Non-invasive cardiac imaging of coronary artery anomalies

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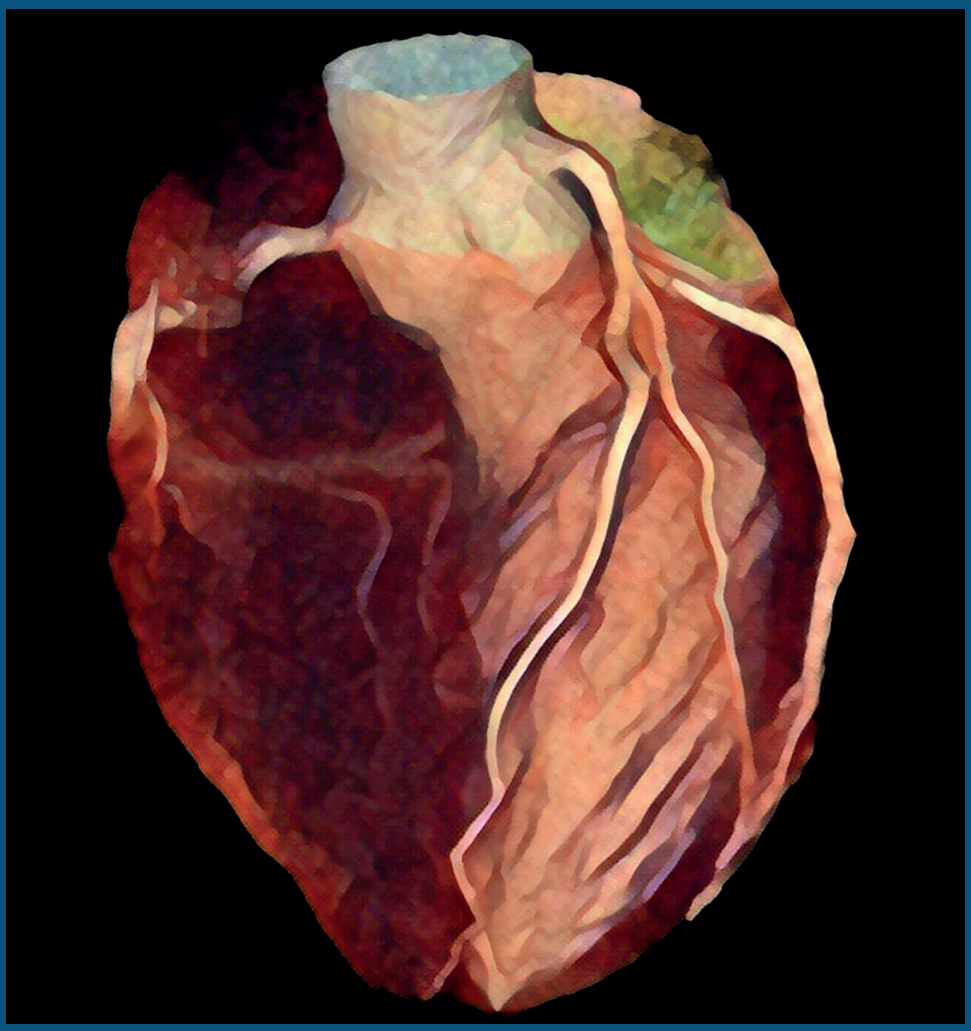

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Non-invasive cardiac imaging of coronary artery anomalies

DISSERTATION

To obtain the degree of Doctor at Maastricht University,
on the authority of the Rector Magnificus
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in accordance with the decision of the Board of Deans,
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Contents

Part I

Introduction

OVERVIEW

Coronary artery anomalies represent a group of congenital disorders with an anomalous location of a coronary ostium, an anomalous course or an anomalous termination of a coronary artery. The prevalence of coronary artery anomalies in the general population is estimated to be around 1% (1-4). Although most individuals with coronary artery anomalies remain undetected as their disease course is clinically insignificant, some individuals, and especially those with an anomalous coronary artery from the opposite sinus of Valsalva (ACAOS), may become symptomatic and experience adverse cardiac events. Several anatomic high-risk features have been described in ACAOS patients. These include interarterial course (IAC) between the aorta and pulmonary artery, an intramural course, a slit-like ostium, an acute take-off angle or a proximal narrowing of the anomalous vessel and are considered to be of special interest due to their predisposition to myocardial ischemia, heart failure, ventricular arrhythmias, and sudden cardiac death (SCD) (1, 5-8). Other coronary artery anomalies include high take-off from the aorta, duplication of coronary arteries or absent left main stem with separate ostium for left anterior descending coronary artery and left circumflex coronary artery, which are rather normal variations without clinical significance in the majority (1).

CORONARY ARTERY ANOMALIES AND CURRENT RECOMMENDATIONS

In particular, young athletes with ACAOS are considered to be at risk for sports-related SCD (5-8). Autopsy series showed that after hypertrophic cardiomyopathy, ACAOS is the second most common underlying cause of sports-related SCD in young competitive athletes during or shortly after strenuous exercise and are believed to be the cause of up to one third of SCD in US army recruits (8-10). In addition to young athletes, an increasing number of coincidentally detected ACAOS is found in the middle-aged and elderly population as the use of non-invasive imaging for the exclusion of coronary artery disease (CAD) is increasing. Currently, guidelines regarding diagnostic evaluation, sport restriction and treatment of ACAOS are lacking Although some recommendations exist, they are inconsistent and are debatable. Recommendations range from a surgical approach in the vast majority of patients to a watchful waiting approach with sports restriction in the remainder. However, optimal diagnostic and therapeutic strategies for anomalous coronary arteries are lacking because of a lack of scientific evidence and guidelines. Therefore, indications for surgical correction remain controversial in certain cases and besides the clinical evaluation, non-invasive imaging techniques in assessing and guidance for the treatment of individuals with ACAOS might be even more important in the future.

CORONARY ARTERY ANATOMY

Formerly, the coronary arteries were considered outgrowths of the aortic root. However, in the most recent decade, evidence was brought up that coronary endothelial precursors self-organize in the subepicardial space (see Figure 1) and form a vascular plexus that only in later stages (of embryological development) connects to the aorta (11) (see Figure 2). Different genes, vascular endothelial growth factor availability, coronary arterio-venous growth coordination, and the vascular density around the aortic trunk, which is modulated by hypoxic domains, are involved in the correct connection between the distal coronary artery parts and the proximal aortic root parts (4).

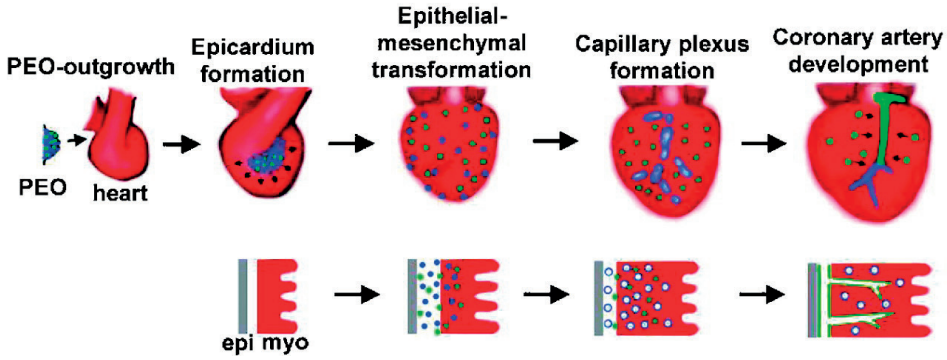

Figure 1: Movement of the proepicardial organ (PEO) to and over the heart is shown in the top panel, and mesenchymal migration and differentiation are shown in the bottom panel. The PEO (blue) is an outgrowth from the dorsal body wall that moves to the looping heart (red). Next, migrating epithelium is seen spreading over the heart. In cross section, the epithelium is a single cell layer. Epithelial/mesenchymal transition provides cells that migrate into the myocardium. Vasculogenic cells differentiate and link to form plexi that induce other mesenchymal cells to become smooth muscle. These plexi are remodeled into definitive arteries, and the most proximal points of the major coronaries finally link up with the aorta. (Adapted from Reese DE et al. Development of the coronary vessel system. Circ Res. 2002 Nov 1;91(9):761-8).

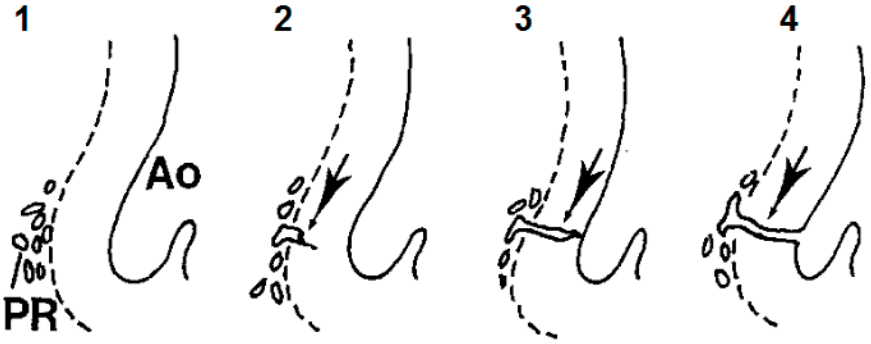

Figure 2: Schematic representation of proximal coronary artery development. 1: Half aortic root (Ao) with no coronary orifices. The peritruncal ring (PR) is already present. 2: Half aortic root with coronary artery (arrow) penetrating the aortic wall out of the peritruncal ring. 3: Half aortic root with coronary artery penetrating the

complete aortic wall, except for the aortic intimal lining. 4: Half aortic root with completely developed coronary artery, (Adapted from Bogers AJ et al. Development of the origin of the coronary arteries, a matter of ingrowth or outgrowth? (Anat Embryol (Berl). 1989;180(5):437-41).

Anatomic high-risk features of coronary artery anomalies

Two variants of ACAOS are considered clinically important: R-ACAOS (anomalous right coronary artery originating from the left coronary sinus) and L-ACAOS (anomalous left coronary artery originating from the right coronary sinus). R-ACAOS are more prevalent than L-ACAOS (12), however, it was previously thought that mainly L-ACAOS were the sole cause of SCD, because a larger amount of myocardium is potentially at risk for arrhythmia (13). Recently, several reports showed that SCD also occurs in patients with underlying R-ACAOS (4, 14). An important high-risk anatomic feature is an IAC, where the anomalous vessel is coursing between the aorta and the pulmonary artery (also called the "malignant" variant) (15). Retroaortic course (anomalous vessel between the left atrium and the aorta), prepulmonic (anomalous vessel ventral to the pulmonary artery) and anomalous vessels originating from the non-coronary sinus are considered as less critical variants (16). Other high-risk anatomic features besides the IAC and the slit-like ostium are an acute take-off angle (<45°), intramural course (anomalous vessel within the tunica media of the aortic wall) and an elliptical vessel shape (defined as height/width ratio of >1.3 of the anomalous vessel) and proximal vessel narrowing of the anomalous vessels (>50% narrowing of the cross-section vessel area compared to the distal part) (17-19).

Underlying mechanisms of adverse cardiac events in patients with coronary artery anomalies

The underlying mechanism of SCD in individuals with ACAOS is unknown, but several hypotheses exist. During exercise, the cardiac output increases and can change the geometry of the anomalous coronary artery. This is a consequence of aortic dilatation and dynamic mechanical compression of the intramural and interarterial segments. Furthermore, the intramural course leads to a segmental hypoplasia with a proximal narrowing compared to the distal part of the anomalous vessel. An elliptic vessel shape of the proximal part is sought to be the consequence of an asymmetrical lateral compression of the anomalous vessel in the intramural course during systole leading to cardiac ischemia (1, 4, 20). Further discussed mechanism are valve-like obstruction of the slit-like ostium, coronary kinking during exercise of ACAOS with acute angulation of the arterial take-off and proximal spasm or extreme tachycardia during exercise, resulting to ischemic arrhythmias (21). A very rare but lethal anomaly presenting almost only in early infancy is the anomalous origin of the left coronary artery arising from the pulmonary artery (ALCAPA, or Bland-White Garland syndrome). In this anomaly, extensive

collaterals develop between the right and left coronary arterial systems and over time the flow reverses causing myocardial ischemia and congestive heart failure due to hypo-perfused myocardium (22).

AIM OF THIS THESIS

I focused my research on coronary artery anomalies and the role of non-invasive cardiac imaging in these patients. This thesis should provide insight in the complexity of coronary artery anomalies, should give information about the incidence, prevalence, the risk of adverse cardiac events and the value of non-invasive imaging modalities including new scanning techniques to reduce radiation exposure in these patients. Finally, it should help physicians in their decision making regarding surgical correction and sports behavior counseling of their patients with coronary artery anomalies. In Chapter 2.1 we describe the incidence and characteristics of sports-related SCD in Switzerland, performed in a retrospective autopsy study. Furthermore, we evaluated the underlying causes including coronary artery anomalies of sports-related SCD. In Chapter 2.2 we present a single center study, looking at prevalence, incidence and characteristics of coronary artery anomalies detected by coronary computed tomography angiography. In Chapter 2.3 we investigated whether hybrid coronary computed tomography angiography and single photon emission tomography myocardial perfusion imaging represents a valuable non-invasive tool in assessing patients with ACAOS. Specifically, we wanted to evaluate whether this technique helps to discriminate whether myocardial ischemia was a result of the coronary artery anomaly, or from coronary artery disease in a middle-aged population with ACAOS. In Chapter 2.4 we describe the value of fused cardiac hybrid imaging with coronary computed tomography angiography and positron emission tomography myocardial perfusion including the additional value of non-invasive measured coronary flow reserve in patients with complex coronary artery anomalies. Due to its non-invasive nature, relatively low cost and high detection rate of coronary artery anomalies, a further increase of the utilization of coronary computed tomography angiography may be expected in the evaluation of ACAOS and therefore reduction of radiation dose is aimed. We therefore analyzed in Chapter 2.5 the image quality of coronary arteries on the latest 256-slice coronary computed tomography angiography using prospective electrocardiogram triggering techniques with a radiation- and contrast-sparing protocol.

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Part II

Non-invasive imaging in coronary artery anomalies and risk of sudden cardiac death

Chapter 2.1.

Sports-related sudden cardiac death in Switzerland classified by static and dynamic components of exercise

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ABSTRACT

Background Sports-related sudden cardiac deaths (SrSCD) occur most frequently in high dynamic and/or static sports. We aimed to assess the incidence and characteristics of SrSCD in Switzerland and to compare SrSCD occurrence according to sports categories with the sports participation behavior in the general population.

Methods Between 1999 and 2010 forensic reports of SrSCD in young individuals (10-39years) were retrospectively reviewed and categorized based on peak static (increasing from I to III) and dynamic sports components (increasing from A to C). Data were compared to the sports participation behavior of the Swiss population.

Results Sixty-nine SrSCD were identified. 48 (69.6%) occurred during recreational (REC) and 21 (30.4%) during competitive (COMP) sports. Incidences (x/100'000 athlete person-years) for COMP and REC were 0.90 and 0.52, respectively (p=0.001). Most SrSCD occurred in IC (23 cases, 33.3%), followed by IIC (13,18.9%), IIIA and IIIC (11 each,15.9%), IIIB (6,8.7%), IIA (4,5.8%) IB (1,1.5%). No SrSCD was found in IA and IIB. Incidences between sports categories (IIIA 0.25, IB 0.25, IC 0.18, IIC 0.33, IIIC 0.25), were not significantly different except to IIA (0.94, p<0,001), due to the fact that only few people were involved in this sports category. Coronary artery disease (CAD) was the most common underlying pathology of SrSCD.

Conclusions In this Swiss cohort, incidence of SrSCD was very low and similar in all sports categories classified by its static and dynamic components. However, the incidence was higher in COMP compared to REC and CAD proved to be the most common underlying cause of SrSCD.

Abbreviations

CAD = coronary artery disease
COMP = competitive sports
CVRF = cardiovascular risk factors
ECG = electrocardiogram
MI = myocardial infarction
PPS = pre participation screening
REC = recreational sports
SrSCD = sports-related sudden cardiac death

INTRODUCTION

Sports-related sudden cardiac death (SrSCD) in the young is rare, but always catastrophic. Although performing sports is related to decreased overall mortality, temporary maximum physical performance is associated with a higher risk for SrSCD during and up to one hour after cessation of sports.(1, 2) It is suggested that sports might be a strong trigger for a cardiovascular event, particularly in congenital heart disease or coronary artery disease (CAD).(2, 3) Recommendations for a pre-participation screening (PPS) with or without resting ECG exist in most countries and is well accepted by the athletes.(4, 5) In Switzerland, mandatory PPS including an ECG exists for elite athletes and in certain sports associations (e.g. football, athletics, cycling). For all other athletes PPS is on a voluntary basis.(6)

For physiologic purposes different sports can be divided into dynamic (isotonic) and static (isometric) components. Dynamic components are represented by the maximal oxygen uptake (max O_2), and result in increased cardiac output (volume load), whereas static components are related to the percentage of maximal voluntary contraction (MVC) with the consequence of increased pressure load.(7, 8) In athletes, absolute numbers of SrSCD are highest in sports with high dynamic and/or static components.(9, 10) Importantly, sports in these categories are very popular. It is unknown which sports categories based on their dynamic and static exercise components are at high risk for SrSCD in a population with a selective PPS program. We aimed to assess the incidence, characteristics and underlying cause of SrSCD and to compare SrSCD occurrence according to sports categories with the sports participation behavior in the general population of Switzerland.

METHODS

Study population

We defined a SrSCD as an unexpected cardiovascular death occurring during or within one hour after physical activity.(11) After the publication of the first PPS recommendation in 1998 in Switzerland, we retrospectively reviewed all forensic reports of German- and French speaking parts of Switzerland from 1999 to 2010 (with an overall population of 7´030´900) for SrSCD in young individuals (10-39 years). We included only German- and French speaking parts of Switzerland as some of the SrSCD cases of the Italian speaking part of Switzerland were investigated in Italy. Data were retrospectively collected in an anonymized fashion in the Swiss REGistry of Athletic Related Death (www.swissregard.ch).(12) The heart examination was performed by the local forensic pathologist, and the diagnosis of the cause of death was established based on macroscopic findings. In selected cases, microscopy and toxicology were performed. Criterion

for hemodynamically relevant coronary artery disease (CAD) was a lumen narrowing of ≥50%.(13) We divided SrSCDs into two groups depending on whether they occurred during recreational sports (REC) or competitive sports (COMP). COMP are defined as athletes who participate in organized teams or individual sports that require systematic training and regular competition against others and requiring a high degree of athletic excellence and commitment.(14) REC is defined as engagement in physical activity with low-, moderate or vigorous intensity and no participation in competitions. Sports in which SrSCDs occurred were further classified based on peak static and dynamic components achieved during training or competition as suggested in the Task Force 8 of the American College for Cardiology.(7) I to III characterizes an increasing static component, whereas A to C represents an increasing dynamic component. I represents <20% of MVC, II 20-50% MVC, and III >50% MVC, whereas A describes <40% of max O_2, B 40-70% of max O_2, and C >70% of max O_2.(7) Incidences and underlying conditions of SrSCD were analyzed. The denominators for the calculation of incidences were derived from the Swiss Federal Office of Statistics (15) and a survey from the year 2008 on sports participation in Switzerland from the Swiss Federal Office of Sports. According to the survey, 73% of the Swiss population participate regularly in sports. Thereof, 80% are engaged in REC and 20% in COMP.(16) The survey also lists participation numbers within the 67 different sports disciplines. We calculated the sports participation rate (multiple sports exposure possible) according to the different sports categories classified by dynamic and static components of sports, based on the above mentioned survey.(16)

In Switzerland, sudden unexpected deaths are reported to the district attorney, which in turn initiates an inquiry. The preliminary forensic examination is a scene investigation of the corpse, mostly performed by a forensic pathologist. The district attorney may mandate further examination such as an autopsy. A recent study in the Swiss canton of Vaud, the autopsy rate of sudden cardiac death in the young is a high as 47.5%.(13) Although the autopsy rate is lower compared to other countries, based on clinical experience and internal communications with other forensic institutes in Switzerland, the autopsy rate seems valid for non- SrSCD and SrSCD and applicable to all cantons in Switzerland.(17) Our cohort includes only autopsied SrSCDs. SrSCDs based on only a scene investigation were not included. Therefore, our recorded numbers of SrSCDs were multiplied by 2.1 times for the adjusted calculated incidences. Incidences between sports categories with reference of the lowest incidence (minimum one case of SrSCD) were compared.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, version 22 (IBM Corporation, Armonk, NY) and MedCalc, Software bvba version 15.10.0 (Belgium). Data are reported as median ± interquartile range (IQR, 25^{th} – 75^{th} percentile), or mean ± standard deviation (SD), or percentages, as appropriate. Continuous variables were

analysed using the Student's t-test or Mann-Whitney U-test, where appropriate. Categorical data were analysed with Chi-squared test or Fisher´s exact test in case of low field numbers. For the comparison of SrCD rates, lowest incidence category (categories without a single SrSCD were excluded) was defined as the reference category. All other incidences of sport categories were compared to that reference category. *P*-values of all outcomes were two-sided; a value less than 0.05 was considered significant. Confidence intervals (CI) were defined as 95%.

Ethics

This study was evaluated by the Ethics committee of the Canton of Bern, Switzerland. Based on the Swiss Human Research Law, an informed consent for the analysis of anonymized, retrospective data was not necessary.

RESULTS

In the 12-year period under investigation, a total of 72 SrSCDs were recorded. One professional Canadian volleyball player, one US American and one German handball player, who died in Switzerland during a sports event, were excluded from the study. Of the 69 remaining SrSCDs used for analyses, 6 (8.7%) concerned females, and 63 (91.3%) males ($p < 0.001$). Of these, 48 (69.6%) died during REC and 21 (30.4%) during COMP. The male-female ratio was comparable between REC and COMP with 45 (93.8%) versus 3 (6.3%), and 18 (85.7%) versus 3 (14.3%), respectively ($p = 0.36$). Mean age at time of SrSCD in REC was 27.6 years (± 9.9) versus 30.0 years (± 7.9) in COMP ($p = 0.29$). Number of SrSCDs in COMP and REC with regard to age classes is shown in Figure 1. The calculated incidence corrected for autopsy rate was higher for COMP with 0.90/100'000 than REC with 0.52/100'000 ($p=0.001$, see Table 1). Underlying diagnoses of 69 SrSCDs are displayed in Figure 2.

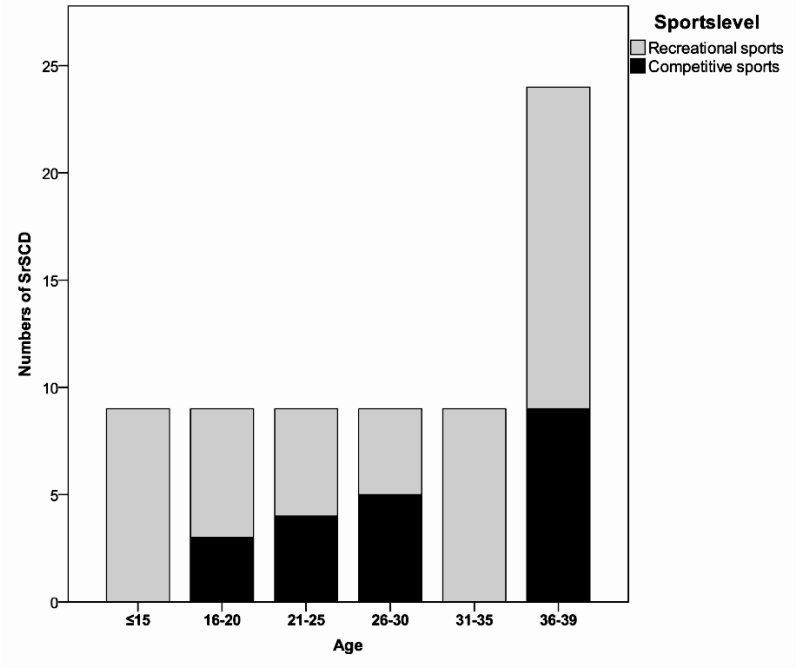

Figure 1: Numbers of SrSCD distribution between REC and COMP according to the age.

Table 1 Calculated incidences of SrSCD in the German and French speaking parts of Switzerland between 1999 and 2010 in individuals aged 10 to 39 years.

	Individuals (10-39 years)	12 person-years	Recorded/ adjusted† number of SrSCDs	Calculated incidence (athlete person-years) of SrSCD with adjusted† number of SrSCDs
Total population*	2'784'561			
Individuals involved in sports activities (73%)*	2'032'730	24'392'760	69/145	0.59/100'000
- **Competitive sports (20%)**	406'546	4'878'552	21/44	0.90/100'000
- **Recreational sports (80%)**	1'626'184	19'514'208	48/101	0.52/100'000

SrSCD = Sports-related sudden cardiac death

* The denominators for the calculation of incidences were derived from the Federal Office of Statistics (www.bfs.admin.ch) and a survey on sports-participation in Switzerland from the Federal Office of Sports (www.baspo.admin.ch).

† * adjustment of SrSCD (x2.1) based on average autopsy rate in Switzerland (47.5%)[16]

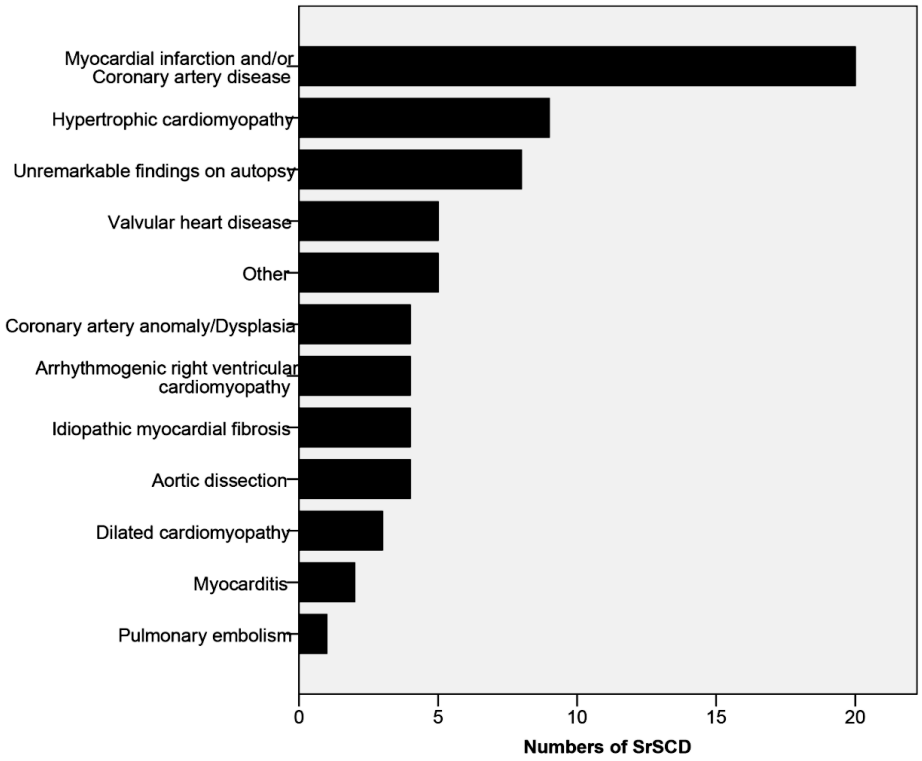

Figure 2: Underlying Diagnoses of SrSCDs in REC and COMP athletes. The group "Other" comprise commotion cordis (n=1), dextro-transposition of the great arteries with patent ductus arteriosus (n=1), Wolff-Parkinson-White syndrome (n=1), and sarcoidosis (n=1) and one unknown case.

Of note, under "other" (n=5) the following cases were summarized: one commotion cordis, one dextro-transposition of the great arteries with patent ductus arteriosus, one Wolff-Parkinson-White syndrome, one sarcoidosis and one unknown case. In REC, CAD with or without myocardial infarction (MI) was the main cause of SrSCD (12, 25%), followed by hypertrophic cardiomyopathy (8, 16.7%), and unremarkable findings on autopsy (8, 16.7%). Similarly, in COMP, CAD with or without MI was the most common cause of SrSCD (8, 38.1%) followed by dilated cardiomyopathy and aortic valve stenosis (each 2, 9.5%). Of the COMP athletes, 3 (14%) were elite athletes and all three died of a MI. All athletes who suffered from SrSCD were Caucasian, except one Swiss athlete who had Afro- American roots.

Based on the classification of peak static and dynamic components achieved during training or competition,(7) most SrSCDs occurred in IC (23, 33.3%), followed by IIC (13, 18.9%), IIIA and IIIC (each with 11, 15.9%), IIIB (6, 8.7%), IIA (4, 5.8%), and IB (1, 1.5%). However, as indicated on Table 2 and Figure 3, incidences between sport categories were similar based on sports behavior.(16)

Table 2. Comparison of incidence based on the classification of peak static and dynamic components achieved during training or competition according to sports participation in Switzerland.

	IA	IIA	IIIA	IB	IIB	IIIB	IC	IIC	IIIC
SrSCD absolute numbers (*n*)	0	4	11	1	0	6	23	13	11
Adjusted[a] SrSCDs (*n*)	0	8	23	2	0	13	49	27	23
Sports participation in Switzerland classified according to sports category (multiple sports) (%)	1.4	3.5	38.0	3.3	1.8	29.8	70.0	33.7	38.2
Individuals involved in different sports categories (*n*)	28,458	71,145	772,437	67,080	36,792	605,753	1,422,911	685,030	776,502
Individuals involved in different sports categories (12 person-years) (*n*)	341,498	853,746	9,269,249	804,961	441,509	7,269,042	17,074,932	8,220,360	9,318,034
Incidence per athlete year		1:213,436	1:842,659	1:804,961		1:1,211,507	1:742,388	1:632,335	1:847,094
−95% CI		1:783,350 to 1:83,361	1:1,688,031 to 1:470,950	1:31,794,148 to 1:144,475		1:3,301,267 to 1:556,611	1:1,171,118 to 1:494,763	1:1,187,578 to 1:369,780	1:1,696,915 to 1:473,428
Incidence rate difference		1:259,080	1:2,767,772	1:2,398,784			1:1,917,231	1:1,322,715	1:2,816,201
−95% CI		1:728,945 to 1:157,535	−1:1,604,648 to 1:743,057	−1:579,087 to 1:390,531			−1:2,348,494 to 1:680,746	−1:2,863,860 to 1:537,282	−1:1,595,349 to 1:747,944
Incidence rate ratio		5.68	1.44	1.51			1.63	1.92	1.43
−95% CI		1.18 to 23.94	0.49 to 4.73	0.03 to 12.41			0.65 to 4.90	0.68 to 6.15	0.48 to 4.71
p-value	NA	<0.001	0.47	0.70	NA	**Reference**	0.28	0.18	0.48
Adjusted[a] incidence per athlete year		1:106,718	1:403,011	1:402,481		1:559,157	1:348,468	1:304,458	1:405,132
−95% CI		1:247,188 to 1:54,161	1:635,750 to 1:268,586	1:3,323,408 to 1:111,418		1:1,050,143 to 1:326,987	1:471,026 to 1:263,581	1:461,995 to 1:209,257	1:639,096 to 1:269,999
Adjusted[a] incidence rate difference		1:131,890	1:1,443,174	1:1,436,397			1:924,815	1:668,395	1:1,470,749
−95% CI		1:251,468 to 1:89,386	−1:1,351,849 to 1:470,464	−1:409,514 to 1:260,804			−1:3,290,070 to 1:405,426	−1:9,304,811 to 1:322,610	−1:1,335,178 to 1:474,200
Adjusted[a] incidence rate ratio		5.24	1.39	1.39			1.60	1.84	1.38
−95% CI		1.88 to 13.64	0.67 to 2.98	0.15 to 6.14			0.85 to 3.22	0.92 to 3.88	0.67 to 2.97
p-value	NA	<0.001	0.34	0.66	NA	**Reference**	0.13	0.07	0.35

I to III represent increasing static components of sports; A to C represent increasing dynamic components of sports.
[a]Adjustment of SrSCD (×2.1) based on average autopsy rate in Switzerland (47.5%).[13]
SrSCD: sports-related sudden cardiac death; CI: confidence interval; NA: not applicable.

Only in sports category IIA incidence of SrSCD was significantly greater than in the reference sports category IIIB. No SrSCD was found in low static and dynamic and moderate static and dynamic sports (IA and IIB).

CAD was the most common underlying pathology in 20 (29%) of all SrSCDs. Of those, 8 (40%) presented with CAD with MI whereas the remaining 12 (60%) had CAD without MI. CAD with or without MI was comparable between REC (12 out of 48, 25%) and COMP (8 out of 21, 38%, p = 0.27). Of all CAD related SrSCDs, soccer was most often represented with 6 cases (30%), followed by wrestling (3, 15%), and cycling and handball (2 cases each, 10%), the rest occurred in running, skiing, ice hockey, weight lifting, dancing, rowing and gymnastics (1 case each, 5%). Performing a subanalysis of all SrSCD cases in athletes aged ≤ 35 years (n=45), CAD with or without MI was the single cause leading to most deaths (n=12, 26.7%). There were no CAD cases in SrSCDs younger than 23 years. The proportion of CAD related SrSCDs increased with age as follows:<20 years:

0%, 21-25 years: 10%, 26-30 years: 25%, 31-35 years: 25%, 36-39 years: 40%. No female SrSCD case presented with CAD.

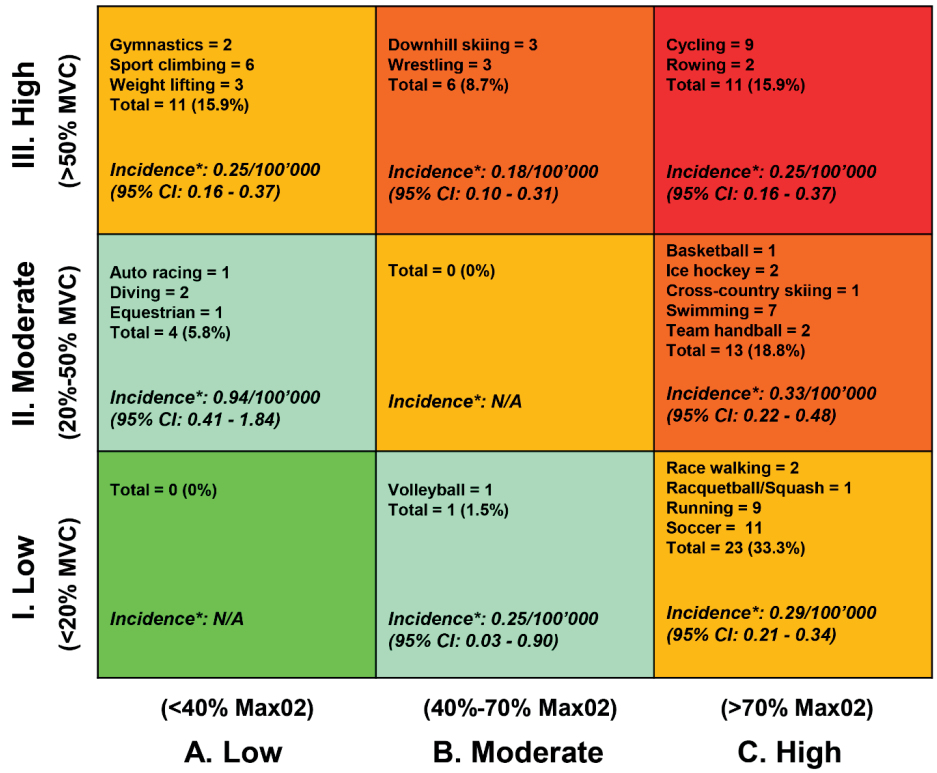

Figure 3: Numbers of SrSCD and incidences in different sport categories. Classification of sports-related SrSCD in REC and COMP athletes based on peak static (isometric) and dynamic (isotonic) components according to the Task Force 8 of the American College of Cardiology.(7) I to III represents increasing static components of sports, A to C represents increasing dynamic components of sports. Max O_2: maximal oxygen uptake; MVC: maximal voluntary contraction. * Incidences are shown in "athlete person-years" and calculated based on the average autopsy rate in Switzerland (47.5%)[13] and adjusted (x2.1) SrSCD numbers
CI = Confidence interval

DISCUSSION

To our knowledge, this is the first study focusing on incidence and the distribution of SrSCD according to dynamic and static components of sports activities as defined by the 36th Bethesda Conference Task Force 8 in a population with selective PPS, including ECG.(7, 8)

Incidences

The analysis of SrSCD in Switzerland with a PPS for elite athletes only and PPS on a voluntary basis for all other athletes showed a relatively low incidence of SrSCDs with a significantly higher incidence of SrSCDs in COMP compared to REC. In contrary, the data from Denmark showed no significant difference in COMP versus REC (0.47 versus 0.43/100,000 athlete person-years), however, their definition of REC athletes differed from ours. They defined REC with a higher threshold regarding to training load, hence absolute numbers of SrSCD in REC were very low in their study and the methodological difference makes comparison difficult between the two studies.(18) Our SrSCD incidence was similar to the one found in a prospective study of France(19) with a similar PPS practice, to retrospective studies from the U.S.A. with 2/100'000 athlete person-years(20, 21) and to data from Norway with 0.9/100'000 athlete person-years.(22) A study from Italy, who has a strict PPS practice, has also shown similar incidences since the implementation of the systematic PPS program.(4, 23) Whether our athletes with SrSCD underwent a PPS is unknown, however, it has been suggested that only 9% of non-elite COMP athletes in Switzerland undergo a PPS.(24)

The clear male predominance in our study population supports findings of many previous studies. Higher training loads and intensities, of males during competitive sports, higher participation rates, but also a predisposition for premature CAD could be an explanation for this observation.(21, 25)

We could show that sports with a high dynamic (e.g. running), static (e.g. weight lifting), or dynamic and static component (e.g. cycling, rowing) were associated with high numbers of SrSCDs. Of note, these are also the type of sports with a high participation rate within the general Swiss population.(16) There were no significant differences between the sports categories with regard to SrSCDs incidence, apart from sport category IIA that differed from IIIB. Only four SrSCD cases were observed in IIA and the higher incidence was driven by the low participation rate in this sports category. Our findings of similar incidences between sports categories is in contrast to the study of Harmon et al. who showed in National Collegiate Athletic Association-athletes in the U.S.A. that "stop-and-go" sports like basketball (high dynamic/moderate static) were at highest risk for SrSCD.(11) However their finding was largely due to SrSCDs in black college athletes, who were not represented in our study.(11) Similarly to our findings, in the Venetian population SrSCDs occurred mostly in soccer players, followed by basketball players and swimmers, with no differences in incidences between these sports. (3) In contrast to our study, participation rates were not known in the studies from the Norwegian and French databases, which showed most SrSCD in high dynamic/low-moderate static sports.(19, 22)

Underlying causes of SrSCD

Interestingly, CAD with and without MI was the most common underlying cause of SrSCD in this study sample of young athletes. The CAD proportion was similarly high in both groups with 38% in COMP and 25% in REC, p = 0.27). CAD was also found to be the main reason for SrSCD in older athletes,(26) whereas in younger athletes hereditary cardiac diseases were found to be the main underlying conditions.(3, 9, 19, 27) This is in contrast to our study, where CAD was the predominant cause of SrSCDs even in our younger athletes (≤ 35 years). The fact that CAD was the leading cause of SrSCD can be interpreted in different ways. As PPS by ECG cannot detect premature CAD, but can detect cardiomyopathies or channelopathies, selection bias might be part of the explanation. Of note, in all three elite athletes with mandatory PPS the underlying cause of death was MI. Interestingly, similar results were found in the Norwegian study with 48% of young athletes suffering from SrSCD related to MI (22) and 66% of SrSCD in Turkish football players related to CAD.(28) CAD was also the main cause of non-sports-associated cardiac arrests in 43% of individuals aged 25 to 35 years in the U.S.(21) Similarly, CAD was the underlying cause of sudden cardiac death in 30% of young non-athletes in French speaking parts of Switzerland (5-39 years).(13) Furthermore, in a large prospective study from France, SCDs mainly occurred in REC and in a large proportion were due to underlying CAD.(10) Likewise, in a recently published study from Germany, SrSCD in older athletes (>35years) was mainly triggered by premature CAD. In the same study however, CAD was also in a high number the underlying cause of SrSCD in younger athletes (<35years).(29) In summary, it seems that there may be regional differences with regard to CAD-associated SrSCD (3, 25, 27) which might be represented in our Swiss cohort, with less frequent cardiomyopathies than premature CAD. Interestingly, familial hypercholesterolaemia is highly prevalent in Europe (1:500) and also in Switzerland.(30) In most countries familial hypercholesterolaemia is largely underdiagnosed (e.g. Switzerland 13%, Italy and France each <1%) (31) and linked to SrSCD in young adults.(32) There is also evidence that diabetes type MODY "maturity onset diabetes of the young" may be underdiagnosed.(33) However, whether cardiovascular risk factors are underdiagnosed in asymptomatic athletes is unclear.

LIMITATIONS

An important limitation is that personal motivation of the athlete and exertion with exercise is not reflected in the classification based on dynamic and static components. A further limitation is the heterogeneity of the forensic reports from the different institutes, which may have led to an underestimation of the true SrSCD incidence. The number of events is small and statistical power is therefore rather low, especially in the low to moderate static/dynamic sports. Moreover, the assumed autopsy rate of about

47.5% for SrSCD in Switzerland(13) may have under- or overestimated the true number. However, it might be hypothesized that the calculated SrSCD by 2.1 rather reflects the "highest possible" incidence rate. A selection bias regarding age, gender, sports category, and diagnosis of autopsies is unknown; nevertheless, this cannot be excluded. Another issue is possible misclassification of the underlying diagnosis, e.g. lack of molecular autopsy in cases with otherwise unremarkable autopsy findings or SrSCDs classified as CAD, where CAD was possibly an uninvolved coincidental autopsy finding. This fact of coincidental findings might also be applicable to other cases (e.g. sarcoidosis). Further, distinction of REC and COMP reflected the physical activity at the time of SrSCD, regardless of fitness and training history of the person and may have led to misclassification of athletes.(34)

CONCLUSION

In this Swiss cohort with a selective PPS, the incidence of SrSCD in young athletes (≤39years) was very low, but higher in COMP compared to REC. Absolute numbers of SrSCD were higher in sports with high dynamic and/or static components. However, since these sports were also the most popular, we found no relevant differences in the incidences of SrSCD between sports categories. CAD proved to be the most common underlying cause of SrSCD in COMP and REC and also in athletes younger and older than 35 years.

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Chapter 2.2.

Prevalence and characteristics of coronary artery anomalies detected by coronary computed tomography angiography in 5 634 consecutive patients in a single center in Switzerland.

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ABSTRACT

Study/Principles: Coronary computed tomography angiography (CCTA) allows three dimensional visualization of the origin, course and ending of the coronary vessels with high spatial resolution, yielding accurate depiction of coronary artery anomalies (CAA). This study sought to determine the prevalence, incidence and characteristics of CAA detected by CCTA in a single center in Switzerland.

Methods: CAAs were retrospectively identified in 5634 consecutive patients referred for CCTA between March 2007 and July 2015. Single coronary arteries, Bland-White-Garland syndrome, anomalous coronary arteries originating from the opposite site of the sinus of Valsalva (ACAOS) with an interarterial course and coronary artery fistulas were classified as potentially malignant CAAs.

Results: We identified 145 patients with CAA resulting in an overall prevalence of 2.6% and cumulative incidence of 2.1% in all patients referred for CCTA in the observed period. Forty-nine (33.8%) patients showed malignant CAAs including 1 (0.7%) patient with Bland-White-Garland syndrome, 7 (4.8%) with single coronary arteries, 36 (24.8%) with ACAOS and an interarterial course, and 5 (3.5%) with coronary artery fistulas. The remaining 96 (66.2%) patients were classified as having benign variants.

Conclusions: The prevalence of CAA detected by CCTA is non-negligible. Due to its non-invasive nature, relatively low cost and low radiation exposure, a further increase of the utilization of CCTA may be expected which may consequently be paralleled by an increasing absolute number of incidentally detected CAAs. Hence, awareness of the main issues and possible management strategies regarding CAAs is of importance for every treating physician.

Abbreviations:

ACAOS	Anomalous coronary arteries originating from the opposite sinus of Valsalva
CAA	Coronary artery anomalies
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
LAD	Left anterior descending coronary artery
LCS	Left coronary sinus of Valsalva
LCX	Left circumflex coronary artery
LM	Left main stem
RIM	Ramus intermedius artery
RCS	Right coronary sinus of Valsalva
RCA	Right coronary artery
SCD	Sudden cardiac death

INTRODUCTION

The incidence of coronary artery anomalies (CAA) in the general population is reported to be 0.3 – 5.6% [1,2]. Coronary computed tomography angiography (CCTA) is considered the primary imaging modality to detect and characterize the anatomy of CAA. It has a higher detection rate of CAA compared to invasive coronary angiography and other non-invasive imaging modalities, because three dimensional visualization of the entire coronary tree [3,4] allows accurate depiction of the origin, course and ending of the coronary vessels [5].

CCTA has seen substantial technical advancements over the last decade, particularly with regard to spatial resolution and an impressive reduction in radiation dose exposure [6]. Consequently, these developments were paralleled by a growing use of CCTA in clinical routine and increasing importance for the non-invasive assessment for coronary artery disease (CAD) in patients with low-to-intermediate pre-test probability [7]. Thus, it may be expected that the incidental detection of CAA will see a further increase and referring cardiologists and general physicians will be confronted to a greater extend with this entity.

Some CAAs like anomalous coronary arteries originating from the opposite site of the sinus of Valsalva (ACAOS), coronary artery fistulas or Bland-White-Garland syndrome are considered to be associated with adverse cardiac events [8–12]. ACAOS can be classified based on the origin of the anomalous vessel and according to the anomalous vessel course as ACAOS with an interarterial, retroaortic or prepulmonic course (Figure 1). ACAOS, especially those with an interarterial course are of particular interest as this anomaly is associated with ventricular arrhythmias, syncope and sudden cardiac death (SCD) [9,13–15]. In fact, ACAOS have been demonstrated to constitute the underlying cause of SCD in up to 20% in young athletes and in up to 30% in military recruits [13,16,17].

This study sought to determine the prevalence, incidence and characteristics of CAA detected by CCTA in a single center in Switzerland.

METHODS

Patients and Anatomy

All 5634 consecutive patients undergoing CCTA at our institution between March 2007 and July 2015 were retrospectively reviewed for CAA. Classification of CAAs was made based on anatomical and functional characteristics. Anatomical characteristics were assessed as following: CAAs were defined as a coronary artery with abnormal origin, course, termination or anomalies of intrinsic coronary arterial anatomy [1]. Myocardial bridging (i.e. an anomalous course of the coronary artery partially within the myocardial

muscle tissue) is considered to be a normal variant [18,19] and was therefore not included in the present study. Coronary artery ectasia is defined as an arterial segment with a diameter 1.5 times the normal adjacent artery segment. In patients with CAD, coronary artery ectasia, a form of abnormal intrinsic coronary arterial anatomy is considered to be CAD correlate. Therefore, we classified coronary artery ectasia as a CAA only in patients without concomitant obstructive CAD. Obstructive CAD was defined as ≥ 50% luminal diameter narrowing as demonstrated by CCTA. In patients with ectasia, associated underlying diseases were assessed. As single coronary arteries, Bland-White-Garland syndrome, ACAOS with an interarterial course and coronary artery fistulas are associated with adverse cardiac events, we further classified these, based on functional characteristics with possible hemodynamic relevance as potentially "malignant CAAs". All other CAAs were considered as benign variants.

CCTA Imaging

CCTA was performed on 64-slice (LightSpeed VCT XT, Discovery 750 HD) and 256-slice (Revolution CT; all GE Healthcare, Waukesha, WI, USA) CT scanners using prospective ECG triggering with the smallest possible x-ray window at 75% of the R-R cycle according to current guidelines and as previously described [20,21]. Prior to examination all patients received 2.5 mg isosorbiddinitrate sublingually (Isoket, Schwarz Pharma, Monheim, Germany) and up to 30mg metoprolol (Beloc Zok, AtraZeneca, London, UK) was administered intravenously if the heart rate per minute was >65 in order to obtain optimal image quality [20]. Iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare) was injected into an antecubital vein followed by 50 mL saline solution. Volume and flow rate were adapted to body surface area [22]. All images were transferred to an external workstation (AW 4.4, GE Healthcare) for image reconstruction and evaluation. Curved multiplanar reconstructions and three dimensional volume rendering techniques were performed for analysis. Values for effective radiation dose were estimated for CCTA as the product of the dose length product (DLP) times a conversion coefficient for the chest (k = 0.014 mSv/mGy × cm) as previously described [23,24].

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 22 (IBM Corporation, Armonk, NY). Data are reported as median ± interquartile range (IQR, 25th – 75th percentile), or mean ± standard deviation (SD), or percentages for non-parametric and parametric data, respectively. Continuous variables were analysed using the Student's t- test or Mann-Whitney U-test, where appropriate. Categorical data were analysed with Chi-squared test or Fisher´s exact test. A p-value <0.05 was considered statistically significant. Overall prevalence of CAA was calculated as the proportion of patients with CAA out of all patients undergoing CCTA during the observed period. Cumulative incidence

was calculated as the proportion of patients with newly diagnosed CAA out of all patients undergoing CCTA during the observed period.

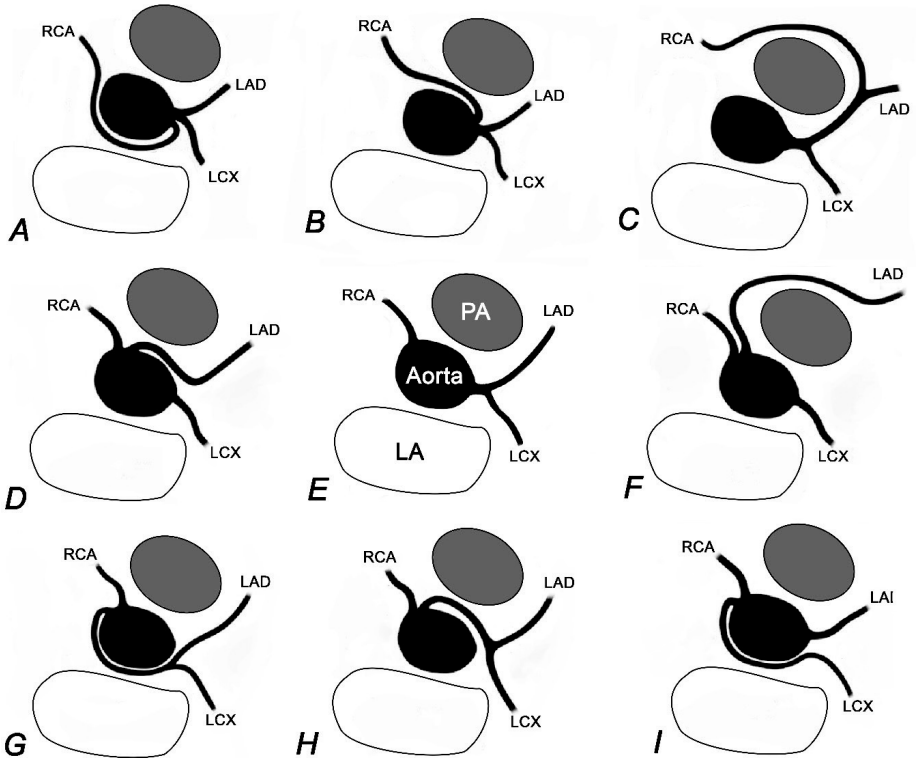

Figure 1: Schematic illustration of a selection of coronary artery anomalies. For comparison, the normal anatomical situs is given in the middle (i.e. Panel E). A: ACAOS with RCA originating from the LCS with a retroaortic course. B: ACAOS with RCA originating from the LCS with an interarterial course. C: "Single left" coronary artery with a RCA originating from the LAD and a prepulmonic course. D: ACAOS with LAD originating from the RCS with an interarterial course. F: ACAOS with LAD originating from the RCS with a prepulmonic course. G: ACAOS with LM originating from the RCS with a retroaortic course. H: ACAOS with LM originating from the RCS with an interarterial course. I: ACAOS with LCX originating from the RCS with a retroaortic course. ACAOS = Anomalous coronary arteries originating from the opposite site of the sinus of Valsalva; RCA = Right coronary artery; LCS = Left coronary sinus; LAD = Left anterior descending artery; RCS = Right coronary sinus; LM = Left main stem; LCX = Left circumflex coronary artery

Ethics

The study was approved by the local ethics committee and the need for written informed consent was waived. KEK-ZH-Nr. 2015-0235.

RESULTS

We identified 145 patients with CAA and an overall prevalence of 2.6%. CAA classified by vessel origination, course and termination and its prevalence are shown in Table 1. CAA was newly diagnosed in 117 (80.1%) of patients with a cumulative incidence of 2.1% in the observed period. Out of these, 12 patients were referred for CCTA specifically for exclusion of CAA due to suspicious findings for CAA during echocardiography. All other patients were referred for CAD exclusion. Thus, CAA was an incidental finding in the remaining 105 (72.4%) patients. Forty-nine (33.8%) patients showed malignant CAAs including 1 (0.7%) patient with Bland-White-Garland syndrome, 7 (4.8%) with single coronary arteries (Figure 2), 36 (24.8%) with ACAOS and an interarterial course (Figure 3), and 5 (3.5%) with coronary artery fistulas (Figure 4). The remaining 96 (66.2%) patients were classified as having benign coronary variants. Of note, typical angina was significantly more frequent (p= 0.006) in patients with potentially malignant CAA compared to patients with benign variants. Twelve (8.3%) patients showed ectasia of the coronary arteries, and out of these 6 (50.0%) had a concomitant dilated ascending or descending aorta (including one patient with known Kawasaki syndrome and one patient with Marfan syndrome). Median effective radiation dose of CCTA was 1.4 mSv [Interquartile range, IQR 1.2 – 2.3].

Table 1: Classification of coronary artery anomalies.

		Cases, n	Cases, %	Prevalence, %
Anomalies of vessel origin and course (n = 107)	Separate ostia for LAD and LCX	27	18.6	0.48
	Single coronary artery*	7		0.12
	Single right coronary artery	6	4.1	0.11
	Single left coronary artery	1	0.7	0.02
	Absent LCX	2	1.4	0.04
	Bland-White-Garland syndrome*	1	0.7	0.02
	High take off LAD	1	0.7	0.02
	High take off RCA	3	2.1	0.05
	ACAOS	66		1.17
	ACAOS with interarterial course*	36		0.64
	ACAOS with prepulmonic course	3		0.05
	ACAOS with retroaortic course	27		0.37
	RCA of LCS	33	22.8	0.59
	LAD of RCS	2	1.4	0.04
	LCX of RCS	10	6.9	0.18
	LAD and LCX of RCS	2	1.4	0.04
	LAD of RCA	2	1.4	0.04
	LCX of RCA	11	7.6	0.20
	LM from non-coronary sinus	5	3.4	0.09
	RCA from non-coronary sinus	1	0.7	0.02
Anomalies of intrinsic coronary arterial anatomy (n = 33)	Duplication of LAD	6	4.1	0.11
	Duplication of RIM	2	1.4	0.04
	Duplication of RCA	1	0.7	0.02
	Ectasia	12	8.3	0.21
	Hypoplasia of LCX	8	5.5	0.14
	Hypoplasia of RCA	4	2.8	0.07
Anomalies of vessel termination (n = 5)	Coronary artery fistula*	5		0.09
	LAD to pulmonary artery	3	2.1	0.05
	LAD and RCA to pulmonary artery	1	0.7	0.02
	LCX to coronary sinus	1	0.7	0.02

ACAOS = anomalous coronary artery originating from the opposite sinus of Valsalva; LAD = left anterior descending coronary artery; LCS = left coronary sinus of Valsalva; LCX = left circumflex coronary artery; LM = Left main stem; RCA = right coronary artery; RCS = Right coronary sinus of Valsalva; RIM = Ramus intermedius artery
* malignant coronary artery anomaly

Baseline characteristics of malignant and benign CAAs are given in Table 2.

Table 2: Patient characteristics.

Characteristic	Malignant CAA n = 49	Benign CAA n = 96	p-value
Male gender, n (%)	36 (73%)	69 (72%)	NS
Age (years), mean ± SD	53 ± 14	57 ± 14	NS
Cardiovascular risk factors, n (%)			
Obesity (BMI ≥30 kg/m^2)	12 (24%)	22 (22%)	NS
Smoking	17 (35%)	29 (30%)	NS
Diabetes mellitus	5 (10.2%)	7 (7%)	NS
Hypertension	17 (35%)	45 (47%)	NS
Dyslipidaemia	15 (31%)	29 (30.0%)	NS
Positive family history for CAD	13 (27%)	22 (23%)	NS
Clinical symptoms, n (%)			
Asymptomatic	14 (29%)	32 (33%)	NS
Typical angina	15 (31%)	11 (12%)	0.006
Atypical angina	9 (18%)	26 (27%)	NS
Dyspnoea	1 (2%)	12 (13%)	NS
Palpitations	8 (16%)	10 (10%)	NS
Vertigo	0	1 (1%)	NS
Syncope	2 (4%)	4 (4%)	NS

BMI = body mass index; CAA = coronary artery anomaly; CAD = coronary artery disease; NS = not significant; SD = standard deviation

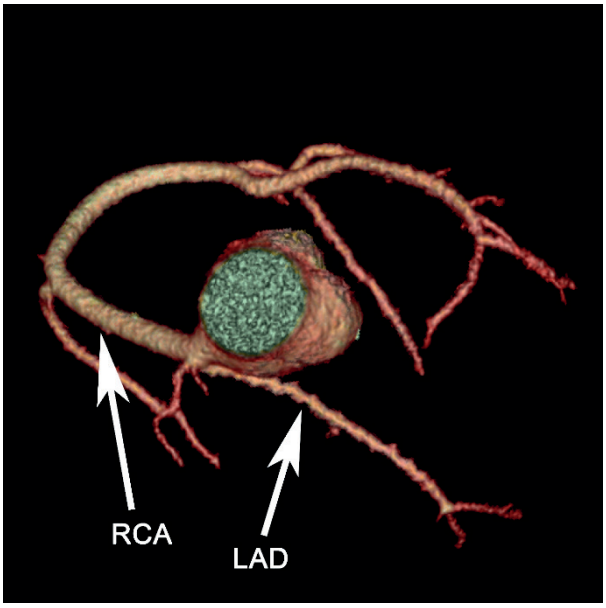

Figure 2: A patient with suspected coronary artery anomaly in echocardiography has a “single right” coronary artery, as depicted by CCTA.

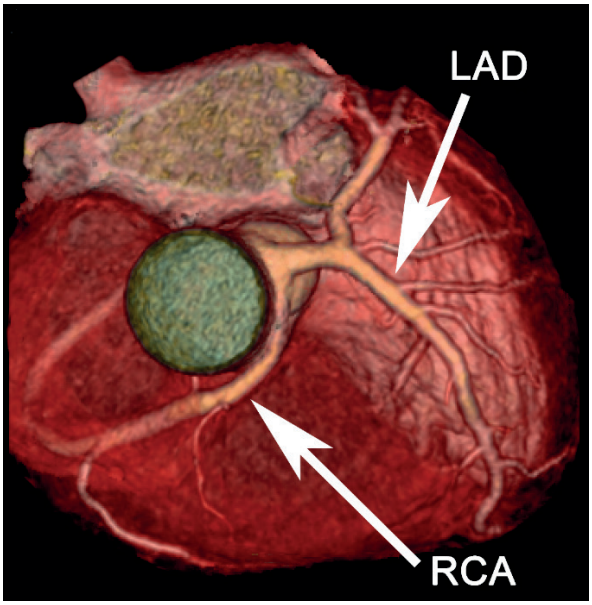

Figure 3: Incidental finding of an ACAOS variant with RCA originating from LCS and a malignant interarterial course of the vessel in a patient referred for CCTA for exclusion of CAD.

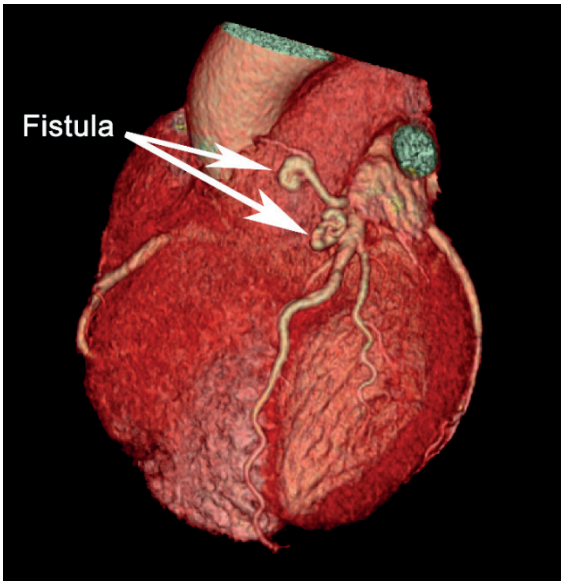

Figure 4: CCTA of a 64year old patient with atypical angina referred exclusion of CAD shows no relevant CAD but a coronary artery fistula originating from the LAD and terminating in the pulmonary artery, potentially causing his symptoms.

DISCUSSION

This is the largest study assessing the prevalence, incidence and characteristics of CAA detected by CCTA in a population referred for CCTA in Switzerland. The overall prevalence of CAA (i.e.2.6%) in the observed period detected in CCTA is comparable to previous studies [1,2,12,25]. A recent smaller study from our institution showed a higher prevalence of CAA (i.e. 7.9%) depicted by CCTA. This difference may be explained by the fact that myocardial bridging (prevalence 3.4%) was included in the mentioned study, contrary to the present work where myocardial bridging was not classified as a true coronary anomaly but rather a normal variant due to its common occurrence [26]. The most commonly found CAA in our study was ACAOS. In line with previous studies, among the ACAOS variants, RCA arising from the LCS were most frequently represented in our population [27, 28]. In a study analyzing 126,595 patients undergoing invasive coronary arteriography over a 28-year period, the rate of RCA originating from LCS was six times higher than the rate of left coronary artery originating from the RCS (0.17% versus 0.047%) [28]. In contrast, we observed a similar proportion of the two ACAOS variants (i.e. 0.59% versus 0.46%). This may be in part due to the better performance of CCTA over invasive coronary angiography, particularly for the detection and characterization of patients with left coronary artery originating from the RCS [27,28].

Imaging modalities

Whenever knowledge of the anatomy of the cardiac vessels is crucial, CCTA represents a highly valuable noninvasive modality because of its capability to accurately and three dimensionally visualize the coronary arteries, yielding a higher detection rate over invasive coronary angiography [26]. Regarding echocardiography, reported data suggest that transesophageal echocardiography is more sensitive than transthoracic echocardiography in identifying CAA. This is mainly driven by the increased sensitivity for assessing the vessel course. However, it remains a semi-invasive technique (i.e. insertion of a tube in the esophagus and sedation) characterized by a significant level of operator dependence. Both echocardiographic techniques as well as cardiac magnetic resonance imaging technique are valid alternatives when radiation is a concern, especially in assessing children with suspected CAA [4,29].

Benign variants of CAA

Absent left main coronary artery (with separate ostia for LAD and LCX, Figure 5) was present second most (i.e. in 18.6 %). Of note, certain authors suggest that separate ostium of LAD and LCX is rather a normal variant than an anomaly with little clinical significance [1], however recognizing this condition before coronary bypass surgery may be crucial. Also in cases of difficulty in cannulating LAD or LCX in invasive coronary angi-

ography, CCTA serves as an ideal backup imaging modality. This is of particular interest as CCTA seemed to outperform invasive coronary angiography also in proximal segment evaluation of the coronary arteries [26] and helps to differentiate between absence of left main stem and LAD or occluded or hypoplastic LCX occlusion [30].

Malignant variants of CAA

A high proportion (i.e. 33.8 %) of CAAs, including Bland-White-Garland syndrome, single coronary artery, ACAOS with an interarterial course and fistulas were considered as potentially malignant variants due to potentially hemodynamic clinical relevance [31]. Previous studies reported that approximately 20% of CAAs are clinically relevant and carry an increased risk of myocardial infarction, malignant ventricular arrhythmia, congestive heart failure, syncope and SCD [8–12,28].

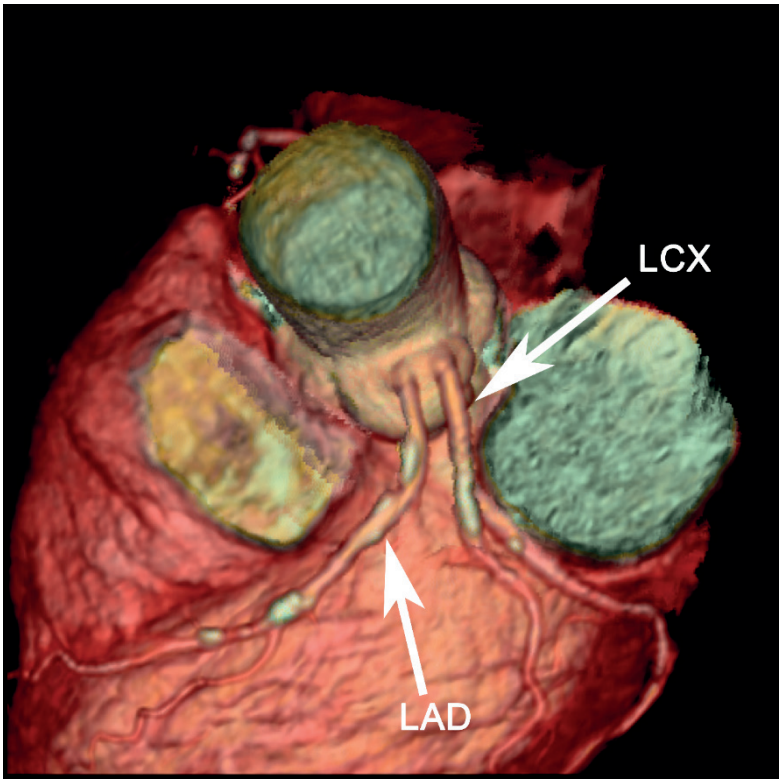

Figure 5: CCTA of a 63year old male shows obstructive CAD and absent left main stem with separate ostium for LAD and LCX. Absent left main stem is considered a benign variant of CAA but the finding may be of clinical importance for eventual revascularization procedures.

Congruently with previous reports, typical angina was significantly more frequently reported in potentially malignant CAA in our cohort [25,32–35]. Due to a lack of clear guideline recommendations, the management of patients with CAAs remains fraught with uncertainty. This is particularly true for asymptomatic individuals with coincidentally discovered CAAs. It has been recommended that in patients with Bland-White-Garland syndrome or ACAOS with origin of the left coronary artery from the right sinus and ACAOS who survived SCD, showed serious ventricular tachyarrhythmia or documented myocardial ischemia, surgical treatment represents first line therapy [11]. Further risk stratification with single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI), positron emission tomography myocardial perfusion imaging (PET-MPI) or stress echocardiography may be warranted in unclear cases [36–38]. As slit-like ostium, intramural course and proximal narrowing of the anomalous vessel are believed to confer a higher risk for adverse cardiac events, exact anatomic depiction as offered by CCTA may be helpful for further risk stratification [8,9,13–15,39–42]. Furthermore, age, sex and physical activity should be incorporated in the risk stratification as well, since there is evidence that especially young (<30years) male athletes or military recruits are at increased risk for SCD [43], whereas in older patients the risk seems to be rather negligible [44]. Surgical revascularization may consist of ectopic coronary re-implantation, creation of a new ostium at the end of the ectopic artery intramural segment (so-called unroofing procedure), or coronary bypass grafting [43]. Of note, there are no controlled studies that have evaluated the outcome of intervention in asymptomatic individuals.

Coronary arterial fistula is a rare anomaly in which a communication is present between a coronary artery and a cardiac chamber or another vascular structure. Even in small coronary artery fistulas, a “steal-phenomenon” caused by redirection of saturated blood away from the myocardium may cause hypoperfusion and reduction of myocardial blood flow distally of the supplying coronary artery. Hemodynamically insignificant fistulae, which are clinically silent and not associated with other abnormal findings, may not require further treatment. However, hemodynamically significant fistulae should be closed by ligation or coiling [11]. Similarly, a “steal-phenomenon” caused by reversed flow in the coronary artery into a pulmonary artery due to decreased pulmonary artery pressure after birth may be present in Bland-White-Garland syndrome patients [45]. International Guidelines suggest that in adults with previous unrecognized Bland-White-Garland syndrome and reduced systolic function surgical myocardial revascularization should be performed in order to achieve a dual coronary supply [11].

Although coronary artery ectasia are not typical malignant CAAs, they carry an increased risk of myocardial infarction due to vasospasm, slower coronary blood flow, and thrombosis, typically within the dilated segments [46,47]. Coronary artery ectasia was present third most frequently present (i.e. in 8.3 %). Besides CAD related ectasia, which were not included in the present study, most common underlying causes of ectasia are associated with small-, medium- and large-vessel vasculitis and sickle cell disease

[46,47]. In our study 50% of patients with coronary artery ectasia showed concomitant dilated arteriopathy, which is in concordance to Papadakis et al. who reported a similarly high coincidence of coronary ectasia in patients with ascending aortic aneurysm [48]. Due to a lack of studies and guidelines, management recommendations for coronary artery ectasia are solely based on personal experiences. Therapy should be tailored to each individual case after assessment of severity, history of complications, underlying etiology, and comorbidities [47]. However, data on optimal treatment strategies (i.e. surgical versus conservative treatment) are scarce and to some extent controversial, rendering patient management challenging, mainly because of the fact that CAAs are rare, their anatomical spectrum is diverse, and the age of first clinical presentation may vary substantially. Thus, assessment of coronary artery anatomy by CCTA plays a central role in management of these entities, especially in CAAs with high risk anatomic features with its potentially hemodynamic relevance [49,50].

LIMITATIONS

CAAs represent a wide group of congenital disorders whose pathophysiological mechanisms and clinical consequences are highly variable. Some experts proposed to categorize CAAs based on functional characteristics as major, minor, hemodynamic relevant and severe versus non-severe CAAs. We are aware that the term potentially “malignant CAA” is an imperfect compromise. Furthermore, in the current study, ACAOS were not analyzed according to other high risk anatomic features such as intramural (in the aortic wall) course, slit-like ostium and proximal narrowing [42,51] and therefore misclassification may be possible in certain ACAOS variants.

There is evidence that in very rare cases myocardial bridging (i.e. an anomalous course of the coronary artery partially within the myocardial muscle tissue) is associated with adverse cardiac events [52] and historically, myocardial bridging was classified as a CAA. However, myocardial bridging is quite common and is found in up to 86% of all autopsies. Thus, the entity of myocardial bridging should rather be considered as a normal variant [18,19] and we excluded these patients from our study. Finally, it may be perceived as a limitation of the present study that there is no control group such as a cohort where the coronary anomalies were detected by invasive coronary angiography. As all patients were referred due to suspected CAD (due to symptoms or high cardiovascular risk) or for CAA exclusion, the prevalence of CAA in our population may be higher than in a general population due to selection bias. Thus, extrapolation of the results of this study to a general population should be made only with caution.

CONCLUSION

The prevalence of CAA detected by CCTA in Switzerland is not negligible. Exact anatomic characterization of CAA is essential for identifying potentially malignant characteristics and guiding further work-up and treatment decisions. Due to its non-invasive nature, relatively low cost and low radiation exposure, a further increase of the utilization of CCTA may be expected which may consequently be paralleled by an increasing absolute number of incidentally detected CAAs. Hence, awareness of the main issues and possible management strategies regarding CAAs is of importance for every treating physician.

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Chapter 2.3.

Hybrid CCTA/SPECT myocardial perfusion imaging findings in patients with anomalous origin of coronary arteries from the opposite sinus and suspected concomitant coronary artery disease

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ABSTRACT

Background Anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS) are associated with adverse cardiac events. Discrimination between ACAOS and coronary artery disease (CAD) related perfusion defects may be difficult. The aim of the present study was to investigate the value of hybrid coronary computed tomography angiography (CCTA) / SPECT-MPI in patients with ACAOS and possible concomitant CAD.

Methods We retrospectively identified 46 patients (mean age 55±14 years) with ACAOS revealed by CCTA who underwent additional SPECT-MPI. ACAOS with an interarterial course were classified as malignant, whereas all other variants were considered benign. CCTA/SPECT-MPI hybrid imaging findings (ischemia or scar) were analyzed according to the territory subtended by an anomalous vessel or a stenotic coronary artery.

Results Twenty-six (57%) patients presented with malignant ACAOS. Myocardial ischemia or scar was found only in patients who had concomitant obstructive CAD in the vessel matching the perfusion defect as evidenced by hybrid CCTA/SPECT imaging.

Conclusion Hybrid CCTA/SPECT-MPI represents a valuable non-invasive tool to discriminate the impact of ACAOS from concomitant CAD on myocardial ischemia. Our results suggest that in a middle-aged population myocardial ischemia due to ACAOS per se may be exceedingly rare and is more likely attributable to concomitant CAD.

Abbreviations

ACAOS	Anomalous coronary arteries originating from the opposite sinus of Valsalva
CCTA	Coronary computed tomography angiography
SPECT	Single photon emission computed tomography
MPI	Myocardial perfusion imaging
CAD	Coronary artery disease

INTRODUCTION

Anomalous coronary arteries originating from the opposite sinus of Valsalva (ACAOS) constitute one category among coronary artery anomalies and can be subdivided into anomalous origin of the right coronary artery (RCA) from the left coronary sinus (LCS), anomalous origin of the main stem, left anterior descending coronary artery (LAD) or left circumflex artery (LCX) from the right coronary sinus (RCS), and anomalous origin of the right or left coronary artery from the non-coronary sinus.[1-3] The incidence of ACAOS is reported to be around 1% in the general population.[4] ACAOS have been associated with angina pectoris, dyspnea, palpitations, ventricular arrhythmia, syncope and sudden cardiac death (SCD).[5-10] The latter is particularly true for the so-called malignant variants of ACAOS, characterized by an interarterial course of the anomalous coronary artery between the aorta and pulmonary trunk. Malignant variants of ACAOS are considered to be the underlying cause of SCD in up to 20% in young athletes and up to 30% in military recruits.[11-13] The increased risk of SCD with this anomaly has been associated, apart from the interarterial course, with other anatomic high-risk features such as slit-like ostium, acute-angle take-off and intramural aortic segments.[13] Coronary computed tomography angiography (CCTA) is considered the primary imaging modality to detect and characterize the anatomy of ACAOS because it has a higher accuracy and detection rate than invasive coronary angiography, echocardiography and magnetic resonance imaging.[14-16] Due to the increasing utilization of CCTA, increased absolute numbers of intentional and incidental diagnosis of coronary artery anomalies may be expected. However, there are no standardized guidelines for the workup of ACAOS detected by CCTA.[17] It remains unclear to what extent vessels with an anomalous course themselves may induce myocardial ischemia. Furthermore, discrimination between ACAOS and concomitant coronary artery disease (CAD) related perfusion defects may be difficult. We hypothesized that hybrid imaging combining CCTA and single photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) may provide the means for such discrimination and offer an added value for risk stratification. The aim of the present study was to investigate the value of hybrid CCTA/SPECT-MPI in patients with ACAOS and possible concomitant CAD.

METHODS

Patient population

We retrospectively identified patients with ACAOS revealed by CCTA who underwent additional clinically indicated SPECT-MPI at our institution between March 2003 and June 2015.

CCTA

CCTA was performed on multi-slice CT scanners (LightSpeed VCT XT, Discovery CT 750 HD, and Revolution CT, all GE Healthcare, Waukesha, WI, USA) according to current guidelines and as previously described.[18, 19] Prior to examination all patients received 2.5 mg isosorbiddinitrate sublingually (Isoket, Schwarz Pharma, Monheim, Germany) and up to 30mg metoprolol (Beloc Zok, AtraZeneca, London, UK) was administered intravenously if the heart rate per minute was >65 in order to obtain optimal image quality.[19] Iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare) was injected into an antecubital vein followed by 50 mL saline solution. Volume and flow rate were adapted to body surface area.[20]

SPECT-MPI

All patients underwent a one-day 99m-Technetium-tetrofosmin stress/rest protocol according to the European procedural guidelines for radionuclide imaging of myocardial perfusion.[21] Briefly, physical stress testing was performed on a bicycle with a target heart rate of at least 85% of the predicted maximum age corrected heart rate. Pharmacological stress was induced by adenosine (continuous infusion at 140 µg/kg per minute, with or without the combination of bicycle exercise) or dobutamine (incrementally infused, starting at 5 µg/kg per minute and increasing at 1-min intervals to a maximum of 60 µg/kg per minute until at least 85% of the predicted maximum heart rate had been reached). 99mTc-tetrofosmin was injected at peak physical or dobutamine stress or after 3 min of induced adenosine stress. Rest MPI was performed thereafter with the identical acquisition protocol after injection of a three times higher dose of 99mTc-tetrofosmin. Acquisition was performed either on a conventional standard dual-detector SPECT camera (Ventri, GE Healthcare) or on a novel gamma camera with cadmium-zinc-telluride (CZT) detector technology (Discovery NM 530c, GE Healthcare). Acquisition time on the conventional dual head SPECT camera was 15 minutes for stress and rest and 3 and 2 minutes for stress and rest, respectively, on the CZT camera.[22] A non-contrast enhanced CT scan was performed for coronary artery calcium scoring (CACS) and attenuation correction of SPECT-MPI.[23] Calculation of CACS was performed in all patients, except in those with previous revascularization.

Coronary anatomy

Coronary anatomic characteristics such as origin and course of ACAOS were recorded from volume rendered images. Virtual angiographic view was used for evaluation of slit-like origin as a high risk anatomic feature.[24, 25] Double-oblique multiplanar reformatted images were used to identify other high risk anatomic features such as take-off angle, intramural course and length, proximal and distal height/width vessel ratio, elliptical

course (defined as height/width ratio of >1.3), proximal and distal vessel diameter area and proximal vessel narrowing (Figure 1) of the anomalous vessels.[24, 25]

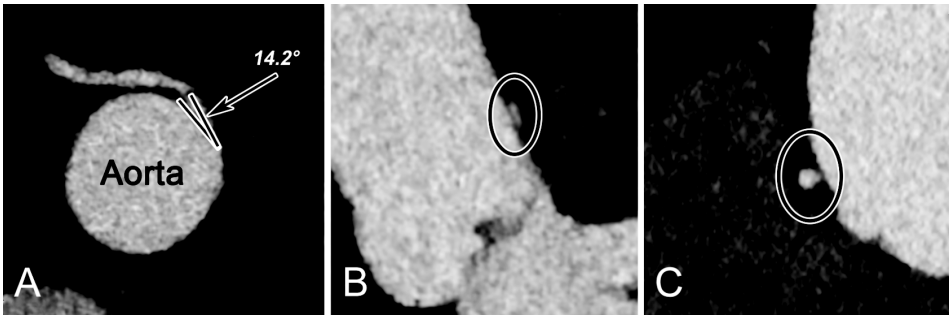

Figure 1: CCTA of a patient with malignant ACAOS variant and a RCA originating from LCS with an interarterial course. This anomaly shows high risk anatomic features such as acute angle take off (**A**), proximal intramural course with elliptic vessel shape and high height/width ratio (**B**). By contrast the distal vessel course shows a normal height/with ratio (**C**)

Coronary vessel dominance was classified as right dominant if the posterior descending artery and posterolateral branch originated from the RCA or as left dominant if originating from the LCX artery, and as balanced if the posterior descending artery originated from the RCA in combination with posterolateral branches originating from the LCX artery.[26] ACAOS with an interarterial course (between the aorta and pulmonary trunk) or a subpulmonary course (between the aorta and the right ventricular outflow tract) were classified as malignant, whereas all other variants were considered benign (Figure 2).[27] CAD was defined as a luminal diameter narrowing ≥ 50% as depicted by CCTA.

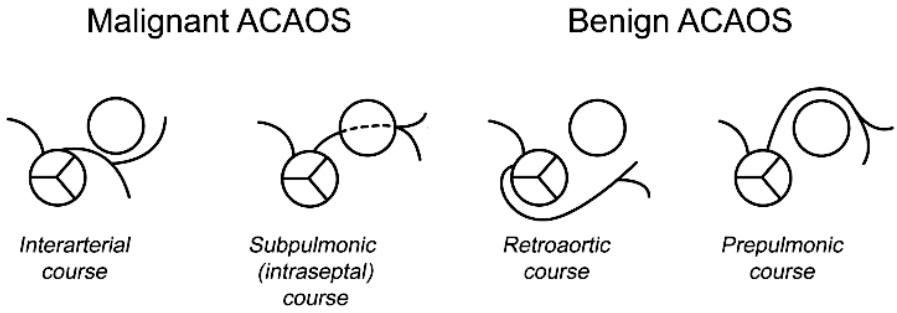

Figure 2: Different vessel courses in patients with anomalous coronary artery origin from the opposite sinus (ACAOS)

Hybrid image fusion

Datasets from SPECT-MPI and CCTA were fused on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) using a commercially available software tool (CardIQ

Fusion, GE Healthcare) to create hybrid CCTA/SPECT-MPI images, as previously described in detail.[28] A matched CCTA/SPECT-MPI hybrid imaging finding was defined as a reversible (ischemia) or fixed (scar) SPECT-MPI defect in a territory subtended by an anomalous vessel or a stenotic coronary artery (defined as narrowing of the coronary luminal diameter ≥50%). All other combinations of pathologic findings were classified as unmatched.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 22 (IBM Corporation, Armonk, NY). Data are reported as median ± interquartile range (IQR, 25th – 75th percentile), or mean ± standard deviation (SD), or percentages for non-parametric and parametric data, respectively. Continuous variables were analysed using the Student's t- test or Mann-Whitney U-test, where appropriate. Categorical data were analysed with Chi-squared test or Fisher´s exact test. A p-value <0.05 was considered statistically significant.

Ethics

The study conformed to the principles outlined in the declaration of Helsinki and was evaluated and approved by the local ethics committee and the need for written informed consent was waived.

RESULTS

We identified 46 patients with ACAOS (mean age 55.2 ± 13.6 years, 74% male) who underwent both CCTA and SPECT-MPI. In 38 (82.6%) of the patients CCTA was followed by SPECT-MPI, whereas in the remaining 8 patients SPECT-MPI was the first imaging modality. Table 1 depicts the types of ACAOS found. Patient characteristics are given in Table 2. Of note, CACS was significantly higher and patients with a history of CAD were significantly more frequent in the group of patients with benign ACAOS variants than in the group of patients with malignant ACAOS. An abnormal resting electrocardiogram was found in 8 (31%) of patients with a malignant and in 6 (30%) of patients with a benign ACAOS variant. During SPECT-MPI, 4 (15%) patients with a malignant ACAOS variant had an abnormal stress electrocardiogram and 4 (15%) complained of chest pain, compared to 2 (10%) and 3 (15%) of patients with a benign ACAOS variants, respectively (p = NS).

Table 1 ACAOS characteristics

Characteristic	All n = 46	Malignant n = 26	Benign n = 20
RCA originating from LCS, n (%)	23 (50.0%)	22 (84.6%)	1 (5.0%)
LCX originating from RCS, n (%)	15 (32.6%)	0	15 (75.0%)
Single right coronary artery, n (%)	4 (8.7%)	2 (7.7%)	2 (10.0%)
LM originating from non-coronary sinus, n (%)	2 (4.3%)	0	2 (10.0%)
LAD and LCX originating from RCS, n (%)	1 (2.2%)	1 (3.8%)	0
LAD originating from RCS, n (%)	1 (2.2%)	1 (3.8%)	0

RCA = Right coronary artery; LCS = Left coronary sinus of Valsalva; LCX = Left circumflex coronary artery; RCS = Right coronary sinus of Valsalva; LM = Left main stem, LAD = Left anterior descending coronary artery

Table 2 Patient characteristics

Characteristic	All n = 46	Malignant n = 26	Benign n = 20	*p-value*
Male gender, n (%)	37 (80%)	19 (73%)	18 (90%)	NS
Age (years), mean ± SD	56 ± 12	54 ± 12	59 ± 13	NS
Cardiovascular risk factors, n (%)				
Obesity (BMI >= 30kg/m^2)	8 (17.4%)	4 (15.4%)	4 (20%)	NS
Smoking	16 (34.8%)	8 (30.8%)	8 (40.0%)	NS
Diabetes mellitus	4 (8.7%)	1 (3.8%)	3 (15.0%)	NS
Hypertension	9 (9.6%)	11 (42.3%)	11 (55.0%)	NS
Dyslipidaemia	20 (43.5%)	8 (30.8%)	12 (60.0%)	0.05
Positive family history	9 (19.6%)	4 (15.4%)	5 (25.0%)	NS
Known CAD, n (%)	19 (41.3%)	7 (26.9%)	12 (60.0%)	0.020
History of revascularization, n (%)	6 (13.0%)	4 (15.4%)	2 (10.0%)	NS
Clinical symptoms, n (%)				
Asymptomatic	12 (26.1%)	6 (23.1%)	6 (30.0%)	NS
Typical angina pectoris	8 (17.4%)	6 (23.1%)	2 (10.0%)	NS
Atypical chest pain	14 (30.4%)	11 (42.3%)	3 (15.0%)	NS
Dyspnoea	3 (6.5%)	0	3 (15.0%)	NS
Palpitations	6 (13.0%)	3 (11.5%)	3 (15.0%)	NS
Syncope	3 (6.5%)	0	3 (15.0%)	NS
CACS, median [IQR]	48 [0-300]	2 [0-143.5]	90 [38.3-387.0]	0.010
Diagnostic test, n (%)				
Bicycle SPECT-MPI	14 (30.4%)	14 (53.8%)	0	<0.001
Bicycle/Adenosine SPECT-MPI	4 (8.7%)	2 (7.8%)	2 (10.0%)	NS
Dobutamine SPECT-MPI	5 (10.9%)	2 (7.7%)	3 (15.0%)	NS
Adenosine SPECT-MPI	23 (50.0%)	8 (30.8%)	15 (75.0%)	0.007

CAD = coronary artery disease; SPECT-MPI = single photon emission computed tomography myocardial perfusion imaging; SD = standard deviation; [IQR] = interquartile range

Of the 26 malignant ACAOS variants, 3 (11.5%) showed a subpulmonary course between the aorta and the right ventricular outflow tract, whereas the remaining 23 (88.5%) showed an interarterial course. Of the bening ACAOS variants 1 (5%) showed a prepulmonic course, whereas the other 19 (95%) showed a retroaortic course.

Malignant ACAOS showed significantly more high risk anatomic features such as slit-like ostium, acute angle take-off of the vessel, intramural course, higher proximal diameter ratio and eliptical form of the proximal vessel (Table 3).

Table 3 Anatomic characteristics among malignant and benign ACAOS variants

Characteristic	Malignant n = 26	Benign n = 20	*p-value*
Slit-like ostium, n (%)	18 (69.2%)	0	<0.001
Intramural vessel course, n (%)	21 (80.8%)	2 (10.0%)	<0.001
Intramural length (mm), median [IQR]	13.5 [10.0-15.3]	0	<0.001
Acute take off angle (<45%), n (%)	19 (73.1%)	7 (35.0%)	0.010
Take off angle (°), median [IQR]	23.0 [14.6-43.6]	66.4 [37.1-68.3]	0.001
Proximal vessel diameter ratio (height/width), median [IQR]	2.2 [1.5-2.6]	1.3 [1.0-1.2]	<0.001
Proximal diameter area (mm^2), median [IQR]	6.6 [5.4-10.5]	4.5 [4.7-11.9]	NS
Elliptic vessel course (proximal diameter ratio >1.3), n (%)	22 (84.6%)	3 (15.0%)	<0.001
Distal diameter ratio (height/width), median [IQR]	1.0 [1.0-1.1]	1.0 [1.0-1.1]	NS
Distal vessel diameter area (mm^2), median [IQR]	11.6 [9.4-14.2]	6.3 [5.0-9.7]	0.001
Proximal vessel narrowing (%), median [IQR]	-37.0 [-50.9-9.5]	4.5 [-34.9-59.0]	0.010
Coronary vessel dominance, n (%)			
Right vessel dominance	21 (80.8%)	17 (85.0%)	NS
Left vessel dominance	4 (15.4%)	1 (5.0%)	NS
Balanced vessel dominance	1 (3.9%)	2 (10.0%)	NS
Coronary vessel dominance supplied by anomalous vessel, n (%)	17 (65.4%)	3 (15.0%)	0.001

[IQR] = interquartile range

CCTA depicted obstructive CAD in 17 (40%) of patients. SPECT-MPI revealed myocardial ischemia in 3.8% of patients with malignant ACAOS variants and in 30% (p<0.05) of patients with benign ACAOS variants (Table 4).

Table 4 Perfusion defects in SPECT characterized by groups

Characteristic	Malignant n = 26	Benign n = 20	*p-value*
Ischemia, n (%)	1 (3.8%)	6 (30.0%)	0.033
Due to CAD, in a non-anomalous vessel	1 (3.8%)	4 (20.0%)	
Due to CAD, within an anomalous vessel	0	2 (10.0%)	
Scar, n (%)	5 (19.2)	5 (25.0%)	NS
Due to CAD, in a non-anomalous vessel	3 (11.5%)	4 (20.0%)	
Due to CAD, within an anomalous vessel	1 (3.8%)	1 (5.0%)	
Not matching the territory of a coronary vessel	1 (3.8%)	0	

CAD = coronary artery disease

Vessel based analysis using hybrid CCTA/SPECT-MPI revealed that ischemia was mainly due to obstructive CAD in a non-anomalous vessel (Figure 3). Two patients with a benign ACAOS variant (one LAD originating from the non-coronary sinus and one retroaortic course of an anomalous LCX) showed myocardial ischemia in the myocardial territory subtended by the anomalous vessel itself. However, in both patients, concomitant obstructive CAD (as diagnosed by CCTA) was also present in the anomalous coronary artery. Scars were present in 5 (19.2%) patients with malignant ACAOS and in 5 (25.0%) patients with benign ACAOS. Similarly, hybrid CCTA/SPECT-MPI showed that scars were due to CAD in non-anomalous vessels (Figure 4). Of note, in one patient with a malignant ACAOS variant, scar tissue could not be attributed to a coronary artery perfusion territory and was subsequently identified by cardiac magnetic resonance imaging as fibrosis due to myocarditis. Five (10.9%) patients in whom relevant ischemia was detected by SPECT-MPI have undergone subsequent revascularization. No revascularization of anomalous vessels without CAD was performed.

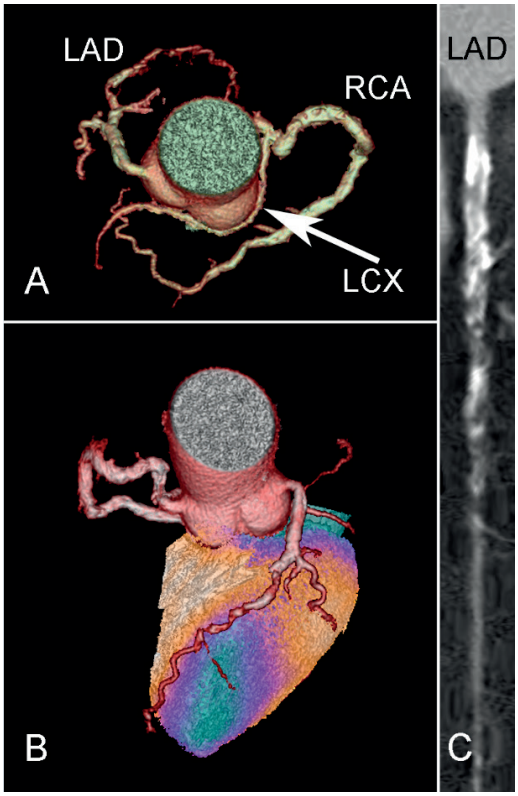

Figure 3: CCTA shows a patient with a benign ACAOS variant and a retroaortic course of the LCX (**A**). Hybrid CCTA/SPECT-MPI (using the CT attenuation corrected stress dataset) reveals an anteroapical ischemia matching the perfusion area of the LAD (**B**). CCTA demonstrates severe coronary atherosclerosis with subtotal stenosis of the middle LAD (**C**).

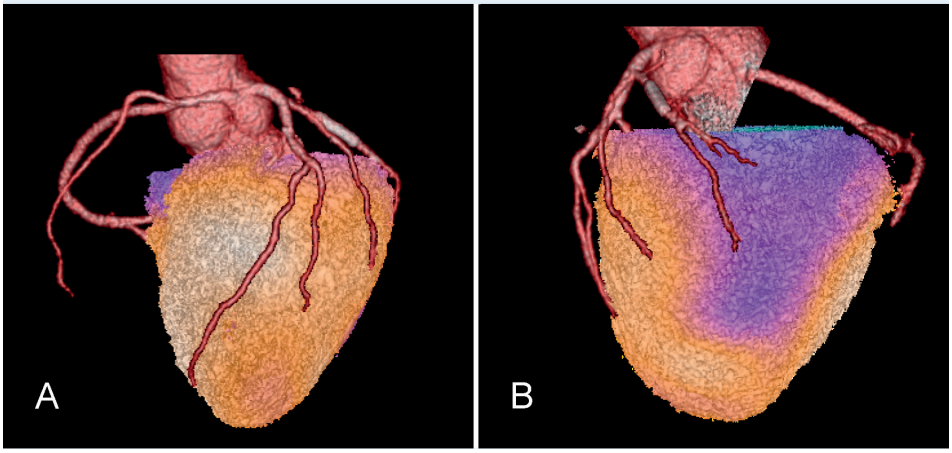

Figure 4: Hybrid CCTA/SPECT-MPI (using the CT attenuation corrected rest dataset) shows a malignant ACAOS with the RCA originating from the LCS with an interarterial course. The inferolateral scar tissue could be clearly allocated to the perfusion territory subtended by the non-anomalous LCX which was previously revascularized with a stent due to occlusion and subsequent myocardial infarction (**A, B**).

DISCUSSION

Our results show that prevalence of CAD is relatively high in a middle-aged population of patients with coronary anomalies referred for non-invasive cardiac imaging due to suspected CAD. In these patients the correct assignment of territories to the subtending coronary arteries may be particularly challenging. Even in patients with no coronary anomalies, the so called standard distribution of myocardial perfusion territories does not correspond with individual anatomy in more than half of the patients.[29] Hybrid cardiac imaging fusing CCTA with SPECT-MPI has been introduced about one decade ago[28, 30] and has been established as a tool for comprehensive anatomical and functional lesion evaluation[31, 32] as well as for allocation of the affected coronary artery with the respective myocardial territory. Implementation of cardiac hybrid imaging may improve outcome prediction[33] and optimize downstream resource utilization.[34]

In our study myocardial ischemia or scar was only found in patients who had concomitant obstructive CAD in the vessel matching the perfusion defect. It may be hypothesized that the anomalous course of the vessel per se may promote coronary insufficiency in coronary arteries additionally affected by CAD. However, the fact that most of the perfusion defects could be attributed to a myocardial territory subtended by a non-anomalous vessel with obstructive CAD or an anomalous vessel of benign variant but with concomitant obstructive CAD, with absence of anatomic high-risk features, suggests that contribution of the anomaly itself may play only a minor role for the manifestation of myocardial perfusion deficits.

In line with the results of the present study, Uebleis et al. demonstrated that out of 17 patients with ACAOS, one third presented with myocardial ischemia in SPECT-MPI. However, only patients without concomitant CAD were included. Similar to our analysis, it could be shown that correlation between the anatomical variants of ACAOS and the presence of myocardial ischemia was low. Only in 3 patients perfusion defects could be matched to the territory of an anomalous vessel, and thereof 2 anomalies were malignant variants.[17] In accordance to previous studies, we found that malignant ACAOS had significantly more high risk anatomic features such as slit-like ostium, intramural course, acute angle take-off of the vessel, higher proximal diameter ratio and eliptical form of the proximal vessel compared to benign variants.[25, 35] In contrast to our study, in a small population with malignant ACAOS revealed by invasive coronary angiography, De Luca et al. demonstrated ischemia by SPECT-MPI in 4 out of 5 patients.[36] However, in this study it remained unclear whether myocardial ischemia or scar was matching the area of anomalous vessel perfusion.[29]

It is not known which study protocol is most adequate for the evaluation of myocardial perfusion in patients with ACAOS. This is to some extent reflected by the heterogeneous choice of stress testing protocols applied in the present study. In fact, bicycle exercise testing was performed in the majority of patients with a malignant variant of ACAOS, while in patients with a benign ACAOS variant stress was mostly induced pharmacologically. Dobutamine has been used in conjunction with intravascular ultrasound (IVUS) imaging in the assessment of ACAOS and demonstrated an anatomic compression of ovoid ostia in some patients as well as changes in the vessel diameter.[37] This suggests that dobutamine stress testing or bicycle exercise stress protocol might be preferable over adenosine, as this may most closely resemble the hemodynamic circumstances leading to dynamic vessel obstruction and potentially inducing myocardial ischemia during sports or daily physical activities.[36] However Lim et al. demonstrated that invasively measured fractional flow reserve in a malignant variant of ACAOS was similarly reduced by dobutamine and also adenosine. Therefore adenosine might be an alternative option for functional evaluation of patients with ACAOS.[37] Furthermore, it remains uncertain whether standard physical stress protocols with a minimal heart rate of 85% of the predicted maximum heart rate is adequate and it might be discussed whether more intense physical exertion beyond the level of established standard test protocols are needed in order to increase the detection rate of potential perfusion defects induced by ACAOS.

The present study extends our limited knowledge by demonstrating that in a middle-aged population significant impairment of myocardial perfusion due to the anomalous vessel in ACAOS per se is exceedingly rare and is much more likely attributable to concomitant CAD. Thus, hybrid imaging of CCTA/SPECT-MPI may offer a beneficial value for risk stratification of patients with either benign of malignant variants of ACAOS.

Whether coronary anomalies may constitute a co-factor promoting the incurrence of coronary insufficiency in case of concomitant coronary atherosclerosis remains yet to be elucidated.

LIMITATIONS

It may be perceived as a limitation that we retrospectively included patients referred for hybrid CCTA/SPECT-MPI as this may have led to a possible selection bias towards inclusion of patients with a higher prevalence of CAD. However, it has to be mentioned that 22% of the patients showed no calcifications. Older patients (over thirty years old) as represented in our population tend to have a decreased incidence of anomalous vessel related sudden cardiac deaths and therefore possibly less anomalous vessel related myocardial ischemia in SPECT-MPI.[38] Hence, extrapolation of our results for younger patients has to be made with caution.

CONCLUSION

Hybrid CCTA/SPECT-MPI represents a valuable non-invasive tool to discriminate the impact of ACAOS from concomitant CAD on myocardial ischemia. The results of this study suggest that in a middle-aged population impairment of myocardial perfusion due to ACAOS per se may be exceedingly rare and is much more likely attributable to concomitant CAD.

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Chapter 2.4.

Fused cardiac hybrid imaging with coronary computed tomography angiography and positron emission tomography in patients with complex coronary artery anomalies

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ABSTRACT

Objective There are no data available on the value of fused cardiac hybrid imaging with computed tomography angiography (CCTA) and positron emission tomography myocardial perfusion (PET-MPI) in patients with complex coronary artery anomalies (CCAA).

Design/Setting Retrospective, single center study.

Patients Seven consecutive patients with CCAA (mean 57±7 years, 86% were male) who underwent clinically indicated hybrid CCTA/PET-MPI between 2005 and 2015 in our clinic were included. The findings from both modalities and fused cardiac hybrid imaging were evaluated in these patients.

Results Out of the 7 patients with CCAA, 2 had Bland-White-Garland anomaly, 2 showed a coronary artery fistula, 2 showed a "single right" and one patient showed a "single left" coronary artery. Semi-quantitative fused hybrid CCTA/PET-MPI depicted inferolateral scar matching the territory of a non-anomalous vessel with significant concomitant coronary artery disease (CAD) in one patient only. By contrast, analysis of quantitative myocardial blood flow (MBF) as assessed by fused hybrid CCTA/PET-MPI revealed abnormally reduced flow capacities in the territories subtended by the anomalous vessels in 4 patients.

Conclusions In this case series of middle-aged patients with CCAA, perfusion defects as assessed by semi-quantitative PET-MPI were rare and attributable to concomitant CAD rather than to the anomalous vessel itself. By contrast, impaired MBF as assessed by quantitative hybrid CCTA/PET-MPI was revealed in the majority of patients in the vessel territories subtended by the anomalous coronary artery itself. Fused hybrid CCTA/PET-MPI incorporating information on morphology and on semi-quantitative and quantitative myocardial perfusion may provide added value for the management of patients with CCAA.

Abbreviations:

ACAOS	Anomalous origin of the coronary artery from the opposite sinus
CCTA	Coronary computed tomography angiography
CFR	Coronary flow reserve
MBF	Myocardial blood flow
PET-MPI	Positron emission tomography myocardial perfusion imaging

INTRODUCTION

Complex coronary artery anomalies (CCAA) such as Bland-White-Garland syndrome, anomalous coronary artery origin from the opposite sinus (ACAOS), "single right" or "single left" coronary arteries and coronary artery fistulas occur with an incidence of 0.002% to 1% in the adult population (1-3). Non-invasive coronary computed tomography angiography (CCTA) has become the primary modality in evaluating and characterizing CCAA, as CCTA offers a higher accuracy and detection rate over invasive coronary angiography, echocardiography and magnetic resonance imaging (4-6). CCAA are considered to be associated with symptoms of myocardial ischemia, angina pectoris, dyspnea, palpitations, ventricular arrhythmia, congestive heart failure, syncope and sudden cardiac death (SCD) (2, 7-10). Although standardized guidelines for the workup of CCAA are lacking, it has been suggested that a hybrid morphological and functional non-invasive imaging approach, including CCTA and single photon emission computed tomography imaging myocardial perfusion imaging (SPECT-MPI) might be of added value for risk stratification and decision making in CCAA (10-16). SPECT-MPI, however, allows assessment of myocardial perfusion on a semi-quantitative basis (i.e. assessing the relative differences of normalized myocardial radiotracer uptake) only. By contrast, positron emission tomography myocardial perfusion imaging (PET-MPI) expands current diagnostic capabilities of SPECT-MPI through its ability to additionally offer absolute quantitation of myocardial blood flow (MBF). It is well known that the assessment of quantitative MBF by PET-MPI exerts an added value for risk stratification and provides prognostic information for patients with subclinical coronary artery disease (CAD), balanced triple vessel CAD, cardiac transplant, and microvascular dysfunction in cardiomyopathies (17-21). However, assignment of territories to the correct subtending coronary artery is challenging. In fact, it has been shown that the so called standard distribution of myocardial perfusion territories does not correspond with individual true anatomy in more than half of the patients with normal coronary anatomy (22), a rate that can be assumed to be much higher in patients with CCAA. Thus, it may be hypothesized that hybrid imaging with fusion of CCTA and semi-quantitative and quantitative PET-MPI offers an added value for patients with CCAA.

METHODS

Patient population and follow-up

We retrospectively identified all consecutive patients with CCAA revealed by CCTA who underwent additional clinically indicated PET-MPI between March 2005 and Mai 2015 in our clinic and recorded the findings. Aside from morphological information on the coronary anatomy as offered by CCTA, we evaluated the following parameters derived from

PET MPI: semi-quantitative perfusion, hyperemic absolute MBF, coronary flow reserve (CFR), and relative flow reserve (RFR). Fused hybrid imaging using CCTA datasets and semi-quantitative as well as quantitative MBF parameters was performed for each patient. Clinical data, symptoms, and outcome data were assessed and follow up was obtained by performing telephone interviews and reviewing electronic patient records. Major adverse cardiovascular events (MACE) were defined as cardiac death, myocardial infarction, revascularization or anomalous vessel related cardiac surgery.

CCTA imaging

CCTA was performed on multi-slice CT scanners (LightSpeed VCT XT and Revolution CT, both GE Healthcare, Waukesha, WI, USA) according to current guidelines and as previously described (23, 24). Prior to examination all patients received 2.5 mg isosorbiddinitrate sublingually (Isoket, Schwarz Pharma, Monheim, Germany) and up to 30mg metoprolol (Beloc Zok, AstraZeneca, London, UK) was administered intravenously if heart rate per minute was >65 in order to obtain optimal image quality (24). Iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare) was injected into an antecubital vein followed by 50 mL saline solution.

PET imaging

Cardiac 13N-ammonia PET was performed using a 1-day rest/stress or stress/rest protocol. Stress was pharmacologically induced using adenosine at a standard rate (0.14 mg/min/kg) over 7 min, as previously reported (18). All patients received a 700- to 900-MBq injection of 13N-ammonia into a peripheral vein during 10 s as a slow bolus. Images were acquired in 2-dimensional mode on a PET or PET/CT scanner (Advance, Discovery LS, Discovery DSTX, Discovery VCT, all GE Healthcare, Milwaukee, Waukesha, WI, USA), with a field of view between 14.6 and 15.7 cm. Dynamic acquisitions of the emission scans were performed using a standard protocol consisting of 9 × 10-s, 6 × 15-s, 3 × 20-s, and 1 × 900-s frames. Transmission scan for photon attenuation correction was performed with low-dose CT attenuation correction (non-gated, tube voltage 140 kV, tube current 120 to 150 mA, and slice thickness: 3.75 to 4.75 mm) (18, 25).

Regional 13N-ammonia uptake was assessed using the 17-segment model and the semi-quantitative scoring system of defect severity and extent, as recommended by the American Society of Nuclear Cardiology (26). Quantitative MBF was determined using the PMOD software package (version 3.7, PMOD Technologies Ltd., Zurich, Switzerland) developed and validated at our institution (27). A spherical region of interest was placed into the blood pool of the left ventricle. Myocardial and blood pool time-activity curves were generated from the dynamic frames and corrected for radioisotope decay. MBF was estimated by model fitting of the blood pool and myocardial time-activity curves (28) correcting for partial volume and spillover, as previously described (29). CFR was

calculated as the ratio of hyperemic to resting MBF, and CFR ≥2.0 was considered normal (30). From the 17 segment model relative and absolute MBF in segments corresponding to anomalous and remote, non-anomalous vessels without CAD were assessed for calculation of RFR. RFR was defined as the ratio of hyperemic MBF in the area of the target vessel (anomalous vessel) to hyperemic MBF in a normally perfused area (non-anomalous vessel without CAD) (31) and a RFR of ≥0.78 was considered normal (32). In 2-dimensional scatter plots integrating hyperemic MBF and CFR of territories perfused by anomalous versus non-anomalous vessels in the same patient with superimposed thresholds for normal, reduced flow capacity or definite ischemia as proposed by Johnson and Gould were drawn (33).

Hybrid imaging

Semi-quantitative and quantitative datasets from PET-MPI were fused with CCTA datasets on a dedicated workstation (Advantage Workstation 4.3, GE Healthcare) using a commercially available software tool (CardIQ Fusion, GE Healthcare), as previously described in detail (34). A matched semi-quantitative CCTA/PET-MPI fused imaging finding was defined as a reversible (ischemia) or fixed (scar) PET-MPI defect in a territory subtended by an anomalous vessel and/or a stenotic coronary artery (defined as narrowing of the coronary luminal diameter ≥50%).

Statistical Analysis

All statistical analyses were performed using SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). Data are reported as median ± interquartile range (IQR, 25th – 75th percentile), or mean ± standard deviation (SD), or percentages as appropriate.

Ethics

The study conforms to the principles outlined in the declaration of Helsinki and was evaluated and approved by the local ethics committee (KEK-ZH-Nr. 2015-0235). The need for informed written consent was waived.

RESULTS

Imaging results

We identified 7 patients with CCAA who underwent both CCTA and PET-MPI. Mean age was 57 ± 7 years and 86% were male. Two patients (28%) had Bland- White Garland syndromes with one anomalous left coronary artery from the pulmonary artery (AL-

CAPA) (i.e. patient no.1) as previously published by our group (12) and one anomalous right coronary from the pulmonary artery (ARCAPA) (i.e. patient no. 2). Two patients (28%) showed a single right coronary artery, i.e. one with a subpulmonic course (between the aorta and the right ventricular outflow tract) of the left anterior descending artery (i.e. patient no.3) and one with a retroaortic course of the left coronary artery and an interarterial course of a septal branch (i.e. patient no. 4). One patient (14%) showed a single left coronary artery with an intramural and interarterial course of the right coronary artery (RCA) (i.e. patient no. 5) and two patients (28%) showed a fistula from the left anterior descending artery (LAD) connecting to the pulmonary artery (i.e. patient no. 6 and 7) (Figure 1).

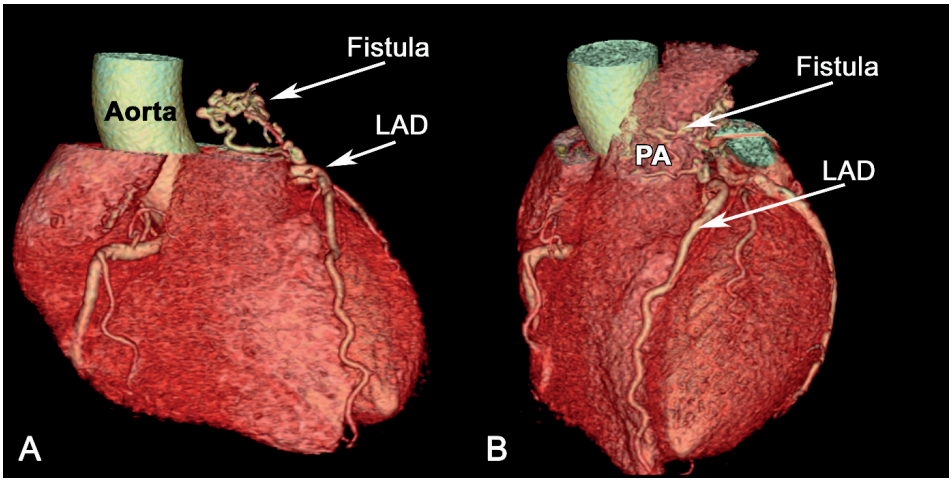

Figure 1: CCTA reveals a fistula from the left anterior descending artery (LAD) to the pulmonary artery (PA). CCTA = Coronary computed tomography angiography;

Table 1 Patient's characteristics and types of anomaly

Patient no.	Age	Sex	Symptoms	Type of anomaly	Origin of anomalous vessel	Course of anomalous vessel	Termination of anomalous vessel
1	56	f	Palpitations	ALCAPA	LM of PA	Normal	Normal
2	48	m	Palpitations	ARCAPA	RCA of PA	Normal	Normal
3	61	m	Typical angina	Single right	LM of RCS	Subpulmonic	Normal
4	55	m	Typical angina	Single right	LM of RCS	Interarterial	Normal
5	57	m	Typical angina	Single left	RCA of LCS	Interarterial	Normal
6	70	m	Syncope	Fistula LAD to PA	Normal	-	A. Pulm
7	52	m	Atypical angina	Fistula LAD to PA	Normal	-	A. Pulm

ALCAPA = Anomalous left coronary from the pulmonary artery; LM = Left main artery, PA = Pulmonary artery; ARCAPA = Anomalous right coronary from the pulmonary artery; RCA = Right coronary artery, RCS = right coronary sinus, LCS = Left coronary sinus, LAD = left anterior descending coronary artery

Patient's characteristics and description of coronary artery anomalies are given in Table 1. Symptoms on referral were angina (43%), followed by palpitations (28%), atypical angina (14%) and syncope (14%). CCTA revealed concomitant CAD in two patients (28%, i.e. patient no. 4 and 5). Semi-quantitative PET-MPI revealed perfusion defects only in the patient with a single left coronary artery (i.e. patient no. 5) with a scar in the inferolateral wall.

Fused hybrid CCTA/PET-MPI revealed that the scar in the inferolateral wall was subtended by a previously stented coronary vessel with concomitant CAD (Figure 2).

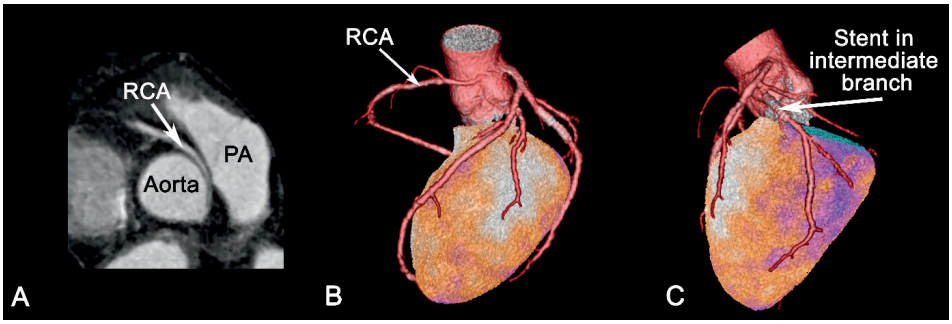

Figure 2: Fused CCTA/PET-MPI of a patient with a single left coronary artery. CCTA revealed a single left coronary artery (i.e. patient no. 5) with an intramural and interarterial course of the anomalous right coronary artery (**A**). Fused CCTA/PET-MPI (using the stress dataset) showed an inferolateral scar matching the perfusion territory of the previous stented non-anomalous intermedius branch with concomitant CAD (**B, C**). CCTA = Coronary computed tomography angiography; PET-MPI = Positron emission tomography myocardial perfusion imagin

Hyperemic MBF in anomalous vessel compared to the remote non-anomalous vessel were lower in all patients (see Table 2 and Figure 3), represented as a RFR below 1.0, except in a single patient (i.e. patient no. 7) with a fistula.

Table 2 Quantitative PET-MPI analysis of anomalous and non-anomalous vessels

Patient no.	Anomalous vessel hyperemic MBF (ml/min/g)	Anomalous vessel CFR	Remote non-anomalous vessel hyperemic MBF (ml/min/g)	Remote non- anomalous vessel CFR	RFR
1	1.46	1.40	2.62	1.47	0.56
2	1.77	1.49	2.55	2.03	0.69
3	2.13	2.62	2.42	2.89	0.88
4	1.76	2.38	2.15	2.27	0.82
5	-	-	1.30	1.52	-
6	2.25	2.36	2.44	2.42	0.92
7	5.50	4.44	5.09	4.38	1.08

MBF = Myocardial blood flow; CFR = Coronary flow reserve; RFR = Relative Flow Reserve

However, RFR was only pathologically reduced (i.e. ≤0.78) in the two patients with Bland-White-Garland syndrome (i.e. patient no. 1 and 2). Similarly, CFR of the anomalous vessel was lower in all patients compared to the remote non-anomalous vessel, except in the patient with single right coronary artery (i.e. patient no. 4) and the patient with a fistula (i.e. patient no. 7). Of note, in the patient with single right coronary artery (i.e. patient no. 4), CFR with 1.94 was also slightly reduced in the segments corresponding to the distal part of the non-anomalous RCA with concomitant CAD, compared to the other, non-anomalous vessel segments. Also in the patient with single left coronary artery (i.e. patient no. 5) the non-anomalous vessels with concomitant CAD showed an impaired CFR. Only in the patient with ALCAPA (i.e. patient no. 1) CFR was reduced in the anomalous vessel (1.40) and - also to a lesser extent - in the remote, non-anomalous vessel (1.47) (see Figure 4). As the patient with single left coronary artery (i.e. patient no. 5) showed left coronary circulation dominance of the non-anomalous vessel, MBF of the anomalous vessel (i.e. RCA) could not be calculated.

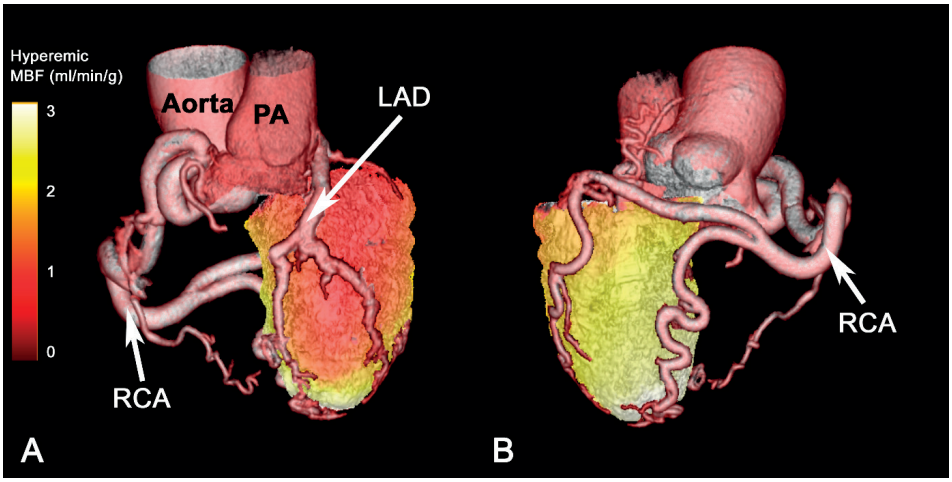

Figure 3: Fused CCTA/PET-MPI including quantitative hyperemic myocardial blood flow (MBF) of patient no. 1 with Bland-White-Garland syndrome (i.e. ALCAPA: anomalous left anterior descending artery origin from the pulmonary artery). On panel A impaired hyperemic MBF in the territory of the anomalous vessel (i.e. LAD) perfusion can be seen compared to normal hyperemic MBF of the non-anomalous vessel perfusion territory of the right coronary artery (RCA) on panel B. MBF = Myocardial blood flow; PA = Pulmonary artery; LAD = Left anterior descending artery; RCA = Right coronary artery; CCTA = Coronary computed tomography angiography; PET-MPI = Positron emission tomography myocardial perfusion imaging

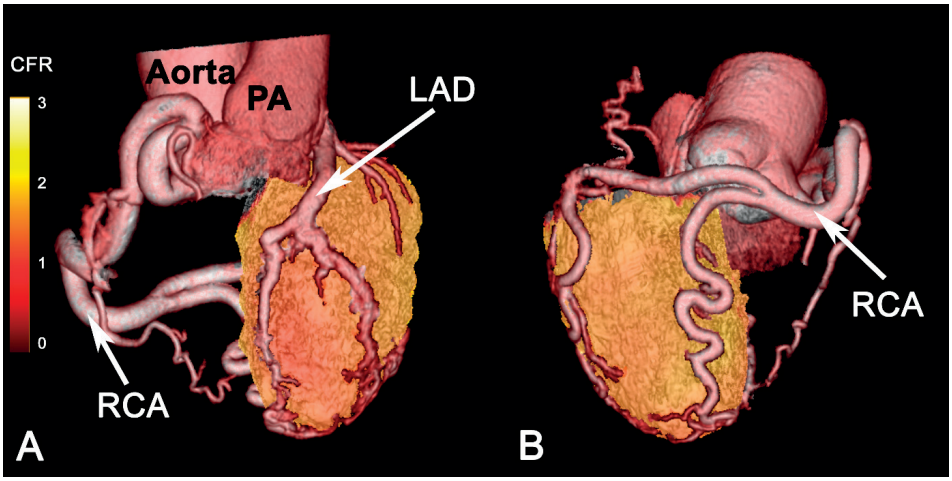

Figure 4: Fused CCTA/PET-MPI including coronary flow reserve of patient no. 1 with Bland-White-Garland syndrome (anomalous left anterior descending artery origin from the pulmonary artery). On panel A CFR in the territory of the anomalous vessel (i.e. LAD) perfusion is impaired to a greater extent compared to the non-anomalous vessel perfusion territory of the right coronary artery on panel B. CFR = Coronary flow reserve; MBF = Myocardial blood flow; PA = Pulmonary artery, LAD = Left anterior descending artery; RCA = Right coronary artery; CCTA = Coronary computed tomography angiography; PET-MPI = Positron emission tomography myocardial perfusion imaging

In Figure 5, 2-dimensional scatter plots of hyperemic MBF and CFR with superimposed thresholds for normal, reduced flow capacity or definite ischemia show that 83% (5 out of 6) of the patients showed a minimally to moderate reduced flow capacity in myocardial territories subtended by the anomalous vessels compared to the remote non-anomalous vessel for each patient.

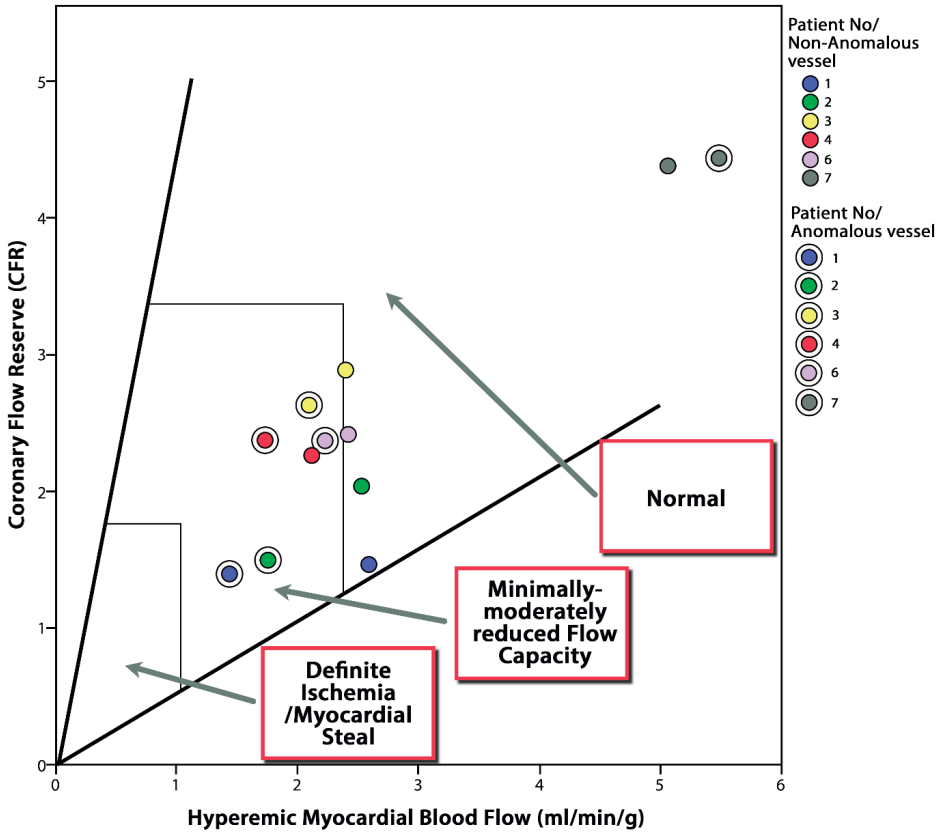

Figure 5: In this figure, 2-dimensional scatter plots integrating hyperemic MBF and CFR of anomalous vessels versus non-anomalous vessel are depicted for each patient with superimposed thresholds for normal, reduced flow capacity or definite ischemia as proposed by Johnson and Gould (33). 83% (5 out of 6) of the patients (i.e. patient no. 1,2,3,4 and 6) showed a minimally to moderate reduced flow capacity in the perfused territories of the anomalous vessels compared to the remote non-anomalous vessel in the same patient. As the patient with single left coronary artery (i.e. patient no. 5) showed left coronary circulation dominance of the non-anomalous vessel, hyperemic MBF of the anomalous vessel could not be calculated and therefore patient no. 5 is not represented on the figure. MBF = myocardial blood flow; CFR = coronary flow reserve

Outcome

During a median follow up of 54 months (IQR 1 -108), 2 patients (29%) experienced MACE. The patient with ALCAPA (i.e. patient no. 1) suffered acute myocardial infarction after 41 months and hemi-arterial switch operation was performed after 72 months due to progressive dyspnea. The patient with single right coronary artery (i.e. patient no. 4) underwent revascularization of the RCA after 1 month due to progressive angina pectoris.

DISCUSSION

To the best of our knowledge, this is the first case series assessing the impact of CCAA on myocardial perfusion through fused hybrid CCTA/PET-MPI, integrating coronary morphology and semi-quantitative and quantitative perfusion parameters. In our study, semi-quantitative perfusion defects (i.e. ischemia or scar) were found in a single patient who had concomitant obstructive CAD in the vessel subtending the perfusion defect. By contrast, quantitative perfusion analysis revealed reduced hyperemic MBF and a reduced CFR in almost all patients with CCAA s in the anomalous vessels compared to a remote, non-anomalous vessel.

Bland-White-Garland syndrome

A steal-phenomenon by reversed flow in the coronary artery into the pulmonary artery caused by decreased pulmonary artery pressure after birth is suggested to be underlying mechanism for perfusion defects in Bland-White Garland patients undergoing SPECT-MPI (35-37). There is evidence that non-invasive quantitative perfusion imaging allows for estimation of fractional flow reserve (FFR) through calculation of RFR (32). As RFR of 0.78 has been suggested as the cut off value for the lower limit of normal (32), the two patients with Bland-White-Garland syndrome (i.e. patient no. 1 and 2) showed abnormal RFR in our case series. Interestingly, in both patients with Bland-White-Garland syndromes, not only RFR but also CFR was reduced in the anomalous vessel, suggesting that quantitative MBF assessment by quantitative PET allows for detection of a presumed steal-phenomenon in Bland-White Garland syndrome.

Coronary artery fistula

Similarly, and even in small coronary artery fistulas, a steal-phenomenon may cause hypoperfusion and reduction of MBF distally of the affected coronary artery, as has been demonstrated using FFR in invasive coronary angiography (15, 38). In line with this study, one patient with coronary artery fistula showed mildly reduced RFR and CFR in the present study. Interestingly, one patient (i.e. patient no. 7) with coronary artery fistula did not show reduced CRF distally to the involved LAD compared to the remote non-anomalous vessel and it was the only patient without a RFR <1. It can be hypothesized that - due to the rather small size of the fistula - the competitive shunting flow through the fistula to the pulmonary artery, compared to the antegrade flow to the distal LAD may not markedly increase during stress perfusion and therefore the fistula is hemodynamically insignificant. Although steal-phenomenon were described also in small coronary artery fistulas, others suggested that a true fistula is characterized by a distinct ectatic vascular segment that exhibits fistulous flow and is connected to two vascular territories with large pressure differences. Small coronary artery fistulas with

long vascular channels may present with high vascular resistance, allowing only limited blood flow to the pulmonary artery, and are therefore mostly not hemodynamically relevant (39, 40).

Anomalous origin of the coronary artery from the opposite sinus

Hyperemic MBF was mildly reduced in one case of ACAOS variant in the myocardium matching the territory subtended by the anomalous coronary artery. Moreover, hyperemic MBF was lower compared to the remote segments with an RFR of 0.82. This is in line with a report by Lim et al. who demonstrated that in a patient with ACAOS the invasively measured FFR of the interarterial variant of the vessel was reduced from 0.96 to 0.87 with adenosine and to 0.86 during a dobutamine challenge (41). In some cases, even ischemia of territories corresponding to anomalous ACAOS vessels have been demonstrated using SPECT imaging (11, 16, 41). By contrast, we have recently demonstrated that myocardial ischemia caused by ACAOS per se seems exceedingly rare in middle-aged patients with ACAOS and is more likely attributable to concomitant CAD (13). With this regard, fused hybrid CCTA/SPECT-MPI proofed a valuable non-invasive tool to discriminate the impact of ACAOS from concomitant CAD on myocardial ischemia (13). Similarly, in the present study, hybrid CCTA/PET-MPI imaging allowed for such discrimination in one patient with ACAOS and concomitant CAD (i.e. patient no. 5). In the same patient and also in the patient with single right coronary artery (patient no. 4), PET-MPI did not show ischemia but revealed that CFR was reduced in the territory subtended by the distal part of a non-anomalous vessel with concomitant CAD. Of note, out of the ACAOS patients only the patient with “single right” coronary artery (i.e. patient no. 3) and a subpulmonic course of the anomalous vessel was showing a normal hyperemic MBF in the anomalous vessel and also a normal, and similar CFR compared to the remote non-anomalous vessel. This finding is of particular interest as it supports the presumption that the subpulmonic course of the anomalous vessel is rather a benign variant and that the anomalous vessel is normally perfused also under stress conditions (42-44).

The present case series extends our limited knowledge by demonstrating that perfusion defects as assessed by semi-quantitative PET-MPI due to CCAA per se are rather rare and are much more likely attributable to concomitant CAD. However hyperemic MBF, CFR and RFR are of additional value as they offer a more accurate and sensitive diagnostic tool in evaluating these patients. In fact, impairment of absolute MBF as demonstrated by quantitative PET-MPI was seen in more than half of CCAA patients in our small cohort. Of note, a number of studies have shown that impaired hyperemic MBF and CFR as assessed by quantitative PET-MPI are powerful independent risk factors for cardiac death (18, 19, 21, 45). Indubitably, larger studies are needed to evaluate whether quantitative assessment of myocardial perfusion through PET-MPI confers an added prognostic value in a population with CCAA. Nevertheless, due to the fact that

the standard distribution models of myocardial perfusion territories are not applicable in patients with CCAA, our results suggest that fused hybrid imaging may constitute a valuable tool in this setting as it allows discrimination of CCAA from CAD in impaired myocardial perfusion. It may, therefore, be hypothesized that hybrid fused CCTA/PET-MPI offers a beneficial value for risk stratification in patients with CCAA.

LIMITATIONS

The sample of patients studied in the present case series is small. However, while CCAA are extremely rare and availability of CCTA/PET-MPI fused imaging is limited, our findings are hypothesis-generating for larger multicenter studies. Nevertheless, due to the small sample size, extrapolation from our results should be made only with caution.

CONCLUSION

In this case series of middle-aged patients with CCAA, perfusion defects as assessed by semi-quantitative PET-MPI were rare and attributable to concomitant CAD rather than to the anomalous vessel itself. By contrast, impaired MBF as assessed by quantitative hybrid CCTA/PET-MPI was revealed in the majority of patients in the vessel territories subtended by the anomalous coronary artery itself. Fused hybrid CCTA/PET-MPI incorporating information on morphology and on semi-quantitative and quantitative myocardial perfusion may provide added value for the management of patients with CCAA.

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Chapter 2.5.

Minimized radiation and contrast agent exposure for coronary computed tomography angiography: First clinical experience on a latest generation 256-slice scanner

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ABSTRACT

Rationale and Objectives: The aim of the study was to evaluate the impact of the latest coronary computed tomography angiography (CCTA) techniques allowing a radiation- and contrast-sparing protocol on image quality in unselected patients referred for exclusion of suspected coronary artery disease (CAD).

Materials and Methods: This prospective study was approved by the local ethics committee, and all patients provided written informed consent. Between March and June 2015, 89 consecutive patients (61% male; mean age 55 ± 11 years) referred for exclusion of CAD by 256-slice CCTA using prospective electrocardiogram triggering were included. Tube voltage (80–120 kVp), tube current (180–310 mA) as well contrast agent volume (25–45 mL) and flow rate (3.5–5 mL/s) were adapted to body mass index. Signal intensity was measured by placing a region of interest in the aortic root, the left main artery, and the proximal right coronary artery. Image noise was measured in the aortic root. Two independent blinded readers semi-quantitatively assessed the image quality regarding motion, noise, and contrast on a 4-point scale.

Results: Median contrast agent volume and median effective radiation dose were 35 mL (interquartile range, 30–40 mL) and 0.5 mSv (interquartile range, 0.4–0.6 mSv), espectively. Mean attenuation in the aortic root was 412 ± 89 Hounsfield units. Diagnostic image quality was obtained in 1050 of 1067 (98.4%) coronary segments and, on an intention-to-diagnosis basis, in 85 of 89 (95.5%) patients. Below a cut-off heart rate of 67 beats/min, only 1 of 974 (0.1%) coronary segments was nondiagnostic.

Conclusion: A radiation- and contrast-sparing protocol for CCTA on a latest generation 256-slice computed tomography scanner yields diagnostic image quality in patients referred for CAD exclusion in daily clinical routine.

INTRODUCTION

Coronary computed tomography angiography (CCTA) has become an important and robust noninvasive imaging tool for the exclusion of significant coronary artery disease (CAD). However, its growing clinical use has raised concerns about the potential induction of malignancies due to the increased burden of radiation exposure for patients (1). Furthermore, the debate on the potential risks associated with cardiovascular imaging has recently been extended to additional components, and contrast agents have been identified as significant contributors of potential risk. In fact, the rate of death and serious acute adverse events due to contrast agent exposure is not negligible and outweighs the radiation-related risks (2). As a consequence, various technological advances have evolved not only to reduce radiation exposure (3), but also to save contrast agent volume (4), potentially enabling a CCTA imaging approach with a combined low radiation and low contrast agent volume exposure. The introduction of prospective electrocardiogram (ECG) triggering (5), including its adaption to high-pitch helical scanning (6,7), has paved the way for a substantial reduction of radiation exposure from initially over 20 mSv with conventional helical acquisition (8) to approximately 2 mSv in current daily clinical routine (5). Nevertheless, prospective triggering is prone to image quality degradation if the patient's heart rate is irregular or high (ie >62 beats/min at a gantry rotation time of 350 ms) (5). Wide-volume 256-slice scanners with 16-cm cranial-caudal coverage and fast gantry rotation time of 280 ms permit acquisition of the whole heart within a single heartbeat, which not only eliminates misalignment artifacts (9), but also results in decreased radiation dose by precluding redundant radiation from overlapping of sequential axial scans (10) and allows for a reduction of contrast agent volume because of shorter acquisition time (4). Furthermore, a more powerful X-ray generator enables acquisition at tube voltages of 100 kVp or below, thereby offering a further reduction of radiation dose, while yielding higher contrast than the standard 120 kVp technique because the X-ray output energy is closer to the iodine K-edge of 33 keV (11). Aside from technological advances in computed tomography (CT) hardware, iterative reconstruction algorithms have been reported to permit a further and substantial reduction in radiation dose (12,13). Most recently, a latest generation adaptive statistical iterative reconstruction algorithm (ASiRV, GE Healthcare, Waukesha, WI, USA) has been proposed to yield substantial noise reduction for CCTA acquired at low tube voltage and current. The aim of the present study was to evaluate the impact of latest CCTA techniques allowing a radiation- and contrastsparing protocol on image quality in unselected patients referred for exclusion of suspected CAD.

METHODS

Patient Population

We prospectively included 89 consecutive patients who were referred for exclusion of CAD with CCTA due to stable symptoms from March to June 2015. Patients with additional clinical questions requiring extension of the scan coverage beyond the heart (eg patients with suspected aortic vessel disease) were excluded. Further exclusion criteria were known hypersensitivity to iodinated contrast agents and renal insufficiency (glomerular filtration rate <60 mL/min). The study was approved by the local ethics committee (KEK-ZH-Nr. 214–0632), and all patients provided written informed consent. The University Hospital Zurich holds a research agreement with GE Healthcare.

Image Acquisition

All patients underwent single-beat contrast-enhanced CCTA during breath-hold at inspiration with prospective ECG triggering at 75% of the R-R interval on a latest generation 256-slice CT scanner (Revolution CT, GE Healthcare, Waukesha, WI, USA). Up to 30 mg of metoprolol (Beloc Zok, Astra Zeneca, London, UK) was administered intravenously before the examination if the heart rate was higher than 65 beats/min to obtain optimal image quality for CCTA (7). Patients received 0.4 mg of sublingual isosorbiddinitrate (Isoket, Schwarz Pharma, Monheim, Germany) 2 min before the CCTA scan. Iodixanol (Visipaque 320, 320 mg/mL, GE Healthcare, Buckinghamshire, UK) was injected into an antecubital vein followed by 50 mL of saline solution via an 18-gauge catheter. Contrast agent volume (25–45 mL) and flow rate (3.5–5 mL/s) were adapted to body mass index (BMI) (Table 1) according to our clinical standards (14). Similarly, for CCTA acquisition, tube voltage (80–120 kVp) and tube current (180– 310 mA) were adapted to BMI (Table 1). A collimation of 256 × 0.625 mm with a z-coverage of 12–16 cm was used with a display field of view of 25 cm. All scans were acquired in high-resolution mode with an in-plane spatial resolution of 0.23 × 0.23 mm. Gantry rotation time was 280 ms. CT raw data were reconstructed with a novel ASiR-V (GE Healthcare) using a high-definition kernel. Radiation dose for CCTA was determined by the dose-length product multiplied by a conversion factor of 0.014 mSv × mGy−1 × cm−1 (8). Heart rate variability was defined as the maximum beat-tobeat variability detected over a default 30-s window, excluding premature heartbeats (eg extrasystolic beats). An unenhanced CT for calculation of calcium scoring was acquired on the same CT scanner (Revolution CT) using the following scan parameters: prospective ECG triggering, 2.5-mm slice thickness, 120-kV tube voltage, 200-mA tube current, and a large field of view of 50 × 50 cm. From this scan, Agatston scores for each coronary vessel were computed with commercially available software (Smartscore 4.0, GE Healthcare) and summed to yield the total coronary artery calcium, as previously reported (15).

TABLE 1. BMI-adapted Scan and Contrast Protocol

BMI (kg/m^2)	Voltage (kV)	Current (mA)	Dose (mL)	Flow Rate (mL/s)
≤20.0	80	180	25	3.5
20.1–22.4	100	180	30	4.0
22.5–24.9	100	215	30	4.0
25.0–27.4	100	270	35	4.5
27.5–29.9	100	310	40	5.0
≥30.0	120	310	45	5.0

BMI, body mass index.

Quantitative Image Analysis

On a dedicated workstation (Advantage Workstation 4.6, GE Healthcare), for every patient, the aortic root was examined at the level of the left main coronary artery on an axial image using a circular region of interest (ROI) with a 20-mm diameter to measure mean attenuation (representing signal) and its standard deviation (SD, representing noise) in Hounsfield units (HU). Similarly, measurements of mean attenuation in the proximal left main artery (LMA) and right coronary artery (RCA) were obtained using a circular ROI with 2-mm diameter on axial images, and due care was taken to avoid calcifications and streak artifacts. Finally, a circular ROI with 2-mm diameter was placed in the adjacent perivascular tissue to measure the vessel contrast expressed as the difference in mean attenuation in HU between the contrast-enhanced vessel and the adjacent perivascular tissue. The obtained measurements were used to calculate contrast-to-noise ratio, for which noise was defined as the SD in the aortic root.

Qualitative Image Analysis

Qualitative image assessment was performed visually by two independent readers experienced in CCTA analysis (D.C.B. and C.G.). The reconstructed images were transferred to a dedicated workstation (AW 4.6, GE Healthcare) and presented to each reader in a randomized order and without any annotations to ensure blinding of the readers to patient information. Coronary arteries were subdivided into 15 segments (16). Axial image stacks were reviewed, and each coronary artery segment larger than 1.5 mm in diameter was evaluated. Small coronary segments were defined as segments 3, 4, 8, 9, 10, 12, 13, 14, and 15 (7), and coronary segments with physiologically higher velocity were segments 1, 2, 3, 4, 9, 12, 13, and 14 (17). Image quality was assessed using a 4-point scale over three individual categories (coronary motion artifact, noise artifact, and contrast agent enhancement), as previously described (18): 1 = nondiagnostic, with severe artifacts rendering diagnostic interpretation impossible; 2 = fair, moderate artifact present, but images were still interpretable; 3 = good, with only mild artifacts; and

4 = excellent image quality. The evaluation of coronary motion artifact focused on apparent blurring, doubling, or discontinuing of the coronary artery contours. Noise artifacts were assessed based on the vessel wall delineation and low contrast resolution. Contrast agent enhancement was assessed by the subjective attenuation differences between the coronary artery and the adjacent myocardium or epicardial fat. The mean value of the image quality scores between the two readers was used for statistical analysis. Disagreements regarding interpretability were solved by consensus agreements with the participation of a third senior reader (R.R.B.).

Statistical Analysis

Quantitative variables are expressed as mean ± SD or as median with interquartile range (IQR) if not normally distributed. Categorical variables are expressed as frequencies or percentages. The data were tested for normal distribution using the Kolmogorov-Smirnov test. The independent-samples t test was used to compare continuous variables, and the Mann- Whitney U test was used to compare nonparametric variables. The $\chi 2$ test was used to evaluate proportions of categorical data. To assess the correlation between different variables, Spearman rank correlation was applied. Inter-rater agreement was assessed using intraclass correlation (ICC) analysis. Receiveroperator characteristic curve was plotted to illustrate the impact of heart rate on image quality. Subsequently, Youden's index was calculated to define the optimal heart rate cut-off. SPSS 20.0 (IBM Corporation, Armonk, NY, USA) was used for analysis. A P value of <0.05 was considered statistically significant.

RESULTS

Study Population

CCTA was successfully performed in all 89 patients referred for exclusion of CAD. Patient baseline characteristics are summarized in Table 2. Intravenous metoprolol (median, 5 mg; IQR, 2–17 mg) was administered in 70 of 89 patients (79%), yielding a median heart rate of 58 beats/min (IQR, 54–61 beats/min; range, 44–167 beats/min) during image acquisition and a median heart rate variability of 3 beats/min (IQR, 1–4; range, 0–13). Median calcium score was 6 Agatston Unit (IQR, 0–63).

CCTA Parameters

A tube voltage of 120 kVp was set in 14 of 89 (16%) patients, and the remaining patients were scanned with 100 kVp (n = 67, 75%) or 80 kVp (n = 8, 9%). Median tube current was 290 mA (IQR, 230–310 mA). The median contrast agent volume used was 35 mL

(IQR, 30–40 mL). The median effective radiation dose was 0.5 mSv (IQR, 0.4–0.6 mSv; range, 0.18–1.22 mSv), and 83 of 89 (93%) patients were exposed to less than 1 mSv (Figs 1 and 2).

TABLE 2. Patient Baseline Demographics ($n = 89$)

Male Gender (%)	61
Age (years)	
Mean ± SD	55 ± 11
Range	27–78
Body mass index	
Median (kg/m^2)	26.1
Interquartile range (kg/m^2)	22.7–28.7
Minimum to maximum (kg/m^2)	17.8–45.2
BMI ≤ 20 kg/m^2 (%)	9
BMI = 20.1–22.4 kg/m^2 (%)	12
BMI = 22.5–24.9 kg/m^2 (%)	25
BMI = 25.0–27.4 kg/m^2 (%)	21
BMI = 27.5–29.9 kg/m^2 (%)	17
BMI ≥ 30.0 kg/m^2 (%)	16
Cardiovascular risk factors (%)	
Smoking	34
Diabetes mellitus	5
Hypertension	44
Dyslipidemia	43
Positive family history	29
Clinical symptoms (%)	
Typical angina pectoris	10
Atypical chest pain	43
Dyspnea	15
Asymptomatic	34

BMI, body mass index; SD, standard deviation.

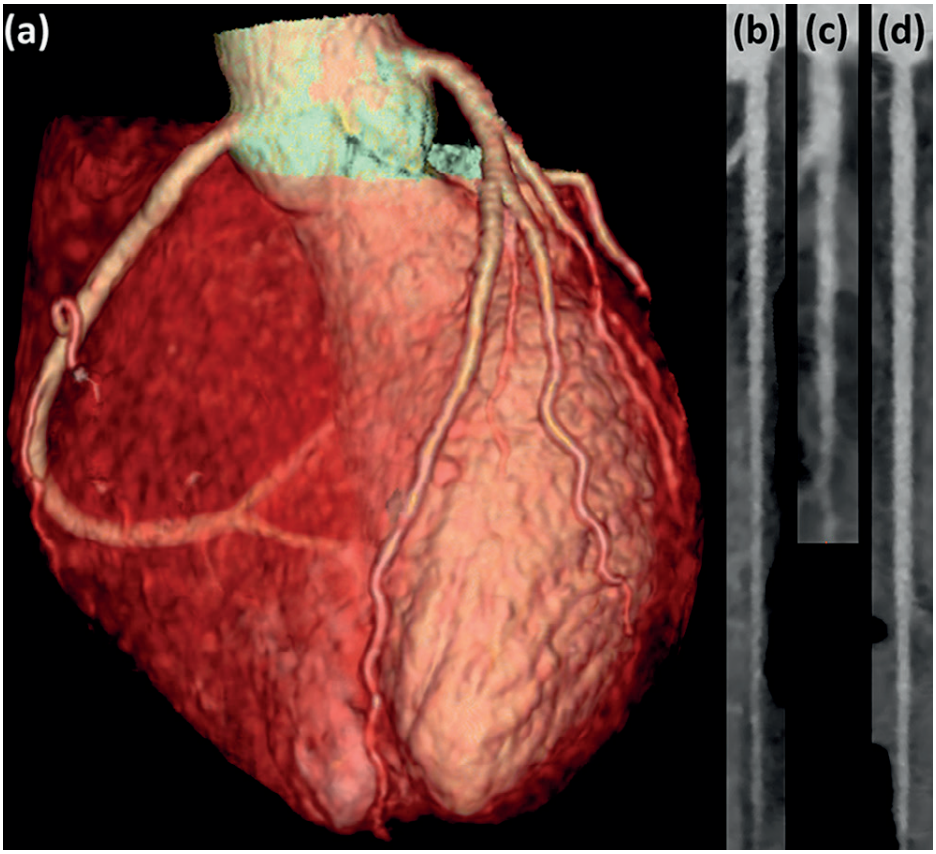

Figure 1: A 43-year-old woman (body mass index = 18.3 kg/m2) with a positive family history for coronary artery disease (CAD) was referred for exclusion of CAD due to dyspnea of unknown origin. The patient was scanned at a heart rate of 47 beats/min and was exposed to 0.22 mSv of radiation dose and 25 mL of contrast agent volume. Threedimensional volume-rendered images revealed normal coronary anatomy (a), and multi-planar reformations could exclude any obstructive CAD in the left anterior descending coronary artery (b), the left circumflex coronary artery (c), and the right coronary artery (d).

Quantitative Image Analysis

Mean attenuation in the aortic root was 412 } 89 HU (range, 248–750 HU) and the mean attenuation in LMA and RCA was 372 } 73 HU (range, 232–631 HU). Noise in the aortic root was 25 } 4 HU, and the average of the contrast-tonoise ratio in the LMA and RCA was 19 ±3.

Qualitative Image Analysis and Study Interpretability

An overview on the qualitative image analysis is given in Table 3. In 89 patients, a total of 1067 coronary artery segments with a diameter of ≥1.5 mm were evaluated (79.9%

of theoretically 1335 possible segments in 89 patients with 15 segments). Inter-rater reliability for image quality assessment was excellent regarding motion (ICC: 0.841), and good regarding noise and contrast agent enhancement (ICC: 0.711 and 0.701, respectively). In total, 1050 of 1067 (98.4%) coronary segments and 81 of 89 (91%) patients were of diagnostic image quality. Nondiagnostic image quality due to motion was found in 9 of 1067 (0.8%) coronary segments in 6 of 89 (6.7%) patients.

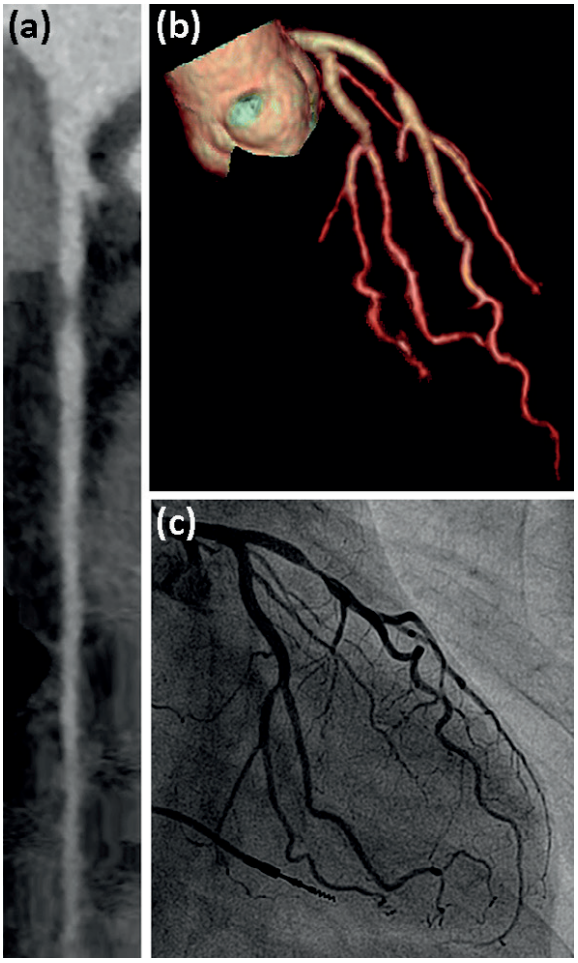

Figure 2: A 61-year-old female smoker (body mass index = 18.7 kg/m2) complained about recurrent atypical chest pain and was referred for exclusion of coronary artery disease. The patient was scanned at a heart rate of 62 beats/min and was exposed to 0.2 mSv of radiation dose and 25 mL of contrast agent volume. Coronary computed tomography angiography revealed a subtotal stenosis in the proximal LAD in the multiplanar reformations (a) and in threedimensional volume-rendered image (b). The diagnosis was confirmed by invasive coronary angiography (c), and the patient was successfully

TABLE 3. Image Quality and Study Interpretability

Variable	Segment Based	Patient Based
Motion		
Excellent (4.0)	907 (85.0%)	NA
Good (3.0–3.9)	112 (10.5%)	NA
Fair (2.0–2.9)	39 (3.7%)	NA
Nondiagnostic (1.0–1.9)	9 (0.8%)	6 (6.7%)
Noise		
Excellent	644 (60.4%)	NA
Good	293 (27.5%)	NA
Fair	122 (11.4%)	NA
Nondiagnostic	8 (0.7%)	4 (4.5%)
Contrast		
Excellent	644 (60.4%)	NA
Good	349 (32.7%)	NA
Fair	72 (6.7%)	NA
Nondiagnostic	2 (0.2%)	2 (2.2%)
Total number	1067	89
Total number of interpretable segments/patients	98.4%	91%

Numbers are given, and percentages of total amount are in parentheses. NA, not applicable.

Insufficient contrast agent enhancement rendered 2 of 1067 (0.2%) coronary segments nondiagnostic in 2 of 89 (2.2%) patients, of which 1 patient had a concomitant motion artifact and both also showed contrast artifacts. Noise artifacts resulting in eight nondiagnostic coronary segments (0.7%) were found in four patients (4.5%), two of which also had motion artifacts. However, in four of eight (50%) patients with a nondiagnostic segment, there was at least one other segment of diagnostic image quality with an obstructive lesion, allowing the reader nevertheless to obtain a firm diagnosis with regard to the presence of obstructive CAD. Thus, on an intentionto- diagnose basis, the radiation- and contrast-sparing protocol yielded a firm diagnosis in 85 of 89 (95.5%) of patients.

Determinates of Image Quality

Although BMI significantly correlated with noise measured in the aortic root (r = 0.196, $P < 0.001$), it did not have a significant impact on the qualitatively assessed noise score (r = −0.051, $P = 0.098$). Moreover, BMI did not significantly differ between patients with diagnostic and nondiagnostic coronary segments ($P = 0.271$). Of note, BMI did neither have an impact on mean attenuation in the proximal coronaries (r = −0.016, $P = 0.566$) nor on image quality regarding contrast agent enhancement (r = −0.016, $P = 0.601$). Image quality was significantly lower in small coronary segments compared to larger coronary segments (3.44 vs. 3.86, $P < 0.001$). Nevertheless, mean coronary attenuation

did not significantly differ between diagnostic and nondiagnostic coronary segments (P = 0.225). Heart rate correlated inversely and significantly with the image quality score regarding motion (r = −0.244, P < 0.001). By contrast, heart rate variability did not have an impact on image quality (r = 0.014, P = 0.645). With receiver-operator curve analysis and Youden's index, a cut-off heart rate of 67 beats/min was determined (Fig 3), below which nondiagnostic coronary segments were significantly less common (1 of 974 [0.1%] coronary segments and 1 of 81 [1.2%] patients) compared to a heart rate above 67 beats/min (8 of 93 [8.6%] coronary segments and 5 of 8 [62.5%] patients; P < 0.001).

DISCUSSION

The results of the present study support the implementation of a radiation- and contrast-sparing protocol as the latter yields excellent image quality. Our results demonstrate that a diagnostic scan can be achieved in 98.4% of all coronary segments. On an intention-to-diagnose basis, CCTA allowed conclusive evaluation with regard to the presence or absence of CAD in 95.5% of all patients. The median effective radiation dose of 0.5 mSv is slightly lower than in most low-dose CCTA studies exploring protocols that resulted in values for radiation dose in the submillisievert range (6,18,19). Only limited data are available on even lower radiation doses such as 0.21 mSv (20) or even 0.06 mSv (21), which may not be extrapolated to a large population because it either used complex iterative reconstruction algorithms that are currently too time consuming to process for clinical implementation or because scanning was confined to a selected population. A major contributor to the feasibility of ultra-low radiation dose CCTA imaging in our study, besides prospective ECG triggering with single-beat coverage, is the iterative reconstruction algorithm used. Compared to its precursor ASiR, ASiR-V uses more advanced system noise statistics as well as objects modeling and has added physics modeling. In the present study, increased noise did not have an impact on image quality (as visually assessed), although image noise (as measured in the aortic root) increased with higher BMI. This finding is most likely attributable to ASiR-V 100%, which reduces image noise so effectively that, apparently, differences in measured noise, although statistically significant, cannot be perceived by the naked eye. As a consequence of the shorter scanning times enabled by 16-cm coverage and because of the high proportion of patients scanned with 80 or 100 kVp, the median contrast agent volume could be substantially reduced. The low contrast agent volume injected in the present study is well in line with previously validated low-dose contrast agent protocols (4,22–24), but its feasibility in an unselected population has not yet been confirmed. Importantly, coronary attenuation compares well to values previously observed (4,25,26) and, as an essential characteristics of any contrast agent protocol, coronary attenuation remains constant across increasing BMI. Finally, the present study demon-

strates that heart rates up to 67 beats/min are acceptable for successful CCTA acquisition on a latest generation CT scanner with a gantry rotation time of 280 ms.

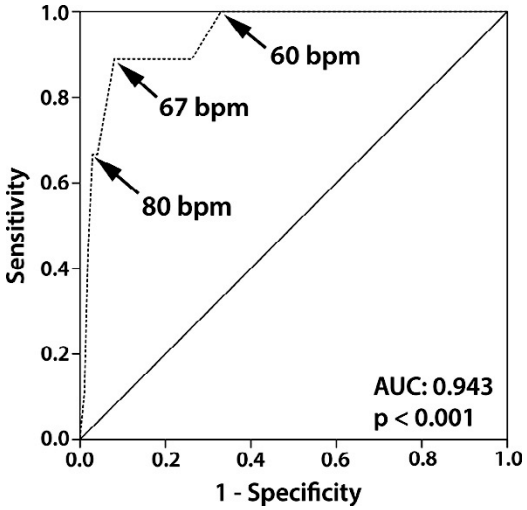

Figure 3: Receiver-operator characteristic curve illustrates the diagnostic performance of heart rate in the interpretability of coronary segments. Subsequently, Youden's index revealed an optimal heart rate cut-off of 67 beats/min for diagnostic image quality, with a sensitivity of 89% and a specificity of 92%.

Although previous studies have mainly focused on reduction of radiation dose, the present study highlights the additional potential of simultaneous reduction of contrast agent volume. This is clinically relevant as contrast-induced nephropathy, linked to increased morbidity and mortality, has a dose-dependent association (27–29). The fact that not only radiation dose, but also contrast agent volume can be substantially decreased shifts the benefit-to-harm ratio of CCTA even further toward the favorable side of clinical benefit. We acknowledge the following limitations to our study. First, the present study should be perceived as a pilot study, proving feasibility of a radiation- and contrast-sparing protocol in a small sample size with low prevalence of coronary atherosclerosis. Although the latter reflects adherence to the current guidelines, recommending CCTA for exclusion of CAD in patients with a low-pretest probability (ie 15–50%), larger follow-up studies are needed to prove the clinical value of this protocol in a more heterogeneous "real-world" population including patients with a higher degree of coronary atherosclerosis. Furthermore, we did not assess the diagnostic accuracy of CCTA by comparing our findings with the reference standard invasive coronary angiography. However, the aim of the present observational study was to evaluate the feasibility of a radiation- and contrast-sparing protocol in CCTA imaging in a real-world clinical setting consisting of an unselected, consecutive population. The fact that none of the patients referred for exclusion of CAD by CCTA presented with arrhythmia may reflect the introduction of a referral bias favoring the feasibility of CCTA in our study.

This, however, reflects a positive aspect of daily clinical routine as it demonstrates the growing awareness of contraindications to CCTA and appropriate patient selection for the best suitable test among the referring physicians. Nevertheless, future studies should assess the feasibility of this latest generation 256-slice CT scanner in patients with arrhythmia and uncontrolled heart rate. Finally, assessment of image quality may have been influenced by subjectivity. The inter-rater reliability, however, indicated good to excellent inter-observer agreement and argues against this bias. In conclusion, a radiation- and contrast-sparing protocol for CCTA on a latest generation 256-slice CT scanner yields diagnostic image quality in patients referred for CAD exclusion in daily clinical routine.

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Part III

Discussion

OVERVIEW DISCUSSION

I focused my research on current issues in patients with coronary artery anomalies, the associated risk of sudden cardiac death (SCD) and how non-invasive imaging can help to further risk stratify these patients. Particularly, young (aged below 35 years), physically active individuals with anomalous coronary arteries from the opposite sinus of Valsalva (ACAOS) are considered to be at higher risk for sports-related SCD (SrSCD) (1-5). Autopsy series showed that after hypertrophic cardiomyopathies, ACAOS are the second most common underlying cause of SrSCD in young athletes during or shortly after strenuous exercise and are believed to be the cause of up to one third of SCD in US army recruits (6, 7). In another large study assessing SrSCD in the USA, 11% of all SCD were due to underlying ACAOS, however, the absolute incidence was very low with of only 0.07/100.000 person-athlete years (8). It has to be mentioned that these calculated numbers reflect the risk of SCD in those who have already died, not the risk of death in those living with ACAOS. We could show (chapter 2.2) that the prevalence of ACAOS is 1.17% (9) and that ACAOS as an underlying cause of SrSCD in autopsied young athletes in Switzerland with only 2 (2.9%) of the cases is low (chapter 2.1) (10). This is in line with another report where SrSCD due to ACAOS were low (11). In another large study including 361 SrSCD, only four individuals died due to an underlying ACAOS in a combined 34 million patient-years (12). However, it is very important to identify those at risk compared to those being at lower risk. High-risk anatomic features such as interarterial course (IAC), slit-like ostium, intramural course, acute take-off angle with tangential vessel course and proximal narrowing of the anomalous vessel are considered to be predisposed for adverse cardiac events and SCD (1-5). In other studies, as well as our own, it could be shown (chapter 2.3) that patients with IAC have other associated high-risk anatomic features (13-15). Therefore, especially this group needs special attention and further evaluation.

Besides the young individuals involved in sports, who are diagnosed with ACAOS, a larger rate of coincidentally detected ACAOS is especially expected in the middle-aged and elderly population as the use of non-invasive imaging for the exclusion of coronary artery disease (CAD) is increasing. This was confirmed by our single center experience (chapter 2.2)(9). Cardiologists, cardiac imaging specialists and cardiac surgeons are often indecisive how to advise their patients since there is a lack of guidelines regarding cardiac imaging, sport restriction and treatment in individuals with ACAOS at all ages. The evidence of the current literature is rather weak and therefore, recommendations, and the variations between them, are broad and are still under debate. Indications for surgical correction remain controversial in certain cases and besides the clinical evaluation, non-invasive imaging techniques (as listed below) might be in the future even more important. With the exact description of anatomic high-risk features and tests for detecting myocardial ischemia as shown in our own experience (chapter 2.2- 2.4) (9, 15, 16) is crucial in the assessment and guidance for the treatment of individuals with ACAOS.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY/NUCLEAR IMAGING AND HYBRID IMAGING

Coronary Computed Tomography Angiography (CCTA) represents the primary non-invasive imaging modality to accurately visualize ACAOS three dimensionally, yielding a higher detection rate over invasive coronary angiography in the adults (9, 17). CCTA has seen substantial technical advancements over the last decade, particularly with respect to spatial resolution and a significant reduction in radiation dose exposure down to 0.21 - 0.5mSv, as also shown in our own study (chapter 2.5) (18, 19). A virtual angiographic view of CCTA helps to evaluate high-risk anatomic features, namely the slit-like origin. We could show that double-oblique multiplane reformatted images can be used to identify other high-risk anatomic features such as acute take-off angle, intramural and elliptical course and proximal vessel narrowing of the anomalous vessel (chapter 2.3) (15).

Nuclear imaging modalities are very useful in detecting underlying perfusion defects in ACAOS patients. Single-photon emission computed tomography myocardial perfusion imaging (SPECT – MPI) and positron emission tomography (PET) - MPI are useful to unmask ischemia in patients with ACAOS. De Luca and co-workers detected ischemia in ACAOS patients with SPECT-MPI in four out of five patients (20) and Uebleis et al. in one third of their patients (21). In contrast, we could show (chapter 2.3) that ischemia was mostly due to concomitant CAD and not due to ACAOS itself and hybrid CCTA/SPECT-MPI helped in this middle-age group to discriminate the impact of ACAOS from concomitant CAD (15). An important issue that should be kept in mind is that the standard vessel territory distribution is not applicable in patients with ACAOS, which therefore must be incorporated into the non-invasive imaging results. We were able to show that fusion hybrid imaging may address this issue by correctly allocating the affected vessel to the correct territory. Furthermore, with the use of hybrid CCTA/PET-MPI we could show in a case series (chapter 2.4) that even in the absence of perfusion defects, the coronary flow reserve was impaired in ACAOS supplied territories (16). Therefore, beside the anatomical description of high-risk features, further nuclear perfusion imaging tests/hybrid imaging is warranted, especially in unclear cases and might be helpful for further treatment decision making (9, 16, 21). However, it is not known which study protocol is most adequate for the evaluation of myocardial perfusion in patients with ACAOS. This is to some extent reflected by the heterogeneous choice of stress testing protocols applied in past studies and in our current study (chapter 2.3) (15). Intuitively, physical stress seems to reflect reality the most. However, there is evidence that results from physical stress tests might be false negative, especially because it is thought that ischemia in patients with ACAOS is intermittent in nature. In a study by Brothers et al. 9 of 16 patients, who had a pre-operative physical stress test presenting with cardiovascular symptoms, only 1 had an abnormal stress test (22). Additionally, the question is raised whether physical stress protocols with a minimal heart rate of 85% of the predicted maximum heart rate might be too low and does not reflect real world situations.

Therefore, it may be discussed whether a more intense physical exertion test beyond the level of the established standard test protocols is needed in order to increase the detection rate of potential perfusion defects induced by ACAOS (15). Invasive angiography studies showed that beside physical exercise stress protocols, dobutamine stress testing could be used as an alternative protocol and most likely imitate the hemodynamic circumstances of physical activity (20, 23). Such hypothetical anticipations have to be integrated into the risk stratification of a negative stress test. It must be mentioned that there are no case series or trials in the literature showing sensitivity or specificity for any form of ischemia detection for ACAOS and that further studies of serial functional imaging tests in corrected and non-corrected ACAOS patients are needed to answer this question.

SURGICAL CORRECTION AND SPORTS RESTRICTION

Recommendations state that patients with ACAOS should be restricted from sports until three months after successful operation and ruling-out ischemia, ventricular arrhythmia or tachyarrhythmia, or left ventricular dysfunction during maximal exercise testing at follow-up (24-26). Although post-operative outcome is favorable (27, 28), exercise restriction might not necessarily prevent the possibility of adverse cardiac events occurring with minimal activity or at rest. In addition, the psychological consequences of sports restriction and the known health sequelae of not exercising have to be taken into account. Moreover, there are even some reports of cases with SCD following successful surgical repair of ACAOS (29). This suggests that the value of an operation also has to come under scrutiny (22). Despite these considerations, it is now widely accepted that all patients with L-ACAOS or any other form of ACAOS with symptoms or signs of ischemia should undergo surgical repair and be restricted from sports until corrected and being without ischemia at follow-up. (27, 28). For R- ACAOS without either symptoms or a positive exercise stress test, permission to perform sports competitively may be considered after adequate counseling of the athlete and/or the athlete's parents (30). On the contrary to young athletes, decisions regarding the management of symptomatic middle-aged/older athletes or non-athletes is even more challenging (22, 28). To differentiate whether a middle-aged/older individual is symptomatic due to the ACAOS or other causes may be very difficult. For example, dyspnea, represented in a high proportion of symptomatic patients, can be of multiple underlying causes ranging from deconditioning to lung and cardiac diseases. Similarly, chest pain, palpitations and dizziness have a high prevalence in the general population and all come with a wide range of underlying causes, which are mostly benign and seldom harmful (31). Assigning these symptoms to the anomaly itself is difficult. We could recently show (chapter 2.3) that it seems that ACAOS in older patients might be less relevant compared to younger patients and that hybrid imaging is helpful in distinguishing CAD related and anomalous

related ischemia in this age group (15). Why older individuals might be less prone to ACAOS related adverse cardiac events is unknown (32, 33). Whether a stiffer aorta and stiffer coronary arteries could lead to less dynamic compression in older patients with ACAOS or a selection bias towards low risk patients is present, can only be speculated.

To sum up, our study showed that the prevalence and incidence of CAAs is not negligible. Although in our autopsy study sport-related SCD due to underlying CAAs, specifically ACAOS are rare, it seems that a certain risk for adverse cardiac events remains. Non-invasive cardiac imaging with the use of CCTA plays a key role in detecting and diagnosing CAAs. Our new low-radiation- and contrast agent protocols help to reduce the exposure to radiation and contrast agent in these patients. It is important to exactly describe the anatomic high-risk features and based on our studies to also identify patients with ischemia/scar related to CAAs. The different cardiac imaging modalities such as hybrid CCTA/SPECT-MPI or CCTA/PET-MPI, especially in middle-aged patients with possible concomitant CAD, allow to differentiate whether ischemia/scar are related to anomalous vessels or CAD. This might have an important impact on further treatment decision making. The possible benefits from surgical correction and sport restriction should be prudently balanced against the risk of an operation and the negative effect of not exercising. Therefore, decision should only be made after integrating all clinical and imaging information as well as discussion of the potential risks and benefits with the patient.

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Part IV

Summary (in English) and Samenvatting (Summary in Dutch)

Summary English

In the introduction section, an overview of coronary artery anomalies (CAAs) and current issues and the possible role of non-invasive imaging is presented. CAAs consist of a group of congenital disorder which can be divided into anomalies with an abnormal origin of the vessel, abnormal course of the vessel or abnormal termination of the vessel. The prevalence of CAA in the general population is low and estimated to be around one percent. Although most individuals with CAA are undetected as the CAA is clinically insignificant, some individuals and especially those with certain variants of CAAs, (namely anomalous coronary artery from the opposite sinus of Valsalva, ACAOS) may become symptomatic and experience adverse cardiac events. Particularly young athletes with ACAOS are considered to be at risk for sports-related sudden cardiac death (SCD). Beside the young individuals involved in sports and diagnosed with CAAs, a larger rate of coincidentally detected CAAs, especially in the middle-aged and elderly population with the increasing use of non-invasive imaging for the exclusion of coronary artery disease (CAD), is expected. The presented research focuses on the incidence of sports-related SCD with underlying CAAs and what role non-invasive imaging plays in the assessment and guidance for the treatment of individuals with CAAs.

Chapter 2.1 discusses the issue of sports-related SCD in young athletes. We were interested in the assessment of the incidence and characteristics of sports-related SCD and in the underlying causes of sports-related SCD including CAAs. We therefore analyzed retrospectively the forensic reports of sports-related SCD in young individuals in Switzerland. Data were compared to the sports participation behavior of the Swiss population. In a total of sixty-nine sports-related SCD, CAD was the most common underlying pathology of sports-related SCD, followed by hypertrophic cardiomyopathy and "unremarkable findings" at autopsy. CAAs were only diagnosed in a very few number of autopsies. This is in contrary to other older reports where autopsy series showed that after hypertrophic cardiomyopathies, CAAs were the second most underlying cause of sports-related SCD. Our findings might underline more recent reports, that the numbers of sports-related SCD associated with CAAs might be overestimated.

In Chapter 2.2 we present a single center study, looking at prevalence, incidence and characteristics of CAA detected by coronary computed tomography angiography (CCTA). CAAs were retrospectively sought in 5634 consecutive patients referred for CCTA. We identified 145 patients with CAA resulting in an overall prevalence of 2.6% and cumulative incidence of 2.1% in all patients referred for CCTA in the observed period. The prevalence of CAAs detected by CCTA is therefore non-negligible. Due to its non-invasive nature, relatively low cost and low radiation exposure, a further increase of the utilization of CCTA may be expected which may consequently be paralleled by an in-

creasing absolute number of incidentally detected CAAs. Hence, awareness of the main issues and possible management strategies regarding CAAs are of importance for every treating physician.

As discrimination between ACAOS and CAD related perfusion defects, especially in middle-aged patients may be difficult, Chapter 2.3 focused on investigating the value of hybrid CCTA/ single photon emission tomography myocardial perfusion imaging (SPECT-MPI) in patients with ACAOS and possible concomitant CAD. We retrospectively identified 46 middle-aged patients with ACAOS revealed by CCTA who underwent additional SPECT-MPI. CCTA/SPECT-MPI hybrid imaging findings (ischemia or scar) were analyzed according to the territory subtended by an anomalous vessel or a stenotic coronary artery. Myocardial ischemia or scar was found only in patients who had concomitant obstructive CAD in the vessel matching the perfusion defect as evidenced by hybrid CCTA/SPECT imaging. Hybrid CCTA/SPECT-MPI represents a valuable non-invasive tool to discriminate the impact of ACAOS from concomitant CAD on myocardial ischemia. Our results suggest that in a middle-aged population myocardial ischemia due to ACAOS per se may be exceedingly rare and is more likely attributable to concomitant CAD.

Chapter 2.4 describes the value of fused cardiac hybrid imaging with CCTA and positron emission tomography myocardial perfusion (PET-MPI) in patients with complex coronary artery anomalies (CCAAs). In this retrospective, single center study, seven consecutive patients with CCAAs who underwent clinically indicated hybrid CCTA/PET-MPI in our clinic were included. The findings from both modalities and fused cardiac hybrid imaging were evaluated in these patients. Out of the seven patients with CCAAs, two had Bland-White-Garland anomaly, two showed a coronary artery fistula, two showed a “single right” and one patient showed a “single left” coronary artery. Semi-quantitative fused hybrid CCTA/PET-MPI depicted inferolateral scar matching the territory of a non-anomalous vessel with significant concomitant CAD in one patient only. By contrast, analysis of quantitative myocardial blood flow (MBF) as assessed by fused hybrid CCTA/PET-MPI revealed abnormally reduced flow capacities in the territories subtended by the anomalous vessels in four patients. In this case series of middle-aged patients with CCAA, perfusion defects as assessed by semi-quantitative PET-MPI were rare and attributable to concomitant CAD rather than to the anomalous vessel itself. By contrast, impaired MBF as assessed by quantitative hybrid CCTA/PET-MPI was revealed in the majority of patients in the vessel territories subtended by the anomalous coronary artery itself. Fused hybrid CCTA/PET-MPI incorporating information on morphology and on semi-quantitative and quantitative myocardial perfusion may provide added value for the management of patients with CCAA.

As CCTA is a primary investigative tool in patients with CAAs to describe the anatomic high-risk features, reduction in radiation dose and contrast agent would be preferable. We therefore aimed to evaluate in Chapter 2.5 the impact of the latest CCTA techniques allowing a radiation- and contrast-sparing protocol on image quality by 256-slice CCTA using prospective electrocardiogram triggering. Consecutive patients for CAD

exclusion were included. Tube voltage, tube current as well contrast agent volume and flow rate were adapted to body mass index. Signal intensity was measured by placing a region of interest in the aortic root, the left main artery, and the proximal right coronary artery. Two independent blinded readers semi-quantitatively assessed the image quality regarding motion, noise, and contrast on a four-point scale. Median contrast agent volume and median effective radiation dose were 35 mL and 0.5 mSv, respectively. This study showed that a radiation- and contrast-sparing protocol for CCTA on a latest generation 256-slice computed tomography scanner yields diagnostic image quality of coronary arteries in daily clinical routine.

The prevalence and incidence of CAAs is not negligible. Although in our autopsy study sport-related SCD due to underlying CAAs, specifically ACAOS are rare, it seems that a certain risk for adverse cardiac events remains. Non-invasive cardiac imaging with the use of CCTA play a key role in detecting and diagnosing CAAs. Our new CCTA protocols help to reduce the exposure to radiation and contrast agent in these patients. It is important to exactly describe the anatomic high-risk features and based on our studies to also identify patients with ischemia/scar related to CAAs. The different cardiac imaging modalities such as hybrid CCTA/SPECT-MPI or CCTA/PET-MPI, especially in middle-aged patients with possible concomitant CAD, allow to differentiate whether ischemia/scar are related to anomalous vessels or CAD. This might have an important impact on further treatment decision making. The possible benefits from surgical correction and sport restriction should be prudently balanced against the risk of an operation and the negative effect of not exercising. Therefore, decision should only be made after integrating all clinical and imaging information as well as discussion of the potential risks and benefits with the patient.

Samenvatting (Summary in Dutch)

In de introductie wordt een overzicht gegeven van bekende coronair anomalieën (CAA's), de mogelijke gevolgen van CAA en methoden van non-invasieve beeldvorming. CAA's vallen onder aangeboren cardiale afwijkingen, en kunnen worden verdeeld in anomalieën met een afwijkende oorsprong, verloop of terminatie van een coronairarterie. De prevalentie van CAA's in de algemene populatie is laag en wordt geschat op circa 1 procent. Aangezien de meeste mensen met een CAA asymptomatisch zijn, blijven ze vaak onopgemerkt. Sommige CAA varianten (oorsprong coronairarterie uit de tegenovergestelde sinus van Valsalva, ACAOS) kunnen symptomatisch zijn, met ongewenste, cardiale manifestaties. Vooral jonge atleten met een ACAOS hebben een verhoogd risico op sport-gerelateerde, plotse hartdood (SCD). Naast jonge atleten met een CAA, worden CAA's in toenemende mate ontdekt bij mensen van middelbare en oudere leeftijd. Dit is te verklaren door toenemende gebruik van non-invasieve beeldvorming van de coronairarteriën om coronarialijden (CAD) uit te sluiten. Dit wetenschappelijk proefschrift onderzoekt en beschrijft de incidentie van sport-gerelateerde, plotse hartdood bij CAA's en de rol van non-invasieve beeldvorming bij screening en behandeling.

In **Hoofdstuk 2.1** wordt sport-gerelateerde, plotse hartdood bij jonge atleten onderzocht en de resultaten beschreven. De incidentie, karakteristieken, en onderliggende oorzaken van sport-gerelateerde, plotse hartdood waaronder CAA's worden beschreven. Hiervoor werd een retrospectieve analyse verricht aan de hand van forensische rapporten van sport-gerelateerde, plotse hartdood bij jonge, Zwitserse atleten. Deze data werd vervolgens vergeleken met gegevens van de algehele Zwitserse populatie. In totaal waren er negenenzestig gevallen van sport-gerelateerde, plotse hartdood, waarbij bij obductie coronarialijden de meest voorkomende onderliggende pathologie betrof, gevolgd door hypertrofische cardiomyopathie en 'alledaagse niet-specifieke bevindingen'. In tegenstelling tot andere studies werd CAA in onze studie minder frequent gevonden. In deze studies werd namelijk aangetoond dat na de hypertrofische cardiomyopathie, juist CAA de op een na meest voorkomende oorzaak was van sport-gerelateerde, plotse hartdood. Onze bevindingen komen overeen met recentere studies, die ook aantonen dat de prevalentie van CAA bij sport-gerelateerde plotse hartdood mogelijk wordt overschat.

In **Hoofdstuk 2.2** beschrijven we de resultaten van een retrospectieve, single-center studie waarin de prevalentie, incidentie en karakteristieken van CAA gedetecteerd bij coronair computer tomografie angiografie (CCTA) wordt onderzocht. Bij 145 van 5634 opeenvolgende patiënten die waren verwezen voor CCTA, werd een CAA gediagnosticeerd. Dit resulteerde in de geobserveerde periode, in een prevalentie van 2.6% en een cumulatieve incidentie van 2.1%. De prevalentie van bij CCTA gedetecteerde CAA's is derhalve niet verwaarloosbaar. Doordat CCTA een non-invasieve vorm van

beeldvorming is, met relatief lage kosten en stralingsbelasting, is te verwachten dat het in toenemende mate gebruikt zal gaan worden. Hierdoor is de verwachting dat ook het aantal per toeval ontdekte CAA's zal toenemen. Derhalve is het van belang dat iedere behandelaar op de hoogte is van de verschillende CAA's, de prognose en behandeling.

Het onderscheid tussen ACAOS en coronarialijden-gerelateerde perfusiedefecten kan, met name bij patiënten van middelbare leeftijd, moeilijk zijn. Hoofdstuk 2.3 onderzoekt de rol en waarde van hybride CCTA/single photon emissie tomografie myocardiaal perfusie imaging (SPECT-MPI) in patiënten met een ACAOS en verdenking op coronarialijden. We onderzochten 46 patiënten, met een door CCTA vastgesteld ACAOS, die aanvullend een SPECT-MPI ondergingen. De bevindingen van de hybride CCTA/SPECT-MPI-beelden (ischemie dan wel littekenvorming) werden geanalyseerd door de desbetreffende coronair anomalie of obstruerende coronairarterie te relateren het stroomgebied van desbetreffende coronairarterie. Myocardischemie of littekenvorming werd alleen gevonden in patiënten met bijkomstig obstructief coronarialijden van de desbetreffende coronairarterie. Hybride CCTA/SPECT-MPI is dus een waardevolle, non-invasieve methode om te discrimineren tussen myocardischemie o.b.v. een ACAOS of o.b.v. coronarialijden. Onze resultaten suggereren daarmee dat in een patiëntenpopulatie van middelbare leeftijd, myocardischemie veroorzaakt alleen ACAOS uiterst zeldzaam is en vooral wordt veroorzaakt door bijkomstige coronarialijden.

Hoofdstuk 2.4 beschrijft de waarde van hybride, cardiale beeldvorming door middel van een fusie van CCTA en positron emissie tomografie myocardiaal perfusie imaging (PET-MPI) in patiënten met complexe coronair anomalieën (CCAA's). In deze retrospectieve, single-center studie werden in totaal 7 patiënten met een CCAA geïncludeerd, met een klinische indicatie voor hybride CCTA/PET-MPI. De bevindingen van individuele en gefuseerde, hybride beelden werden geëvalueerd. Van de 7 patiënten met een CCAA, hadden twee een Bland-White-Garland anomalie, twee een coronaire fistel, twee enkel een rechter coronairarterie en één enkel een linker coronairarterie. Een semi-kwantitatieve analyse van de gefuseerde, hybride CCTA/PET-MPI beelden toonde slechts bij één patiënt littekenvorming inferolateraal, overeenkomend met het stroomgebied van een normale verlopende coronairarterie waarin bijkomstig stenostisch coronarialijden. Kwantitatieve analyse van de myocardiale perfusie (MBF) toonde een afgenomen perfusiecapaciteit in de stroomgebieden van de coronair anomalieën van vier patiënten. Perfusiedefecten werden alleen gezien bij semi-kwantitatieve analyse van de gefuseerde, hybride CCTA/PET-MPI-beelden en toe te schrijven aan bijkomstig coronarialijden. Een verminderde MBF in het stroomgebied van de desbetreffende coronair anomalie werd in de meerderheid van de patiënten aangetoond. Hybride CCTA/PET-MPI waarbij zowel morfologische informatie als informatie over (semi-)kwantitatieve myocardiale perfusie wordt verkregen, kan van toegevoegde waarde zijn bij de behandeling van CCAA.

Vanwege het feit dat CCTA uitermate geschikt is als primaire onderzoeksmethode om hoog risico kenmerken in patiënten met CAA's te beschrijven, is het van belang de

bestralingsbelasting en de hoeveelheid contrastvloeistof te reduceren. In Hoofdstuk 2.5 wordt m.b.v. de meest recente CCTA technieken die bestralingsbelasting en contrastmiddel reduceren de beeldkwaliteit van een 256-slice CCTA met prospectieve, elektrocardiogram triggering onderzocht. Opeenvolgende patiënten verwezen voor het uitsluiten van coronarialijden werden geïncludeerd. Het voltage en de spanning van de röntgenbuis, alsmede de hoeveelheid contrastvloeistof en de snelheid van de injectie (flow rate) werden aangepast o.b.v. lichaamsgewicht van de patiënt. De signaalintensiteit werd gemeten in de aortawortel, de linker coronairarterie en de rechter coronairarterie. De beeldkwaliteit werd door twee onafhankelijke, beoordelaars beoordeeld op beweging, ruis en contrast, gebruikmakend van een vierpuntenschaal. Het mediane volume van de gebruikte contrastvloeistof en de mediane bestralingsbelasting waren respectievelijk 35 milliliter en 0.5 mSv. Deze studie toont aan dat een CCTA protocol met een gereduceerde bestralingsbelasting en hoeveelheid contrastvloeistof op een een 256-slice CCTA, in staat is een diagnostische beeldkwaliteit te produceren voor het afbeelden van de coronairarteriën in de dagelijkse kliniek.

De prevalentie en de incidentie van CAA's in niet verwaarloosbaar. Hoewel in onze obductiestudie bij sport-gerelateerde plotse hartdood door ACAOS slechts zelden voorkomt, lijkt het risico op ongewenste, cardiale manifestaties bij CAA toch verhoogd. Non-invasieve beeldvorming door middel van CCTA speelt een belangrijke rol in het detecteren en diagnosticeren van CAA's. Onze moderne CCTA protocollen en technieken kunnen de hoeveelheid contrastmiddel en stralingsbelasting reduceren, zonder dat dit ten koste gaat van de diagnostische kwaliteit. Verder is het belangrijk om de anatomische en hoog risico kenmerken te beschrijven en patiënten met ischemie en/of littekenvorming t.g.v. CAA's te identificeren. Onze studies tonen aan dat m.b.v. hybride CCTA/SPECT-MPI of CCTA/PET-MPI het mogelijk is te differentiëren tussen ischemie en/of littekenvorming bij patiënten van middelbare leeftijd door obstructief coronarialijden of door een CAA. Deze differentiatie heeft belangrijke gevolgen voor de behandelingsstrategie. Desalniettemin zouden de mogelijke positieve effecten van chirurgisch ingrijpen/correctie van de anomalie en een sportverbod opgewogen moeten worden tegen het risico van een operatie en de negatieve effecten van inactiviteit. De uiteindelijke beslissing kan daarom pas worden genomen na verzameling van alle klinische informatie, optimaal afbeelden van de anomalie en kritische bespreking van de voor-/en nadelen van operatief ingrijpen met de patiënt.

Part V

Valorization

Valorization

Possible valorization based on the present research in sudden cardiac death in athletes

In order to decrease the burden of sudden cardiac death in athletes, advances have been made in incorporating a pre-participation screening, including an electrocardiogram (ECG) and a questionnaire in individuals engaged in competitive physical activity prior to commencing sports. Although the ECG is useful in detecting certain underling cardiac conditions, interpretation of the ECG is examiner and experience dependent. Furthermore, physician involved in sports medicine can be from all different specialties, also some, not involved in every day ECG reading. It would be therefore useful, and in the future hopefully available to read these ECG automatically. This would allow consistency throughout the different readers and all the ECGs information, clinical information and questionnaires could be easily stored and be available for future prospective outcome studies. Furthermore, automated risk calculation for possible presence of coronary artery anomalies would propose downstream imaging testing only in selected athletes depending on clinical data, questionnaire, ECG data, age, gender and sports behavior. The combination of specific patient selection and the new scanning protocols in coronary computed tomography angiography or the use of other imaging modalities such as cardiac magnetic resonance imaging (MRI) would prevent athletes from unnecessary high radiation and contrast agent exposure. Finally, incorporation all the information from the imaging studies, calculation of the risk of sudden cardiac death would be possible and would markedly help the physician in proper sports behavior and surgical correction counseling of patients/athletes.

Future valorization based non- invasive cardiac imaging and anomalous coronary arteries

Non-invasive cardiac imaging is a young sub-specialization of cardiology/radiology/ nuclear medicine and is developing very fast. The future will lead us in the direction of automated reconstruction and analysis tools. Further, radiation dose reduction, reduction of artifacts and evaluation of the different modalities, with the question of which patient with which coronary artery anomaly needs which imaging modality to best guide decision making and treatment will be future research fields. In patients with anomalous coronary arteries, automated reconstruction of coronary computed tomography angiography data with exact, reproducible automated measurements of the anatomic high-risk features would help to maintain a consistency between readers and to avoid inaccuracies. Further, outcome association of different automated measured anatomic high-risk features of CAA's and non-invasive stress imaging testing's of existing registries would be facilitated and would help us in the understanding of this complex entity.

Part VI

Acknowledgments and curriculum vitae

Acknowledgments

Beside its very simple purpose of pumping blood in the circulatory system and providing oxygen to the different organs, the heart has been connected to emotions and feelings within the different time periods of mankind. In Egyptian mythology, the heart was considered to contain some vital essence of the soul. The heart was preserved with mummification because it was believed that the heart was the seat of thinking and the source of the soul, memories, emotions and personality. Moreover, it was thought the heart would be weighed during judgement after death. The Greeks firmly believed that the heart is controlling everything. In addition to that, Aristotle was sure that the heart is the source of intelligence and sensation. Furthermore, the Roman physician Galen developed a theory that the heart was said to be where emotions originated, while rational thought took place in the brain, and passions originated in the liver. The heart is indeed connected to our feelings and reacts instantaneously by changing heart rate, stroke volume and blood pressure depending on our emotions, thoughts and physical activity. Nowadays, we know that a heart can even be truly broken after an emotional event. As cardiologists, we not just simply want to treat the heart, but also raise a claim to treat the patient by a holistic approach.

During my life and my medical education, I met many people who became friends, accompanied me, helped me, from whom I learned, with whom I shared. I would like to take the opportunity to thank a few of them.

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> “The best and most beautiful things in the world cannot be seen or even touched - they must be felt with the heart» – Helen Kell

Curriculum vitae

Christoph Gräni was born (25th , May 1981) in Bern and raised in Tafers, Switzerland. He attended the Rudolf Steiner School in Bern and Ittigen and after finishing the College Ste Croix in Fribourg, he started his first two years of undergraduate medicine at the University of Fribourg. He continued medicine school at the University of Zurich and during that time, Christoph spent half a year on elective as well as travelling in Australia, New Zealand and Asia. He also obtained his medical degree and doctoral thesis at the University of Zurich and he completed all the USMLE steps in order to receive the Educational Commission for Foreign Medical Graduates certificate for the USA. Before starting his clinical residency, Christoph spent two months working and travelling in Tanzania, Africa. After completing a year of surgery in Horgen, Zurich and completing his internal medicine residency in Zug and Zurich, he started his cardiology residency at the University Hospital in Bern under Prof. Bernhard Meier and Prof. Stephan Windecker. He finished his cardiology residency with a fellowship in cardiac imaging (coronary computed tomography angiography, cardiac magnetic resonance imaging and nuclear cardiology, which included single photon emission computed tomography and positron emission tomography) at the University Hospital in Zurich under Prof. Philipp Kaufmann. Christoph was thereafter board certified in internal medicine and cardiology. He also underwent the executive four year postgraduate studies in medical sciences at the Private University of Liechtenstein. Beside his research interest in cardiac imaging and sudden cardiac death, Christoph has also attained his certification in sports medicine and has an avid interest in clinical work and research in the field of sports cardiology. He received grants from Switzerland and got the unique opportunity to undergo a fellowship in non-invasive cardiac imaging with a focus on cardiac magnetic resonance imaging at the well renown Brigham and Women's Hospital, Harvard Medical School, Boston, USA under Prof. Raymond Kwong. Christoph is currently working at the Brigham and Women's Hospital on a project of myocarditis detection and finding new predictors in cardiac magnetic resonance imaging for the risk stratification in patients with suspected myocarditis in order to prevent sudden cardiac death in these patients.

Beside his fascination for cardiology, cardiac imaging and sports cardiology, Christoph loves to practice all kinds of sports including running, cycling, hiking, snowboarding and skiing. He is fascinated by different cultures, keeps an open mind and loves to travel the world - he is always in search of exploring the human being and all aspects of life.

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PRESENTATIONS/POSTERS

(10) **Gräni C. et al.** Sports behavior in middle-aged individuals with uncorrected anomalous coronary artery from the opposite sinus of Valsalva, poster presentation AHA, New Orleans 11/2016

(9) **Gräni C. et al.** Middle-aged individuals with anomalous coronary artery from the opposite sinus of Valsalva – a retrospective matched cohort outcome study. Poster presentation ESC, Rome 08/2016

(8) **Gräni C. et al.** Cardiac computed tomography angiography and positron emission tomography myocardial perfusion hybrid imaging in complex coronary artery anomalies – case series. Poster presentation SCR, Davos 05/2016

(7) **Gräni C. et al.** Outcome in middle-aged individuals with anomalous coronary arteries originating from the opposite sinus – A case control study. Poster presentation ACC, Chicago 04/2016

(6) **Gräni C. et al.** Sports-related sudden cardiac death in Switzerland classified by static and dynamic components of exercise. Poster presentation SGSM, Tenero 10/2015

(5) **Gräni C. et al.** SPECT myocardial perfusion imaging findings in malignant coronary artery anomalies. Poster presentation ESC, London 08/2015

(4) **Gräni C. et al.** Sports behavior and occurrence of first event in young and normal weight myocardial infarction patients. Oral and Poster presentation SGSM, Interlaken 10/2014

(3) **Gräni C. et al.** Sudden cardiac death in young athletes – data from the Swiss registry. Oral presentation ESC, Barcelona 08/2014

(2) **Gräni C. et al.** Diagnostic accuracy of reproducible chest wall tenderness as a bedside test to rule out suspected myocardial infarction in patients presenting with acute chest pain. Best Poster tour ESCIM, Geneva 05/2014

(1) **Gräni C. et al.** The impact of autonomic nervous system activity on markers of arterial stiffness in male amateur endurance athletes. Poster presentation EACPR, Amsterdam 05/2014