the atria leading to clinical consequences[26]. Although recognized as a potential cause of atrial myopathy[27], ischemic atrial disease is not fully recognized as a clinical entity. The present study provides an "in vivo model" of the effect of atrial ischemia complicating STEMI and defines the time course of both structural and functional changes of the LA induced by atrial ischemia during 1-year follow-up. Our findings will help to understand this often underdiagnosed problem and to define the potential clinical effects associated.

Study limitations

Several limitations should be acknowledged. This is a retrospective, observational study of patients referred to a tertiary center and therefore selection bias cannot be excluded. The dominant CAB was defined as the largest visible coronary atrial branch. Therefore, dominant CAB with flush ostial occlusion may have been overlooked during coronary angiography, although this is highly unlikely as previously reported in a subset of patients from this cohort who underwent a follow-up coronary angiography[9]. In addition, there might be an important variability in the total amount of supplied myocardium by a given dominant CAB. Due to the nature of the study, there was no objective quantification of the extension of the ischemia-induced atrial myocardial damage. Although the rate of previous MI is rather low, whether this could have induced pre-existent atrial remodeling in these patients and, therefore, impacted the observed results cannot be excluded.

CONCLUSIONS

Impaired coronary flow in the dominant CAB in patients with STEMI is associated with LA adverse both anatomical and functional LA remodeling. Functional remodeling, assessed by LA strain, preceded anatomical structural remodeling in early phases after STEMI.

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II

Prognostic value of coronary angiography in acute myocardial infarction in specific scenarios

5

Prevalence and Long-term Outcomes of Patients with Coronary Artery Ectasia Presenting with Acute Myocardial Infarction.

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ABSTRACT

Coronary artery ectasia (CAE) is described in 5% of patients undergoing coronary angiography. Previous studies have shown controversial results regarding the prognostic impact of CAE. The prevalence and prognostic value of CAE in patients with acute myocardial infarction (AMI) remain unknown. In 4788 patients presenting with AMI referred for coronary angiography the presence of CAE (defined as dilation of a coronary segment with a diameter ≥1.5 times of the adjacent normal segment) was confirmed in 174 (3.6%) patients (age 62 ± 12 years; 81% male), and was present in the culprit vessel in 79.9%. Multivessel CAE was frequent (67%). CAE patients were more frequently male, had high thrombus burden and were treated more often with thrombectomy and less often was stent implantation. Markis I was the most frequent angiographic phenotype (43%). During a median follow-up of 4 years (1-7), 1243 patients (26%) experienced a major adverse cardiovascular event (MACE): 282 (6%) died from a cardiac cause, 358 (8%) had a myocardial infarction, 945 (20%) underwent coronary revascularization and 58 (1%) presented with a stroke. Patients with CAE showed higher rates of MACE as compared to those without CAE (36.8% versus 25.6%; p <0.001). On multivariable analysis, CAE was associated with MACE (HR 1.597; 95% CI 1.238-2.060; p <0.001) after adjusting for risk factors, type of AMI and number of narrowed coronary arteries. In conclusion, the prevalence of CAE in patients presenting with AMI is relatively low but was independently associated with an increased risk of MACE at follow-up.

INTRODUCTION

Coronary artery ectasia(CAE) is defined as a dilation of acoronary arterysegment with at least 1.5 times the diameter of the adjacent normal segments[1] .The prevalence of CAE in patients undergoing coronary angiography ranges from 0.3% to 5.3% [2]. CAE may be detected as anincidental findingin asymptomatic patients during coronary angiography (i.e. prior to valve surgery or atrial fibrillation ablation) or in the context of anacute myocardial infarction(AMI)[3].Clinical symptoms could be caused by the presence of concomitant obstructive atherosclerotic disease or distalembolizationdue to local thrombosis in the lumen of a large aneurysmatic coronary segment[4].In patients presenting with AMI, the presence of CAE may influence the procedural success and the long-term outcome. However, current knowledge is based on small sample size studies which showed contradictory results[5,6,7,8,9]. Accordingly, we aimed at: 1) assessing the prevalence of CAE in a large cohort of patients presenting with AMI, 2) defining the main phenotypical angiographic characteristics of patients with and without CAE and 3) at investigating the long-term prognostic impact of CAE.

METHODS

Consecutive patients presenting with AMI at the Leiden University Medical Center (Leiden, the Netherlands) between February 2004 to October 2015, who underwent acute invasive coronary angiography, were included in the analysis. Patients with previous history of coronary artery bypass grafting were excluded. Invasive coronary angiography was performed in a standard fashion andrevascularizationof the culprit lesion was performed according to contemporary recommendations. Patients were subsequently treated according to the institutional protocol[10],remaining hospitalized for at least 48 hours. Baseline demographic and clinical data, including cardiovascular risk factors and medications at discharge, were retrospectively collected from the Departmental Cardiology Information System (EPD-Vision: Leiden University Medical Center, Leiden, The Netherlands). This retrospective study of clinically acquired data was approved by the Institutional Review Board and the need for patient writtenin-formed consentwas waived.

CAEwas defined as a dilation of acoronary arterysegment with a diameter ≥1.5 times of the adjacent normal segment. Patients with CAE in any of thecoronary vesselsduring index coronary angiography were identified. Thestudy cohortwas divided into two groups, according to the presence or absence of CAE. Coronary angiograms obtained during the index procedure were retrospectively evaluated by two independent interventional cardiologists blinded to the clinical outcomes. The angiographic anatomical distribution of CAE was categorized according to the Markis classification[11]: type I was defined as the presence of diffuse CAE in 2 or 3 coronary vessels; type II as diffuse CAE in one coronary vessel and localized CAE in another vessel; type III as diffuse CAE in only one coronary vessel and type IV as localized or segmental CAE (Figure 1).

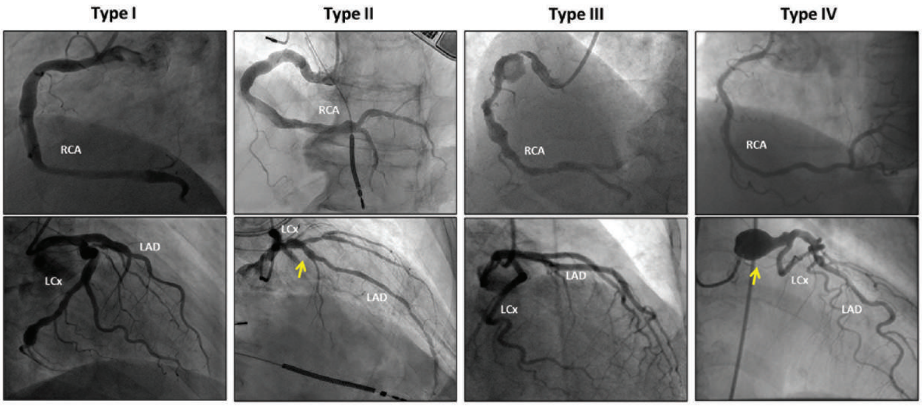

Figure 1. Angiographic characterization of CAE distribution according to the Markis classification. Type I: diffuse CAE in 2 or 3 coronary vessels. In these case, all 3 vessels present diffuse CAE. Type II: diffuse CAE in one coronary vessel (RCA) and localized CAE in another vessel (proximal LAD, arrow). Type III: diffuse CAE in only 1 coronary vessel (RCA, arrows). Type IV: localized or segmental CAE (in this case, massive dilatation of the LMCA, arrow). CAE = coronary artery ectasia; LAD = left anterior descending; LCx = left circumflex; LMCA = left main coronary artery; RCA = right coronary artery.

Multivessel disease was defined by the presence of a coronary stenosis >50% in ≥2 major coronary arteries. Coronary artery flow was evaluated by using the Thrombolysis In Myocardial Infarction (TIMI) frame count method[12]. Thrombus burden was graded from 0 to 5 according to the TIMI-thrombus scale[13]. High thrombus burden was defined as a TIMI-thrombus scale ≥4. Angiographic success was defined as final TIMI 3 distal flow with less than 20% of vessel stenosis and no immediate mechanical complications. No-reflow phenomenon was defined as TIMI flow ≤2 at the end of the procedure without angiographic evidence of mechanical vessel obstruction[14].

Patients were followed-up according to the institutional guideline-based care-track protocol[10]. The primary endpoint was composite of major adverse cardiovascular events (MACE) which included cardiac death, myocardial infarction, stroke and repeated coronary revascularization, including percutaneous coronary intervention or coronary artery bypass grafting. Secondary endpoints were the individual components of the composite outcome. Deaths were considered to be attributable to a cardiac cause unless a noncardiac death could be confirmed. Myocardial infarction was defined as an increase of cardiac troponin with at least 1 value above the 99th percentile upper reference limit and ischemic symptoms and/or new or presumed new ST-segment, T-wave changes or new left bundle branch block[15]. Stroke was defined as any cerebrovascular event (intracranial hemorrhage or non-hemorrhagic stroke) meeting the following criteria: 1) rapid onset of neurological deficit; 2) duration ≥24 hours or <24 hours if therapeutic intervention, neuro-imaging or death; 3) absence of non-stroke cause; 4) confirmation by neurologist/neurosurgeon, neuro-imaging or lumbar puncture. Medical records review and survival status information were obtained through the hospital information systems (EPD-Vision and EZIS; Leiden University Medical Centre, Leiden, The Netherlands).

Normally distributed continuous variables are presented as mean ± standard deviation while non-normally distributed continuous variables are presented as median with interquartile range. Categorical data are presented as numbers and percentages. Unpaired Student's t-test was used for comparison of normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables, and chi-square test for categorical data. The cumulative events were calculated using the Kaplan–Meier curves and comparison between groups was performed using the log-rank test. Uni- and multivariable Cox regression analyses were performed to identify independent demographic, clinical and angiographic variables associated with MACE. The hazard ratio (HR) and 95% confidence interval are presented. All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant. Data analyses were performed using SPSS version 25.0 software (IBM SPSS Statistics for Windows. Armonk, NY, USA)

RESULTS

Among 4788 patients (62 ±12 years old, 74% men), CAE was observed in 174 (3.6%) patients. Baseline characteristics of patients with and without CAE are shown in Table 1. Patients with CAE were more frequently men as compared to patients without CAE. There were no other significant differences in clinical variables. Angiographic and procedural data are summarized in Table 2. Regarding distribution of the culprit vessels, the right coronary artery (RCA) was the most frequent culprit vessel in patients with CAE, whereas in patients without CAE, the left anterior descending (LAD) was the most frequent. Thrombectomy was more often used in patients with CAE whereas the rate of stent implantation in the culprit lesion was lower than in those without. Furthermore, patients with CAE were treated with stents of larger diameters as compared to patients without CAE.

TABLE 1. Baseline clinical characteristics.

	Total population (n=4788)	CAE (n=174)	Non-CAE (n=4614)	P Value
Age (years)	63±13	62 ± 12	63 ± 12	0.766
Male	3540(73.9%)	142 (81.6%)	3398 (73.6%)	0.019
Diabetes mellitus	620(12.9%)	12 (6.9%)	608 (13.2%)	0.052
Hypertension	1838(38.4%)	58 (33.3%)	1780 (38.6%)	0.316
Dyslipidemia	2889(60.3%)	112 (64.4%)	2777 (60.2%)	0.243
History of smoking	2500(50.2%)	105 (60.3%)	2395 (51.9%)	0.089
BMI (kg/m^2)	27 ± 9	27 ± 9	28 ± 12	0.130
Previous MI	417(8.9%)	19 (11.1%)	398 (8.9%)	0.394
Previous PCI	361(7.5%)	13 (7.6%)	348 (7.5%)	0.127
STEMI at presentation	4373(91.3%)	158 (90.8%)	4215 (91.4%)	0.801
Killip class >2	176(3.7%)	2 (1.1%)	174 (3.8%)	0.071
LVEF	47 ± 9	48 ± 9	47 ± 9	0.832
Laboratory data				
Total cholesterol (mg/dl)	205 ± 47	203 ± 45	205 ± 48	0.617
LDL-cholesterol, (mg/dL)	43 ± 1	41 ± 3	43 ± 1	0.785
Peak CK (units/L)	1392(539-2149)	1494 (506-2099)	1389 (541-2151)	0.854
Creatinine (µmol /L)	80(68-89)	79 (68-88)	80 (68-89)	0.488
CRP (mg/L)	3(3-11)	3 (3-11)	4 (3-11)	0.311
Medication at discharge				
Aspirin	4419(92.3%)	161 (92.5%)	4258 (92.3%)	0.906
DAPT	4415(92.2%)	161 (92.5%)	4254 (92.2%)	0.873
Oral anticoagulation	149(3.2%)	8 (4.7%)	141 (3.2%)	0.254
DAPT + oral anticoagulation	116(2.4%)	5 (2.9%)	111 (2.4%)	0.694
ACE-I/ARB	4276(92.9%)	156 (92.9%)	4120 (92.9%)	0.967
β-Blockers	4174(90.7%)	153 (91.1%)	4021 (90.7%)	0.873
Statins	4435(96.4%)	163 (97.0%)	4272 (96.4%)	0.655

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CAE = coronary artery ectasia; CK = creatine kinase; CRP = C-reactive protein; DAPT = dual antiplatelet therapy; LDL = low-density lipoprotein; ; LVEF = left ventricular ejection fraction

The specific angiographic characteristics of patients with CAE are summarized in Table 3. CAE was predominantly observed in the RCA followed by the LAD, left circumflex artery and left main coronary artery. CAE was present in the culprit vessel in the vast majority of patients, being the presence of multivessel CAE frequently observed. Large thrombus burden was present in 92% of patients. CAE extension was assessed according to the classification proposed by Markis et al[11].: 43% patients were classified as type I (diffuse CAE in 2 or 3 coronary vessels); 14% as type II (diffuse CAE in 1 vessel and localized CAE in another vessel); 26% as type III (diffuse CAE in only 1 vessel) and 17% as type IV (localized or segmental CAE).

TABLE 2. Angiographic and procedural characteristics.

	Total population (n=4778)	CAE (n=174)	Non-CAE (n=4614)	P Value
Culprit lesion location,				0.310
Left anterior descending	1943(40.6%)	57 (32.8%)	1886 (40.9%)	0.032
Left circumflex	732(15.3%)	29 (16.7%)	703 (15.2%)	0.607
Right	1711(35.7%)	72 (41.4%)	1639 (35.5%)	0.114
Left main	65(1.4%)	3 (1.7%)	62 (1.3%)	0.570
No. of narrowed coronary arteries	2(1-2)	2 (1-3)	2 (1-2)	0.115
Three-vessel disease	1178(24.6%)	48 (27.6%)	1130 (24.5%)	0.352
Mechanical hemodynamic support	119(2.5%)	3(1.7%)	116(2.5%)	0.511
Balloon pre-dilatation	3757(84.0%)	114(82.8%)	3610(78.2%)	0.056
Balloon post-dilatation	1624(36.5%)	66(37.9%)	1558(33.8%)	0.208
Thrombectomy	461(9.6%)	33(20.5%)	428(9.3%)	<0.001
Stent implanted	4246(93.0%)	146(84.4%)	4100(93.3%)	<0.001
No. of stents	1(1-2)	1(1-2)	1(1-2)	0.830
Stent diameter (mm)	3.5(3.0-3.5)	3.5(3.0-4.0)	3.0(3.0-3.5)	<0.001
Total Stent length (mm)	23(16-34)	23(16-36)	23(16-34)	0.884
Initial TIMI flow				
0/1	3012(68.4%)	121(76.1%)	2891(68.1%)	0.034
2	603(13.7%)	17(10.7%)	586(13.8%)	0.261
3	787(17.9%)	21(13.2%)	766(18.1%)	0.117
Final TIMI flow				
0/1	99(2.3%)	5(3.2%)	94(2.2%)	0.418
2	200(4.6%)	11(7.1%)	189(4.5%)	0.130
3	4054(93.1%)	139(89.7%)	3915(93.3%)	0.083
Final TIMI flow < 3	299(6.9%)	16 (10.3%)	283 (6.7%)	0.083

CAE = coronary artery ectasia; TIMI = Thrombolysis in Myocardial Infarction.

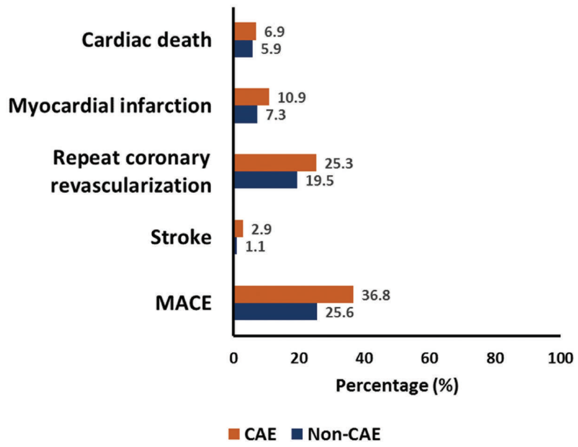

Figure 2. Distribution of individual MACE in patients with and without CAE during follow-up. CAE = coronary artery ectasia; MACE = major adverse cardiovascular events.

TABLE 3. Anatomical angiographic features of patients with CAE.

	Coronary artery ectasia (n = 174)
CAE affected vessel, n (%)	
Right coronary artery	138 (79.3)
Left anterior descending artery	115 (66.1)
Left circumflex artery	90 (51.7)
Left main coronary artery	55 (31.6)
Diagonal branches	15 (8.6)
Obtuse marginal branches	35 (20.1)
Posterior descending artery	64 (36.8)
CAE in infarct-related artery, n (%)	139 (79.9)
CAE single vessel involvement, n (%)	57 (32.8)
CAE multivessel involvement, n (%)	117 (67.2)
CAE distribution according to Markis classification, n (%)	
Type I	75 (43.1)
Type II	24 (13.8)
Type III	45 (25.9)
Type IV	30 (17.2)
Large thrombus burden, n (%)	160 (91.9)

CAE = coronary artery ectasia.

During a median follow-up of 4 years (IQR 1-7 years), 1243 patients (26%) presented with MACE. The individual components of MACE occurred as follows: 282 patients (6%) died from a cardiac cause, 358 (8%) had a myocardial infarction, 945 (20%) underwent coronary revascularization and 58 (1%) suffered a stroke. The distribution of events in patients with and without CAE is presented in Figure 2. Survival analysis showed higher rates of MACE in patients with CAE compared with those without CAE (Figure 3). There were no significant differences between groups regarding cardiac death rate and myocardial infarction. There were significant differences between groups in terms of any repeat revascularization and stroke, as displayed in Figure 4.

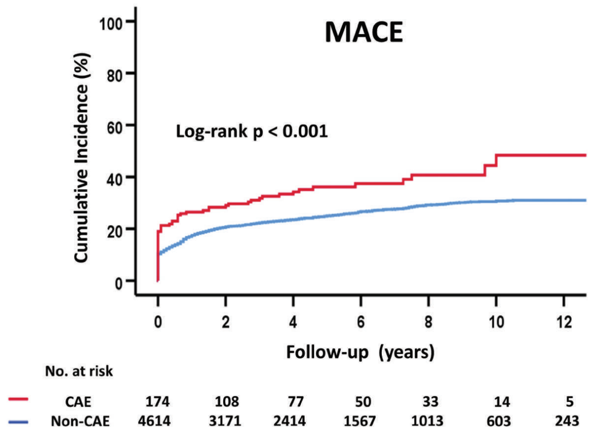

Figure 3. Kaplan-Meier survival curves of cumulative MACE incidence in patients with CAE (red) versus patients without CAE (blue). CAE = coronary artery ectasia; MACE = major adverse cardiovascular event.

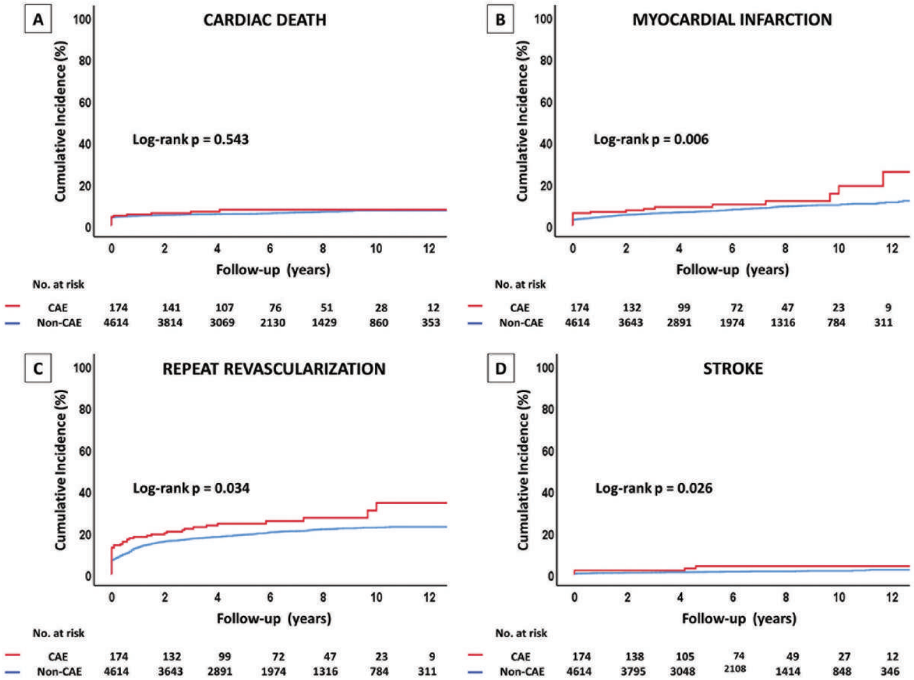

Figure 4. Kaplan-Meier survival curves of cumulative incidence of (A) cardiac death; (B) MI; (C) repeat revascularization and (D) stroke in patients with CAE (red line) versus patients without CAE (blue line). CAE = coronary artery ectasia; MI = myocardial infarction.

Table 4. Univariable and multivariable analysis to evaluate the association between CAE and MACE.

Variable	Univariate analysis		Multivariate analysis	
	HR 95% CI	P value	HR 95% CI	P value
Age, (per one year increase)	1.010 (1.006-1.015)	<0.001	0.997 (0.992-1.003)	0.374
Male sex	1.097 (0.963-1.249)	0.163	-	
BMI, (per one unit increase)	1.001 (0.994-1.008)	0.744	-	
Diabetes mellitus	1.463 (1.284-1.669)	<0.001	1.394 (1.158-1.678)	<0.001
Hypertension	1.049 (0.935-1.177)	0.413	-	
Smoking history	1.034 (0.927-1.152)	0.551	-	
Previous MI	1.288 (1.097-1.512)	0.002	1.161 (0.952-1.415)	0.140
STEMI at presentation	2.834 (2.090-3.842)	<0.001	5.052 (2.701-9.450)	<0.001
Three-vessel coronary artery disease	2.443 (2.180-2.738)	<0.001	2.218 (1.918-2.566)	<0.001
Final TIMI flow < 3	1.911 (1.603-2.279)	<0.001	2.003 (1.586-2.530)	<0.001
Peak CK, units/L, (per 1000 unit increase)	1.013 (1.008-1.019)	<0.001	1.004 (0.997-1.010)	0.254
Creatinine, (per one unit increase)	1.002 (1.001-1.003)	<0.001	1.001 (1.000-1.002)	0.063
Killip class > 2	3.661 (3.007-4.457)	<0.001	2.055 (1.568-2.691)	<0.001
LVEF	0.980 (0.950-1.011)	0.198		
Presence of CAE	1.551 (1.206-1.995)	0.001	1.417 (1.033-1.944)	0.031

BMI = body mass index; CAE = coronary artery ectasia; CK = creatine kinase; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MI = myocardial infarction; STEMI = ST-segment elevation myocardial; TIMI = Thrombolysis in Myocardial Infarction.

To investigate the association between CAE and the occurrence of MACE, uni- and multivariable Cox regression analyses were performed (Table 4). On univariable analysis, age, diabetes, previous myocardial infarction, ST-segment elevation myocardial infarction at presentation, three-vessel coronary artery disease, final TIMI flow <3, peak creatine kinase, creatinine, Killip class >2 and CAE showed a significant association with MACE. On multivariable analysis, diabetes, previous MI, STEMI at presentation, three-vessel coronary artery disease, TIMI flow <3, Killip class >2 and CAE remained independently associated with MACE

DISCUSSION

The prevalence of CAE in a large cohort of patients presenting with AMI was 3.6%. Patients with CAE presented with ectasia affecting 2 or more coronary arteries in 67%. CAE in the culprit vessel was found in 80% of patients, representing 3.2% of the total study population. Patients with CAE presenting with AMI had an increased rate of MACE at 4-years follow-up compared with those without CAE. This association was independent from cardiovascular risk factors, type of AMI and number of diseased vessels.

The pathogenesis of CAE has not been fully elucidated, and multiple pathophysiological mechanisms have been involved[8]. Given the frequent coexistence of CAE with obstructive CAD (up to 85%), it has been suggested that CAE and atherosclerosis share a similar pathogenesis[2,16,17]. In addition, several systemic inflammatory disorders have been related to CAE, such as Kawasaki disease, Wegener's granulomatosis, lupus and rheumatic fever[18,19]. CAE has also been linked with genetic susceptibility, infections, drug use, trauma and implantation of drug-coated stents[8].

Previous studies have reported a prevalence of CAE ranging from 0.3% to 5.3% in patients undergoing coronary angiography[2,5,16,20]. reaching up to 11% in a study including 250 patients with ischemic heart disease from India[21]. An analysis of the Coronary Artery Surgery Study (CASS) registry, which enrolled 20087 patients who underwent coronary angiography, CAE was found in 4.9%[2]. However, there are limited data regarding the prevalence of CAE in patients presenting with AMI. The presence of CAE in the culprit vessel has been previously analyzed in studies with smaller sample sizes: Yip et al[22]. found CAE in the culprit vessel in 2.6% of a cohort of 924 patients, whereas in another study consisting of 643 patients with myocardial infarction, the frequency of CAE was 4.8%[23]. The results of the present study, with 5 times larger population, confirm previous series and reported a frequency of CAE (irrespectively of its location) of 3.6% and 3.2% when considering the presence of CAE in the culprit vessel.

Regarding the angiographic findings, CAE involved the RCA in the majority of cases (79.3%). This higher predisposition of the RCA to develop CAE as compared to the other coronary arteries has been previously described[2], but the underlying pathophysiology remains unknown. In addition, multivessel CAE is infrequent and it has been described in only 25% of patients with CAE[16]. This is contrasting to the present study, where multivessel CAE was observed in 2/3 of the patients and the Markis type I pattern the most frequently anatomical phenotype observed. This marked discrepancy might be explained by the characteristics of the study population (AMI versus stable/asymptomatic patients).

A large thrombus burden and a low initial TIMI flow was observed in patients with CAE, which is consistent with previous studies[22,24]. A large thrombus burden may result from a decreased coronary flow velocity and a turbulent flow pattern, leading to platelet activation and thrombus formation in the dilated lumen[25]. Additionally, in patients with CAE complicated by obstructive coronary artery disease, the coexistence of both dilated and stenotic coronary segments may further impair coronary flow hemodynamics[26], favoring the progression of atherosclerotic disease. Thrombus aspiration was subsequently more often used in patients with CAE. Thrombus aspiration in acute myocardial infarction has been shown to reduce distal embolization and improve coronary perfusion, myocardial blush grade and prevent no-reflow[27]. However, although thrombus aspiration and glycoprotein IIb/IIIa inhibitors have been frequently used in patients with AMI and CAE, the occurrence of no-reflow or distal embolization is very frequent[24,28]. We observed a non-significant higher frequency of final TIMI flow <3 in patients with CAE compared to non-CAE patients. In the present study, patients with CAE were less often treated with stent implantation when compared with their counterparts and larger stents were used. Percutaneous coronary intervention for culprits lesion in ecstatic coronary segments in the setting of AMI is associated with a higher rate of procedural failure and a higher incidence of adverse events[28,29]. Proper selection of stent according to the size and extent of CAE is critical to reduce the risk of stent thrombosis and stent migration. Intracoronary imaging techniques may be helpful for the assessment of the lumen diameter and landing[30].

Previous studies have shown conflicting results on the prognostic impact of CAE. In the CASS study, the presence of CAE showed no effect on survival at 5-years after adjusting for confounding factors[2,16]. In a retrospective study of 203 patients with CAE, CAE did not confer added risk of MACE at 2-years when compared to a control group without CAE[16]. However, among 32,372 patients undergoing coronary angiography, Baman et al[2]. showed that the presence of CAE was associated with 1.56-fold adjusted 5-year mortality compared to those without CAE. In patients with AMI, we observed that the presence of CAE was associated to a 1.60-fold adjusted 4-year MACE compared to patients without CAE. These differences might be explained by the different characteristics of the study population and the definitions of CAE applied in each particular case. Furthermore, there is no consensus on the optimal therapeutic approach to CAE which potentially may determine clinical outcomes. Future investigations in this field should address these challenges.

Several limitations should be acknowledged. This is a single-center, observational retrospective analysis of prospectively clinically acquired data, with all the inherent limitations associated to the nature of the study. Patients with previous coronary artery bypass graft surgery were excluded, which may imply a selection bias. Systematic evaluation of intracoronary thrombus burden according to the TIMI thrombus scale was only performed in patients with CAE. Percutaneous coronary intervention optimization with intracoronary imaging was not routinely performed, which may have impacted on the procedural outcome. Due to the relatively small sample size of patients with CAE, underestimation of the association between CAE and MACE cannot be excluded.

In conclusion, the prevalence of CAE in patients presenting with AMI was 3.6 %. The presence of CAE was independently associated with an increased risk of MACE at 4-year follow-up. This association was independent from cardiovascular risk factors, type of AMI and number of diseased vessels.

DISCLOSURES

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6

Angiographic and clinical profile of patients with COVID-19 referred for coronary angiography during SARS-CoV-2 outbreak: results from a collaborative, European, multicenter registry.

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ABSTRACT

Data regarding angiographic characteristics, clinical profile and in-hospital outcomes of patients with Coronavirus Disease 2019 (COVID-19) referred for coronary angiography (CAG) are scarce. This observational study analyzed 57 COVID-19 patients (66±15 years, 82% male) referred for CAG from 10 European centers. Of them, 18% had previous myocardial infarction (MI) and 29% renal insufficiency and chronic pulmonary disease. ST-segment elevation MI (STEMI) was the most frequent indication for CAG (58%). COVID-19 was confirmed after CAG in 86% patients and before in 14% and classified as mild in 49%, with 21% asymptomatic. A culprit lesion was identified in 79% and high thrombus burden in 42%; 7% had stent thrombosis. At 40-days, 16 patients (28%) experienced a major adverse cardiovascular event (MACE): 12 deaths (92% non-cardiac); 1 MI; 2 stent thrombosis and 1 stroke. In an European multicenter registry, patients with COVID-19 referred for CAG during the first wave of the SARS-CoV2 pandemic presented mostly with STEMI and were predominantly males with comorbidities. COVID-19 severity was generally non-critical and 21% were asymptomatic. Culprit lesions with high thrombus burden were frequently identified, with a rate of stent thrombosis of 7%. The incidence of MACE at 40-days was high (28%), mostly due to non-cardiac death.

INTRODUCTION

The pandemic caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV2) has led to coronavirus disease 2019 (COVID-19). Although in the majority of patients, COVID-19 manifests as a mild upper respiratory tract infection, a significant proportion of patients may present with severe forms of the disease, characterized by systemic inflammation, cytokine storm and hypercoagulability[1-3]. Cardiac injury is frequent in critically ill patients with COVID-19, especially in those with pre-existent cardiovascular conditions, and has been associated to a worse prognosis[1-3]. Several pathophysiological mechanisms leading to myocardial damage in COVID-19 patients have been described. Ischemic cardiac injury can result from type I myocardial infarction (MI) derived from a prothrombotic state or type 2 MI as a result of an imbalance of oxygen supply/demand in patients with respiratory distress or severe hypoxemia, shock or coronary artery dissection[4]. Non-ischemic cardiac injury may result as well from myocarditis[5], stress-cardiomyopathy[6], acute heart failure, pulmonary embolism, sepsis, or direct viral myocardial injury[3-6]. In addition, patients with suspected or confirmed COVID-19 may present with an acute coronary syndrome (ACS) as the first clinical manifestation of the disease, even in the absence of respiratory symptoms[3]. The role of invasive coronary angiography (CAG) may thus be crucial in defining the underlying mechanism and establishing the subsequent treatment in COVID-19 patients presenting with cardiac injury.

The potentially associated risks for health care workers and specific institutional logistics during the pandemic led to development of clinical algorithms to identify COVID-19 patients who would benefit from an invasive strategy. Current recommendations advise restricting invasive CAG to COVID-19 patients in whom type I MI is suspected[7]. However, lack of understanding of the pathophysiological mechanisms of cardiac injury, especially in the early phases of the pandemic, resulted in a heterogeneous COVID-19 population referred for CAG.

We aimed to describe the clinical and angiographic characteristics, related to each particular clinical context, in a cohort of confirmed COVID-19 patients referred for invasive CAG in 9 different centers in 2 European countries. In addition, we evaluated the occurrence of major adverse cardiac events (MACE) at 40-days follow-up.

METHODS

Study population

Patients with confirmed COVID-19 referred for invasive CAG, irrespective of the clinical setting, between 15 February 2020 and 30 April 2020 in 9 hospitals with a 24/7 available cardiac catheterization laboratory in 2 European countries (Spain and The Netherlands) were studied. We included both patients with COVID-19 confirmed by reverse transcription–polymerase chain reaction (PCR) assays prior to invasive CAG and persons-under-investigation with subsequently PCR-confirmed COVID-19 diagnosis during hospitalization.

The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Interventional procedure analysis

Coronary angiograms were retrospectively analyzed by an experienced interventional cardiologist at each center. The procedure was performed using current recommendations. Safety measures and protection of healthcare workers during the invasive procedures were applied according to local protocols at each participating center[8]. Vascular access, use of intravascular imaging and stent type were left at operator´s discretion. Coronary artery flow at baseline and at the end of the procedure was assessed by the Thrombolysis In Myocardial Infarction (TIMI) frame count method[9]. The presence of coronary thrombus was reported and thrombus burden was graded from 0 to 5 according to the TIMI-thrombus scale[10]. High thrombus burden was defined as a TIMI-thrombus scale grade ≥4. Multivessel disease was defined as the presence of >1 vessel with luminal narrowing ≥50%. The use of thrombus aspiration was left at operator´s discretion. Both TIMI-flow and TIMI-thrombus scales were reassessed after thrombus aspiration. Angiographic no-reflow phenomenon was defined as a TIMI flow <3 without evidence of mechanical obstruction[11]. Angiographic success of the procedure was defined as a final TIMI 3 flow with residual stenosis <20% and no immediate mechanical complications. The anatomical synergy between percutaneous coronary intervention (PCI) with taxus and cardiac surgery (SYNTAX) score calculations were performed by an experienced interventional cardiologist at each site using the predefined SYNTAX score calculation definitions and algorithm. SYNTAX scores were calculated at baseline coronary angiograms before primary PCI, when performed, using a web-based calculator (www.syntaxscore.com). In patients presenting with ST-segment elevation myocardial infarction (STEMI), time points were defined according to current myocardial infraction guidelines[12]. Patient delay was specified as the time interval from the onset of symptoms until the emergency service number was dialed.

Door to balloon times were collected when appropriate, defining "door" time as the time of arrival at the PCI center and balloon time as the first intracoronary balloon inflation or reperfusion obtained by another device.

Data collection and follow-up

Demographic, clinical and laboratory data during admission were collected by study investigators from electronic medical records. COVID-19 severity at admission was graded according to the definitions proposed by the China Centers for Disease Control and Prevention: mild (non-pneumonia and mild pneumonia), severe (dyspnea, respiratory frequency ≥30 breaths/min, SpO2 ≤93%, PaO2/FiO2 <300, or lung infiltrates >50%), and critical (respiratory failure, septic shock, or multiple organ dysfunction or failure[13]. Data regarding COVID-19 pharmacological therapy during hospitalization were obtained. Outcome data at 30-days were collected from electronic clinical records. The primary endpoint of the study was the occurrence of MACE at 40-days, defined as a composite of all-cause mortality, non-fatal myocardial infarction (MI), stent thrombosis, target vessel revascularization or stroke. All deaths were considered cardiac unless another specific cause was documented. MI was defined according to current guidelines[14]. Target vessel revascularization and stent thrombosis were defined according to the Academic Research Consortium criteria[15]. If cases with stent thrombosis were subsequently complicated by a myocardial infarction, the event was defined as stent thrombosis.

Statistical analysis

Continuous variables are presented as either means ± standard deviation or medians with interquartile range as appropriate. Categorical variables were reported as frequencies and percentages. Kaplan-Meier analysis was performed to show the cumulative probability of MACE. Statistical analysis was performed using SPSS v23.0 (IBM, Armonk, New York).

RESULTS

A total of 57 patients with PCR-confirmed COVID-19 referred for invasive CAG during the study period and were included in the registry. Of them, 49 patients (94%) were referred to Spanish centers and 5 (6%) to Dutch centers. Baseline clinical characteristics are shown in Table 1. The mean age was 66±15 years and 47 patients (82%) were males. Comorbidities were often present: 18% had a previous MI, and 29% renal insufficiency and chronic obstructive pulmonary disease (COPD). ST-segment elevation was the most common electrocardiographic finding (58%). Overall, echocardiography prior to CAG was available in 42 patients (74%). A reduced left ventricular ejection fraction (LVEF) with regional wall motion abnormalities was often observed (33%). No echocardiographic abnormalities were observed in up to 19% of the cases. Of note, a takotsubo cardiomyopathy diagnosis was established in 1 case presenting with left ventricular apical ballooning with normal coronary arteries.

Regarding laboratory findings, elevated cardiac injury markers (troponin, creatine kinase) and inflammatory parameters (C-reactive protein; ferritin) were observed. Additionally, elevated levels of D-dimers and lymphopenia were present. COVID-19-related clinical characteristics are presented in Table 2.

COVID-19 diagnosis was confirmed after CAG in the majority of cases (86%). COVID-19 severity was classified as mild in 28 patients (49%); severe in 12 (23%) and critical in 16 (28%). Only 12 patients (21%) did not have typical COVID-19 symptoms at the time of CAG. The most common COVID-19 related symptoms at hospital admission were fever (51%), fatigue (27%) and dyspnea (27%). Of note, in 29/32 (81%) of patients who presented with STEMI, this was the first documented clinical manifestation of COVID-19. Three patients (5%) developed a systemic inflammatory response syndrome with subsequent distributive shock during hospitalization.

TABLE 1. Baseline clinical characteristics.

	COVID-19 patients referred for CAG n = 57
Age, years	66±15
Male, n (%)	47 (82)
Diabetes mellitus, n (%)	21 (37)
Hypertension, n (%)	38 (67)
Dyslipidemia, n (%)	29 (51)
History of smoking, n (%)	15 (26)
Family history coronary artery disease, n (%)	5 (12)
Body mass index, kg/m2	27±9
Previous myocardial infarction, n (%)	10 (18)
Previous PCI, n (%)	7 (12)
Previous CABG, n (%)	3 (5)
Renal insufficiency, n (%)	16 (29)
COPD, n (%)	16 (29)
Electrocardiographic findings, n (%)	
Normal electrocardiogram	10 (18)
ST-segment elevation	33 (58)
ST segment depression	5 (9)

TABLE 1. Baseline clinical characteristics. (*continued*)

	COVID-19 patients referred for CAG n = 57
Inverted T waves	6 (11)
Ventricular tachycardia/fibrillation	2 (4)
Q waves	4 (8)
Left bundle branch block	1 (2)
Echocardiogram available before CAG, n (%)	42 (74)
Echocardiographic findings, n (%)	
Normal LVEF, no regional wall motion abnormalities	8 (19)
Normal LVEF, regional wall motion abnormalities	12 (29)
Reduced LVEF, no regional wall motion abnormalities	3 (7)
Reduced LVEF, regional wall motion abnormalities	19 (45)
Medication	
Aspirin, n (%)	52 (93)
P2Y12 inhibitors, n (%)	50 (88)
Low molecular-weight heparin, n (%)	15 (26)
Oral anticoagulation, n (%)	8 (14)
Fibrinolytic agents, n (%)	2 (3)
ACE-I/ARB, n (%)	41(72)
β-Blockers, n (%)	31 (54)
Statins, n (%)	47 (82)
Laboratory findings	
Hemoglobin, g/dL	13.5±2.2
White blood cell count, × 10^9/L	10.3±4.8
Lymphocyte count, × 10^9/L	1.3±1.6
Platelet count, × 10^9/L	248±127
C-reactive protein, mg/L	12 (4.8-44.3)
Peak creatine kinase, IU/L	523 (135-32626)
Peak troponin T, ng/mL (20 patients)	2180 (138-4819)
Peak troponin I, ng/mL (32 patients)	12099 (661-32626)
Lactate dehydrogenase, u/L	343 (240-617)
Albumin, g/dl	0.38 (0.32-0.42)
Ferritin, ng/mL	789 (307-789)
D-dimers, ng/mL	900 (452-3019)
Prothrombin time, seconds	32.5±26.9
Interleukin 6, pg/mL	17.6±9.6
eGFR (mL/min/1.73 m2)	80 (68-89)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CAG = coronary angiography; COVID-19 = coronavirus disease 2019; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

TABLE 2. COVID-19 related clinical characteristics.

	COVID-19 patients referred for CAG n = 57
Timing COVID-19 diagnosis confirmation, n (%)	
Prior to CAG	8 (14)
After CAG	49 (86)
COVID-19 disease severity, n (%)	
Mild	28 (49)
Severe	17 (30)
Critical	12 (21)
Symptoms, n (%)	
Asymptomatic	12 (21)
Fever >37.3°C	28 (51)
Cough	21 (38)
Sputum	2 (4)
Myalgia	7 (13)
Fatigue	15 (27)
Shortness of breath	15 (27)
Diarrhea	2 (4)
Nausea/vomiting	3 (5)
Shock	3 (5)
Radiological findings, n (%)	
None	12 (21)
Consolidation	19 (34)
Ground-glass opacity	3 (5)
Bilateral pulmonary infiltration	21 (37)
Others	1 (2)
Pharmacological treatment, n (%)	
None	
Steroids	19 (34)
Lopinavir/ritonavir	17 (30)
Remdesivir	1 (2)
Hydroxychloroquine	35 (62)
Tocilizumab	1 (2)
Azithromycin	22 (39)
Others	10 (18)
Combination ≥2	26 (46)
Other treatment modalities, n (%)	
High-flow nasal cannula	9 (16)
Non-invasive mechanical ventilation	1 (2)
Invasive mechanical ventilation	1 (2)
ICU admission, n (%)	8 (14)
Median time ICU admission, days	2 (2-5)
Median time hospitalization, days	9.5 (4.2-17)

COVID-19 = coronavirus disease 2019; CAG = coronary angiography; ICU = intensive care unit.

Eight patients (14%) were admitted to the intensive care unit with a median stay of 2 (0-5) days. Median length of hospital stay of the entire cohort was 9.5 (4-17) days. COVID-19 pharmacological treatment was started in 43 patients (75%), being combinations of several agents used in up to 26 (46%), with a significant heterogeneity of treatment regimens as shown in Table 2. Hydroxychloroquine was widely used (61%), as well as lopinavir-ritonavir (30%). Only 2% of patients were treated with remdesivir or tocilizumab. Concomitant antibiotic therapy was prescribed in 17 patients (30%). Chest radiographic imaging was available in 44 patients (77%). Bilateral pulmonary infiltration was the most common radiological pattern, observed in 21 patients (38%). Unilateral consolidations were detected in 19 patients (34%), whereas diffuse ground-glass opacity was described in only 3 (5%).

Invasive CAG findings and procedural characteristics are presented in Table 3. The indication of CAG was widely established in the context of a suspected ACS, with STEMI being the most frequent indication (58%). A culprit lesion was identified in 45 (79%) patients, including 3 patients with >1 culprit lesion (Figure 1). Of them, 35/45 (78%) patients showed obvious angiographic thrombus, with high thrombus burden (defined as TIMI-thrombus scale grade ≥4) present in 19/45 (42%) patients. Importantly, in 3/45 (7%) patients, a stent thrombosis was identified as the culprit lesion. Thrombus aspiration was performed in 11/45 patients (24%), being used in the majority of cases (7/11) as the initial strategy. All patients treated with thrombus aspiration showed high thrombus burden. Thrombus aspiration resulted in an improvement of 2.2±1.6 TIMI-thrombus scale grades and 2.2±1.6 TIMI flow scale grades. Multivessel coronary disease was observed in 26 (46%) patients. Median SYNTAX score before and after revascularization was 13 (9-24) and 5 (0-17), respectively, reflecting the presence of low complexity coronary artery disease. Two major procedural complications were documented: a femoral bleeding requiring surgical repair and a coronary perforation treated with prolonged balloon inflation.

After a follow-up of 40 days, 16 patients (28%) experienced a MACE (Table 4). A total of 12 patients died, all of them during hospitalization: 11 (92%) died due to non-cardiac causes (9 because of refractory respiratory failure, 1 because of shock with multiorgan failure and 1 because of severe neurological damage after reanimation) and 1 patient died due to electrical storm. One patient suffered a non-fatal myocardial infarction, treated conservatively. Two patients presented stent thrombosis (1 intraprocedural in a stent implanted in the left anterior descending artery; 1 in the proximal left circumflex 30 minutes after PCI requiring percutaneous treatment) with subsequent myocardial infarction. One patient experienced a stroke (Figure 2).

TABLE 3. Procedural and angiographic characteristics.

	COVID-19 patients referred for CAG n = 57
Indication for CAG, n (%)	
Progressive angina	2 (3)
NSTEMI	18 (32)
STEMI	33 (58)
Cardiac arrest	2 (3)
Echocardiographic reduced LVEF/wall motion abnormalities	2 (3)
Anginal complains before CAG, n (%)	37 (64)
Systolic arterial blood pressure, mmHg	116±22
Need of inotropics/vasopressors, n (%)	9 (16)
Need of ventricular assist device, n (%)	1 (2)
Multivessel coronary artery disease, n (%)	24 (42)
Culprit artery identified, n (%)	45 (79)
Culprit artery type, n (%)	
Left main artery	1 (2)
Left anterior descending artery	19 (33)
Left circumflex artery	6 (10)
Right coronary artery	15 (26)
Bypass graft	1 (2)
>1 culprit lesion	3 (5)
Stent thrombosis as culprit lesion, n (%)	3/45 (7)
Presence of coronary thrombus, n (%)	35/45 (78)
TIMI-thrombus grade	3.3±1.6
TIMI-thrombus grade ≥ 4, n (%)	19/45 (42)
Baseline TIMI flow	1.4±1.3
PCI performed, n (%)	41/45 (91)
Thrombus aspiration, n (%)	11/45 (24)
Number of stents implanted	1.1±0.8
Stent length, mm	31.2±15.6
Stent diameter, mm	3.2±0.4
Final TIMI flow	2.8±0.6
No-reflow phenomenon, n (%)	3/45 (7)
Successful PCI, n (%)	39/41 (95)
SYNTAX score pre-PCI	13 (9-24)
SYNTAX score post-PCI	5 (0-17)
Time from CAG indication to cath-lab arrival, min	60 (20-4320)
Total ischemic time, min	115 (69-270)
Door-to-balloon time (in STEMI cases), min	40.9±27.3

CAG = coronary angiography; COVID-19 = coronavirus disease 2019; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; NSTEMI = non-ST segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

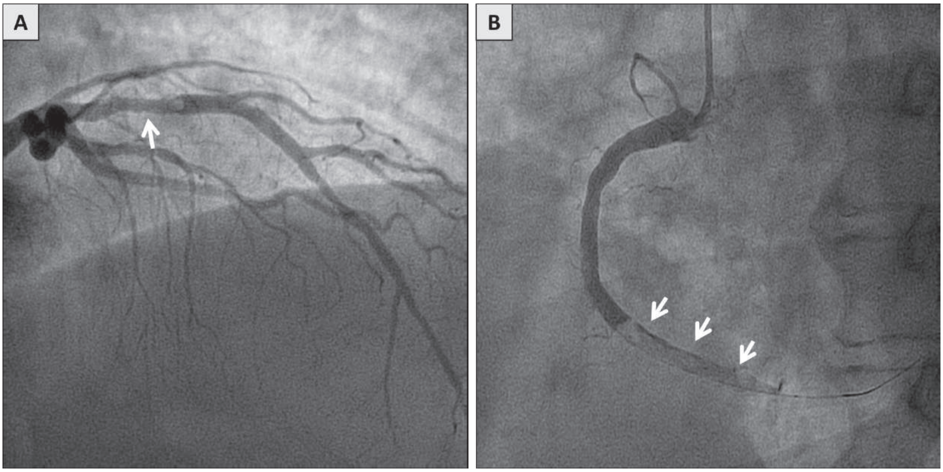

Figure 1. Example of COVID-19 patient presenting with ST-elevation myocardial infarction, in whom two culprit lesions with high thrombus burden were identified on coronary angiography, located at the proximal left anterior descending artery (panel A, arrow) and distal right coronary artery (panel B, arrows).

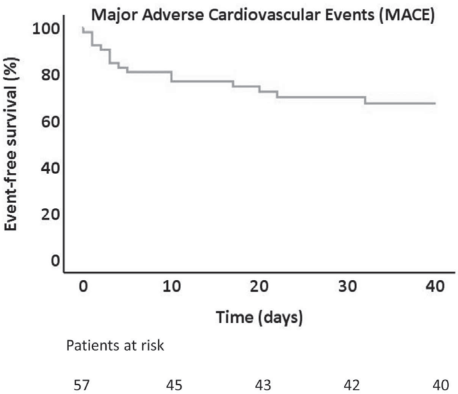

Figure 2. Kaplan-Meier cumulative incidence of MACE of COVID-19 patients from invasive coronary angiography performance.

DISCUSSION

The main findings of the present descriptive study are: 1) the most common indication for CAG in COVID-19 patients during outbreak's first wave was STEMI, representing 58% of the cases. 2) Patients referred for CAG were predominantly males and had often comorbidities (previous MI 18%, renal insufficiency 29%, COPD 29%). 3) COVID-19 diagnosis was confirmed prior to CAG in only 14% of the cases. 4) COVID-19 severity was predominantly non-critical; 21% of patients asymptomatic at the time of CAG. 5) A culprit lesion was identified in the majority of cases (79%) (often associated with a high thrombus load); stent thrombosis was detected in 7%; however, the complexity of coronary artery disease assessed by SYNTAX score was low (13 [9-24]).

5) The incidence of MACE at 40-days follow-up was very high (28%), mostly due to non-cardiac death (11/12 deaths, 68% of total MACE), of note, 3 patients presented with thrombotic events (2 stent thrombosis and 1 stroke).

The decrease of STEMIs worldwide during the COVID-19 pandemic has been extensively reported, showing up to a 42-48% reduction in hospitalizations for ACS and a 38-40% reduction in primary PCI for STEMI in areas with high COVID-19 prevalence[16, 17]. Nevertheless, STEMI remained the main indication for invasive CAG in our study. Despite the observed heterogeneity of CAG indication, CAG was ultimately indicated due to a suspected acute coronary event in the majority of patients regardless of the clinical presentation. However, in 21% of patients no evident culprit coronary lesion was observed. Interestingly, 17% of patients referred for CAG because of STEMI did not show an evident culprit lesion. In those patients presenting with an indication other than STEMI, no culprit lesion was identified in 27%. In a study comprising 28 COVID-19 patients with STEMI referred for CAG, Stefanini et al. reported the absence of a culprit coronary lesion in 39.3%[18]. This illustrates the particular challenges of ACS diagnosis in COVID-19 patients. As observed in our study, elevated cardiac biomarkers, electrocardiographic changes suggesting ischemia and/or echocardiographic abnormalities (reduced LVEF and/or regional wall motion abnormalities) are often present and may not necessarily be linked to a coronary event. Elevated cardiac troponins are frequently detected in COVID-19 patients, often secondary to a broad spectrum of non-coronary etiologies, such as non-specific myocardial injury, myocarditis, pulmonary embolism[19] or takotsubo syndrome[6] (which was found in 1 patient in our cohort). Myocardial injury is more frequent in critically ill patients with COVID-19, especially in those with previous comorbidities, and is independently associated with a high mortality[1, 2]. Indeed, comorbidities were frequently present in our study cohort (previous MI 18%, renal insufficiency 29%, COPD 29%). However, almost 50% had mild severity COVID-19. It has been shown that ACS in COVID-19 patients may occur in the absence of a severe systemic inflammation, being STEMI reported as the first clinical manifestation of COVID-19[18, 20].

Importantly, up to 21% patients of our study cohort were completely asymptomatic for COVID-19 at the time of CAG. Furthermore, only 14% of the patients had a confirmed COVID-19 diagnosis before being referred to the catheterization laboratory. This highlights the need of establishing strategies to effectively identify patients who may benefit from an invasive approach and avoid unnecessary procedures with subsequent risk of contagion among catheterization laboratory personnel.

COVID-19 is linked to a multifactorial prothrombotic state, resulting from the hyper-inflammatory state, endothelial dysfunction and hemostatic abnormalities[21]. A high rate of both venous and arterial thrombotic events has been described[22, 23]. Similarly to other viral infections, COVID-19 may trigger an ACS by different mechanisms, such as plaque rupture, coronary spasm or microthrombi[3]. Direct viral endothelial injury may trigger thrombus formation and subsequently ACS[24]. This prothrombotic state is translated angiographically in a high thrombus burden (42% TIMI thrombus grade ≥4), stent thrombosis as culprit lesion (7%) and even involvement of several coronary vessels (5%, Figure 1), typically associated with a low complex underlying coronary artery disease phenotype (SYNTAX pre-PCI 13 [9-24]). Similarly, Choudry et al. reported a high rate of intracoronary thrombus burden (grade 4-5, 84%), multivessel thrombosis (17.9%) and stent thrombosis (10%) in a cohort of 39 patients with COVID-19 presenting exclusively with STEMI[23].

Finally, it is important to elucidate the high incidence of MACE at 40-days follow-up (28%, Figure 2) in spite of having performed a successful PCI in 95% of patients without significant delays. The most frequent adverse event was non-cardiac death (11/12 deaths, 68% of total MACE), mostly due to respiratory and systemic involvement. Of note, 3 patients presented thrombotic events: 2 stent thrombosis (4.8%), and 1 stroke (1.7%).

LIMITATIONS

The main limitations of this study are its observational and retrospective design and its small sample size. Lack of a control group of non-COVID-19 patients prevents drawing definitive conclusions, and therefore the results cannot be generalized. However, the present study presents information regarding angiographic and clinical features of COVID-19 patients referred for CAG irrespective of the indication. This provides an overview of the potential value of an invasive approach in this clinical scenario.

CONCLUSION

In a European multicenter registry, patients with confirmed COVID-19 infection referred for CAG during the first wave of the SARS-CoV2 pandemic presented mostly with STEMI and were predominantly male, often with comorbidities. COVID-19 severity was in general non-critical, with 21% of asymptomatic patients at the time of CAG. Culprit coronary lesions with high thrombus burden were frequently identified, with a rate of stent thrombosis of 7%. The incidence of MACE at 40-days follow-up was high (28%), mostly due to non-cardiac death.

DISCLOSURES

The authors declare that there is no conflict of interest related to this manuscript.

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7

Summary, conclusions and future perspectives
Nederlandse samenvatting
Dankwoord
List of publications
Curriculum vitae

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

The aim of this thesis was to provide new insight about the the role of invasive coronary angiography for risk stratification in patients presenting with myocardial infarction in specific clinical scenarios. The proposed methods for angiographic characterization of certain angiographic features, such atrial coronary branches or coronary ectasia, will hopefully contribute to a better understating of its prognostic implications in particular patients subsets.

Part I of this thesis focuses on the clinical impact of atrial ischemia resulting from coronary flow impairment of the coronary atrial branches in patients presenting with acute myocardial infarction.

In **chapter 2,** we assessed the frequency of coronary atrial branch occlusion complicating a primary percutaneous coronary intervention in patients with acute myocardial infarction and its impact in the occurrence of atrial arrythmias. We included 900 patients who underwent a primary percutaneous coronary interventions in a coronary segment involving the origin of an atrial branch. Patients were followed up for a year, including 24-hour Holter ECG at 3 and 6 month. Procedural-related coronary atrial branch occlusion was observed in 18 (5%) individuals). During 1-year follow-up, 33% of patients with procedural-related atrial branch occlusion presented atrial arrhythmias, as compared with 55% in those with a patent atrial branch (P=0.088). On multivariate analysis, age, no previous history of myocardial infarction and a reduced flow in the culprit vessel were found to be only independent correlates of atrial arrhythmias. Importantly, in patients who underwent a follow-up coronary angiography, the majority of the atrial branches lost during primary percutaneous coronary interventions were patent.

Chapter 3 focused on the impact of coronary flow limitation in the most developed coronary atrial branch, introducing for the first time the term of "atrial coronary dominance", and evaluating its potential role in the development of atrial arrythmias at one year follow-up. The concept of dominant atrial branch emerges from the concept that theamount of myocardial mass supplied by a given coronary artery is proportional to the anatomical and morphometric characteristics of the artery (such as vessel volume, length and diameter), larger atrial myocardium territories will be perfused by larger atrial coronary arteries. We hypothesized that flow impairment in the largest coronary atrial branch may consequently impact the integrity of a significant amount of atrial myocardium, leading to the occurrence of atrial arrhythmias. A dominant CAB was identified in 897 of 900 patients with ST-segment elevation myocardial infarction. A reduced coronary flow (TIMI<3) in the dominant CAB was present in 69 (8%) patients. Compared to those with dominant CAB preserved flow, patients with dominant CAB flow impairment presented with higher levels of troponin T (3.9 [2.2-8.2] vs. 3.1 [1.3-5.8], P=0.008) and higher rates of atrial tachycardia at 3 months (68% vs. 37%, P= 0.007) and more supraventricular ectopic beats both at 3 months (58 [21-235] vs. 33 [12-119], P=0.02) and at 6 months (62 [24-156] vs. 32 [12-115];P=0.04) on 24-hour Holter ECG. Age and an impaired coronary flow at the dominant CAB were independently related to a higher risk of developing atrial arrhythmias at 1-year follow-up. Based on the observed results, we concluded dominant CAB flow impairment in patients presenting with acute myocardial infarction is infrequent but it is associated with the occurrence of atrial arrhythmias, in the form atrial tachycardia and supraventricular ectopic beats, at follow-up.

In **chapter 4**, we evaluated the effects of atrial ischemia - resulting from coronary flow limitation in the dominant coronary atrial branch- in both functional and structural remodelling of the left atrium (LA), by using serial advanced echocardiography techniques. For this purpose, we retrospectively analysed 897 patient with acute myocardial infarction treated with primary PCI. Of them, 69 patients showed and impaired coronary flow in the dominant CAB (defined as TIMI flow<3) and were compared to a matched control group of 138 patients with normal dominant CAB coronary flow. LA remodeling assessment included maximum LA volume, speckle tracking echocardiography-derived LA strain and total atrial conduction time assessed by tissue Doppler imaging (PA-TDI) at baseline, 6 and 12 months. Patients with dominant CAB-impaired flow presented larger LA maximal volumes (26.9±10.9 vs.18.1±7.1 ml/m2,p<0.001) and longer PA-TDI (150±23 vs.124±22 msec., p<0.001) at 6-months, remaining unchanged at 12-months. However, all LA strain parameters were significantly lower from baseline (reservoir 20.3±10.1% vs.27.1±14.5%,p<0.001;conduit 9.1±5.6% vs.12.8±8%,p<0.001; booster 9.1±5.6% vs.12.8±8%, p<0.001),being these differences sustained at 6- and 12-months follow-up. Our results show that atrial ischemia resulting from an impaired coronary flow in the dominant CAB in patients with STEMI is associated with LA adverse anatomical and functional remodeling. We described as well the timeline of the LA remodeling resulting from atrial ischemia n this scenario, in which LA functional remodeling (reduced LA strain) preceded LA anatomical remodeling in early phases after STEMI.

Part II of this thesis focuses on the evaluation of the prognostic value of coronary angiography in acute myocardial infarction in specific scenarios.

Chapter 5 focused in patients with coronary artery ectasia presenting with acute coronary syndromes, providing a systematic angiographic phenotypical classification and evaluating its impact in the occurrence of major cardiovascular events. Coronary artery ectasia(CAE) is described in 5% of patients undergoingcoronary angiography. We retrospectively evaluated 4788 patients presenting with acute myocardial infarction and referred for urgent coronary angiography. The presence of CAE was confirmed in 174 (3.6%) patients, being present in the culprit vessel in 79.9%. Multivessel CAE was frequent (67%). CAE patients were more frequently male, had highthrombusburden and were treated more often withthrombectomyand less often was stent implantation. Markis I was the most frequent angiographic phenotype (43%). During a median follow-up of 4 years (1-7), 1243 patients (26%) experienced a major adverse cardiovascular event (MACE): 282 (6%) died from a cardiac cause, 358 (8%) had a myocardial infarction, 945 (20%) underwent coronary revascularization and 58 (1%) presented with a stroke. Patients with CAE showed higher rates of MACE as compared to those without CAE (36.8% versus 25.6%; p <0.001). On multivariable analysis, CAE was associated with MACE (HR 1.597; 95% CI 1.238-2.060; p <0.001) after adjusting for risk factors, type of AMI and number of narrowedcoronary arteries. In conclusion, the prevalence of CAE in patients presenting with AMI is relatively low but was independently associated with an increased risk of MACE at follow-up. The design of the study and the relatively small sample size prevent us from drawing any conclusion regarding the benefit of the different treatment strategies. Further studies are needed to: 1) Understand the underlying mechanisms leading to CAE and its natural course; 2) stratify the risk of developing major adverse events; 3) identify and homogenise the therapeutical strategy (technical, pharmacological) in patients requiring percutaneous interventions.

Finally, in **Chapter 6** we evaluated the angiographic and clinical profile of patients with COVID-19 referred for invasive coronary angiography from an international registry during outbreak's first wave, analysing as well the prognosis of this specific population. We found that the most common indication for coronary angiography in COVID-19 patients was STEMII, representing 58% of the cases. Patients referred for coronary angiography were predominantly males and had often comorbidities. COVID-19 severity was in general non-critical, with 21% of asymptomatic patients at the time of CAG. Culprit coronary lesions with high thrombus burden were frequently identified, with a rate of stent thrombosis of 7%. The incidence of MACE at 40-days follow-up was high (28%), mostly due to non-cardiac death.

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SAMENVATTING EN TOEKOEMSTPERSPECTIEF

Het doel van dit proefschrift was om nieuwe inzichten te verschaffen over de rol van invasieve coronaire angiografie voor risicostratificatie bij patiënten met een myocardinfarct in specifieke klinische scenario's. De voorgestelde methoden voor angiografische karakterisering van bepaalde angiografische kenmerken, zoals atriale coronaire vertakkingen of coronaire ectasie, zullen hopelijk bijdragen tot een beter onderschatting van de prognostische implicaties in bepaalde subgroepen van patiënten.

Deel I van dit proefschrift richt zich op de klinische impact van atriale ischemie als gevolg van coronaire stroomstoornissen van de coronaire atriale takken bij patiënten met een acuut myocardinfarct.

In **hoofdstuk 2,** we hebben de frequentie beoordeeld van occlusie van de atriale kransslagader die een primaire percutane coronaire interventie compliceert bij patiënten met een acuut myocardinfarct en de impact ervan op het optreden van atriale aritmieën. We includeerden 900 patiënten die primaire percutane coronaire interventies ondergingen in een coronair segment waarbij de oorsprong van een atriale tak betrokken was. Patiënten werden gedurende een jaar gevolgd , inclusief 24-uurs Holter-ECG na 3 en 6 maanden. Procedure gerelateerde occlusie van de atriale kransslagader werd waargenomen bij 18 (5%) individuen. Tijdens de 1-jaars follow-up vertoonde 33% van de patiënten met procedure-gerelateerde occlusie van de atriale tak atriale aritmieën, in vergelijking met 55% van de patiënten met een patente atriale tak (P=0,088). Bij multivariate analyse bleken leeftijd, geen voorgeschiedenis van een myocardinfarct en een verminderde doorstroming in het vat van deculprit vat onafhankelijke geassioceerd te zijn van atriale aritmieën. Belangrijk is dat bij patiënten die een follow-up coronaire angiografie ondergingen, de meerderheid van de atriale takken die tijdens primaire percutane coronaire interventies verloren gingen, open waren.

Hoofdstuk 3 concentreerde zich op de impact van coronaire stroombeperking in de meest ontwikkelde coronaire atriale tak, waarbij voor het eerst de term "atriale coronaire dominantie" werd geïntroduceerd en de potentiële rol ervan in de ontwikkeling van atriale aritmieën na een jaar follow-up werd geëvalueerd. Het concept van dominante atriale vertakking komt voort uit het concept dat de hoeveelheid myocardmassa die door een bepaalde kransslagader wordt geleverd, evenredig is met de anatomische en morfometrische kenmerken van de slagader (zoals vatvolume, lengte en diameter) worden geperfundeerd door grotere atriale kransslagaders. Onze hypothese was dat stoornissen in de doorstroming in de grootste coronaire atriale tak e integriteit van een aanzienlijk deel van het atriale myocard kunnen aantasten, wat kan leiden tot het optreden van atriale aritmieën. Een dominante CAB werd geïdentificeerd bij 897 van de 900 patiënten met een myocardinfarct met ST-segmentstijging. Een verminderde coronaire flow (TIMI<3) in de dominante CAB was aanwezig bij 69 (8%) patiënten. Vergeleken met patiënten met dominante CAB-geconserveerde flow, vertoonden patiënten met dominante CAB-flowstoornis hogere niveaus van troponine T (3,9 [2,2-8,2] vs. 3,1 [1,3-5,8], P=0,008) en hogere percentages atriale tachycardie op 3 maanden (68% vs. 37%, P= 0,007) en meer supraventriculaire ectopische slagen zowel na 3 maanden (58 [21-235] vs. 33 [12-119], P=0,02) als na 6 maanden (62 [24 -156] vs. 32 [12-115];P=0,04) op 24-uurs Holter ECG. Leeftijd en een verminderde coronaire flow bij de dominante CAB waren onafhankelijk gerelateerd aan een hoger risico op het ontwikkelen van atriale aritmieën na 1 jaar follow-up. Op basis van de waargenomen resultaten concluderen we dat een dominante CAB-stroomstoornis bij patiënten met een acuut myocardinfarct niet vaak voorkomt, maar wel geassocieerd is met het optreden van atriale aritmieën, in de vorm van atriale tachycardie en supraventriculaire ectopische slagen, bij de follow-up.

In **hoofdstuk 4** evalueerden we de effecten van atriale ischemie - als gevolg van coronaire stroombeperking in de dominante coronaire atriale tak - op zowel functionele als structurele remodellering van het linker atrium (LA), door gebruik te maken van geavanceerde echocardiografietechnieken. Voor dit doel analyseerden we retrospectief 897 patiënten met een acuut myocardinfarct behandeld met primaire PCI. Van hen vertoonden 69 patiënten een verminderde coronaire flow in de dominante CAB (gedefinieerd als TIMI flow <3) vergeleken met een gematchte controlegroep van 138 patiënten met een normale dominante CAB coronaire flow. Beoordeling van LA-remodellering omvatte maximaal LA-volume, speckle-tracking-echocardiografie-afgeleide LA-stam en totale atriale geleidingstijd beoordeeld door tissue Doppler-beeldvorming (PA-TDI) bij baseline, 6 en 12 maanden. Patiënten met dominante CAB-gestoorde flow vertoonden grotere LA maximale volumes (26,9 ± 10,9 vs. 18,1 ± 7,1 ml/m2, p < 0,001) en langere PA-TDI (150 ± 23 vs. 124 ± 22 msec., p < 0,001) na 6 maanden maaronveranderd waren na 12 maanden. Alle parameters voor LA-stam waren echter significant lager ten opzichte van de uitgangswaarde (reservoir 20,3 ± 10,1% vs. 27,1 ± 14,5%, p < 0,001; conduit 9,1 ± 5,6 % vs. 12,8 ± 8 %, p < 0,001; booster 9,1 ± 5,6 % vs. .12,8±8%, p<0,001) , aangezien deze verschillen aanhielden na 6 en 12 maanden follow-up. Onze resultaten tonen aan dat een proefischemie als gevolg van een verminderde coronaire stroom in de dominante CAB bij patiënten met STEMI geassocieerd is met ongunstige anatomische LA en functionele remodellering. We beschreven ook de tijdlijn van de LA-remodellering als gevolg van atriale ischemie in dit scenario, waarin LA functionele remodellering (verminderde LA-stam) voorafging aan LA anatomische remodellering in vroege fasen na STEMI.

Deel II van dit proefschrift richt zich op de evaluatie van de prognostische waarde van coronaire angiografie bij acuut myocardinfarct in specifieke scenario's.

Hoofdstuk 5 concentreerde zich op patiënten die zich presenteerde met acute coronaire syndromen met coronaire arterie-ectasie , door een systematische angiografische fenotypische classificatie te geven en de impact ervan op het optreden van ernstige cardiovasculaire gebeurtenissen te evalueren. Coronaire arterie-ectasie (CAE) wordt beschreven bij 5% van de patiënten die een coronaire angiografie ondergaan . We evalueerden retrospectief 4788 patiënten met een acuut myocardinfarct en verwezen voor urgente coronaire angiografie. De aanwezigheid van CAE werd bevestigd bij 174 (3,6%) patiënten, aanwezig in de culprit bij 79,9%. Multivessel CAE kwam frequent voor (67%). CAE-patiënten waren vaker mannelijk, hadden een hoge trombusbelasting en werden vaker behandeld met trombectomie en minder vaak met stentimplantatie. Markis I was het meest voorkomende angiografische fenotype (43%). Tijdens een mediane follow-up van 4 jaar (1-7) ervoeren 1243 patiënten (26%) een ernstige cardiovasculaire gebeurtenis (MACE): 282 (6%) overleden aan een cardiale oorzaak, 358 (8%) hadden een myocardinfarct., 945 (20%) ondergingen coronaire revascularisatie en 58 (1%) kregen een beroerte. Patiënten met CAE vertoonden hogere percentages MACE in vergelijking met degenen zonder CAE (36,8% versus 25,6%; p <0,001). Bij multivariabele analyse was CAE geassocieerd met MACE (HR 1,597; 95% BI 1,238-2,060; p < 0,001) na correctie voor risicofactoren, type AMI en aantal vernauwde kransslagaders . Concluderend, de prevalentie van CAE bij patiënten met AMI is relatief laag, maar was onafhankelijk geassocieerd met een verhoogd risico op MACE bij follow-up. Door de opzet van het onderzoek en de relatief kleine steekproefomvang kunnen we geen conclusies trekken over het voordeel van de verschillende behandelstrategieën. Verdere studies zijn nodig om: 1) te te begrijpen de onderliggende mechanismen die leiden tot CAE en het natuurlijke verloop ervan; 2) te stratificeren het risico op het ontwikkelen van ernstige cardiovasculair events; 3) te identificeren de meest adequaat therapeutische strategie (technisch, farmacologisch) bij patiënten die percutane interventies nodig hebben.

Ten slotte evalueerden we in **Hoofdstuk 6** het angiografisch en klinisch profiel van patiënten met COVID-19 die tijdens de eerste golf van de uitbraak waren doorverwezen voor invasieve coronaire angiografie vanuit een internationaal register, waarbij we ook de prognose van deze specifieke populatie analyseerden. We ontdekten dat de meest voorkomende indicatie voor coronaire angiografie bij COVID-19-patiënten

STEMII was, wat neerkomt op 58% van de gevallen. Patiënten die werden doorverwezen voor coronaire angiografie waren voornamelijk mannen en hadden vaak comorbiditeiten. De ernst van COVID-19 was over het algemeen niet kritiek, met 21% van de asymptomatische patiënten ten tijde van CAG. Oorzaken van coronaire laesies met een hoge trombusbelasting werden vaak vastgesteld, met een percentage stenttrombose van 7%. De incidentie van MACE na 40 dagen follow-up was hoog (28%), voornamelijk als gevolg van niet-cardiale dood.

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LIST OF PUBLICATIONS

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CURRICULUM VITAE

José M. Montero Cabezas was born on December 3 1983 in Badajoz (Spain). After graduating at the Zurbarán secondary school in Badajoz, he started his studies of medicine at the School of Medicine of the University of Extremadura, where he graduated in 2007. In 2008, he successfully passed the M.I.R exam and joined the prestigious cardiology training program at the "12 de Octubre" University Hospital (Complutense University of Madrid), where he became a cardiologist in May 2013. During his residency, he completed his training with a three-month stage at the Center for Arrythmia Research of the University of Michigan (Ann Arbor, United States). In 2013, he won the Spanish Society of Cardiology grant for a one-year training fellowship in interventional cardiology, which he underwent at the Leiden University Medical Center (LUMC) under the supervision of Prof. dr. Martin Schalij. After completing two years of fellowship, he obtained a position as a staff member of the Cardiology department at the LUMC, where he still works. Since his arrival at the LUMC in July 2013, José has been actively involved in complex clinical scenarios requiring different modalities of invasive techniques, as well as in the development of multidisciplinary teams. His special interest in cardiogenic shock and the use of different mechanical support devices and in invasive techniques for the treatment of pulmonary embolism, lead to the introduction and standardization of novel treatment options at the LUMC. He is co-founder and core member of the institutional Shock/ECMO Team, focused on the treatment of cardiogenic shock patients, and the *Acute Longembolie Response Team* (ALERT), focused on patients with severe pulmonary embolism. José is also involved in the treatment of complex coronary artery disease substrates, with special focus in coronary total occlusions and calcific coronary artery disease. Furthermore, he is an active member of the local structural cardiac interventions program, with special interest in transcatheter aortic valve implantation. The main interest of his research has been the use of coronary angiography and multimodality imaging techniques in ischemic heart disease under the supervision of Dr. Victoria Delgado and Prof. Jeroen Bax, which is the focus of this thesis. The results of his research have been presented in different international conferences. In addition, he participates in research projects on complex coronary interventions, extracorporeal membrane oxygenation (ECMO) and other modalities of mechanical circulatory support and pulmonary embolism, being local principal investigator of several national and international trials. In the last years, Jose has complemented his education with a master degree in healthcare management and administration (CEU University, Spain) and a 1-year postgraduate program in clinical research at Harvard Medical School (United States).