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Protocol

Screening for coronary artery disease using primary evaluation with coronary CTA in aviation medicine (SUSPECT): study design

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ABSTRACT

Background: Sudden in-flight incapacitation of aircrew may cause an airplane crash. Important causes are major adverse cardiac events, such as myocardial infarction and sudden cardiac arrest. Aircrew of the Royal Netherlands Air Force (RNLAF) are required to undergo periodic cardiac screening, including bicycle exercise-testing. Unfortunately, this modality lacks diagnostic accuracy for relevant coronary artery disease (CAD) in low-risk populations similar to military aircrew. Cardiac CT, however, comprising Coronary Artery Calcium score (CACS) and coronary CT angiography (CCTA), is able to adequately detect (subclinical) CAD with high negative predictive values in low-risk populations and may provide opportunity for early interventions.
Methods: This was a prospective, single-center, cohort study of 250 military aircrew. Asymptomatic aircrew ≥40 years are asked to undergo a voluntary cardiac CT following routine aeromedical examination. Prevalence and severity of CAD will be described according to the CAD-RADS system, including coronary artery calcium score (CACS) and high risk plaque features. The primary endpoint is relevant CAD, defined as a composite of a coronary stenosis ≥50% and/or CACS >100 Agatston Units. The secondary endpoint is ‘aeromedically significant CAD’, defined by national military regulations as a left main stenosis of >30%, any luminal stenosis ≥50%, and/or an aggregate coronary stenosis of ≥120%.
Conclusions: The aim is to assess the value of cardiac CT for routine aeromedical screening in asymptomatic Dutch military aircrew aged ≥40 years, in comparison to the current cardiac screening protocol which includes an exercise ECG.
Trial Registration: Clinical trial registered on clinicaltrials.gov number NCT05508893.

Keywords: Coronary artery disease, Computed tomography angiography, Aerospace medicine, Coronary artery calciumscore, Pilots

INTRODUCTION

Cardiac events are a leading cause of sudden in-flight incapacitation in both civilian and military aviation and can have significant consequences.[1,2] Military pilots suffer higher levels of occupational stress than civilian pilots due to accelerating Gz forces, (mild) hypoxia, and irregular work in austere environments, (unhealthy) squadron lifestyle and combat stress. This makes screening for (sub) clinical CAD important.[3] The relevance of screening for heart disease in asymptomatic subjects in occupations involving high-hazard populations (e.g. military aircrew) is well recognized.[4] As determined by Military Aviation Regulations (MAR) of the RNLAF, all military aircrew are required to undergo cardiac screening. In addition to clinical definitions of CAD, the MAR uses aeromedically significant CAD, defined according to the definitions of the NATO working group on aviation cardiology as a left main stenosis of >30%, a luminal stenosis ≥50%, or an aggregate stenosis of ≥120%.[5] This is based on the '1% rule' used in civil aviation, stating that the risk of an aeromedical event must be lower than 1 % per year.[6] Since a coronary artery calcium score (CACS) >100 A° bears a risk for coronary events of more than 1%, this is also considered aeromedically significant CAD (Table 1).[3]

Table 1: Calcium score (CACS) related to cardiac events.[3]

CAC	0	1-9	10-99	100-399	400-1000	>1000
Number	249	51	202	263	212	112
Revascul-arisation/MI/SCD	3	0	6	8	17	12
Annual event rate (%)	0.45	0	1.11	1.14	3.00	4.01

Note: Event rates for revascularisation, myocardial infarction (MI) and sudden cardiac death (SCD) with various coronary calcium scores in over 32 months in 1153 patients, median age 58±10 years.

Routine aeromedical screening for cardiovascular disease consists of a resting electrocardiogram (ECG), a clinical risk score (i.e. the Reynolds risk score) and an exercise ECG. In case of an abnormal exercise ECG, subjects are referred to the cardiologist in the Central Military Hospital in Utrecht for further assessment. The efficacy of a screening protocol using exercise ECG, however, has been questioned because of suboptimal diagnostic value for detection of CAD in populations similar to aircrew.[7,8]

We hypothesize that primary screening using cardiac CT may improve both diagnostic and prognostic characteristics. Cardiac CT comprises CACS and Coronary CT angiography (CCTA). Both modalities have proven to be an effective modality for the detection of CAD in different populations.[9-11] CACS is a good surrogate measure for CAD, with excellent predictive value that surpasses standard risk factors, even in persons with no cardiovascular risk factors.[3,12,13] However, CACS does not provide any information about coronary anatomy, the non-calcified part of the atherosclerotic plaque or the presence of coronary stenoses, which can cause cardiovascular events.[14] CCTA offers an excellent visualization of the coronary anatomy and luminal stenosis, at an acceptable radiation exposure. Specificity and sensitivity of CCTA for the detection of CAD are high, resulting in a negative predictive value of obstructive CAD of almost 100% in low-risk subjects.[9,15] In addition, detailed information can be obtained on atherosclerotic plaque characteristics and plaque burden, including high risk plaque features (i. e.; spotty calcium, 'napkin ring sign', positive remodeling, low attenuation plaque).[16] A number of studies have reported that up to 50% of patients who present with an ST-elevation myocardial infarction (STEMI) do not have clinically significant obstructive CAD.[17]

Study aim

The aim of the study was to assess the value of cardiac CT for clinically and 'aeromedically' relevant CAD in asymptomatic Dutch military aircrew aged ≥40 years, in comparison to the current cardiac screening protocol, including exercise ECG.

The primary endpoint is relevant CAD, defined as a composite of a coronary stenosis ≥50% and/or CACS >100 Agatston Units. The secondary endpoint is 'aeromedically significant CAD' (defined by national military regulations as a left main stenosis of >30%, any luminal stenosis ≥50%, and/or an aggregate coronary stenosis of ≥120%). This is of particular interest in our population, because of its relevance for flying restrictions. In addition, the prevalence of mild coronary stenosis defined as 25-49% stenosis and vulnerable (high risk) plaque features will be described.

METHODS

Design and population

SUSPECT is a prospective cross-sectional study. Asymptomatic military aircrew ≥40 years old, who are employed by the RNLAF and required to undergo cardiac screening during their aeromedical examination, are eligible for study inclusion. Participation is on a voluntary basis. All collected data is pseudonymised and stored on a secured computer, in accordance with General Data Protection Regulations. Exclusion criteria are (1) (a)typical angina, (2) prior myocardial infarction, percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG), (3) left ventricular ejection fraction <35%, (4) CT related contraindications such as irregular heart rhythm or tachycardia unresponsive to beta blockade, allergy to iodine contrast fluid, (5) renal insufficiency (eGFR <60 ml/min/1.73 m^2), or (6) pregnancy.

Routine proceedings

All aircrew of the RNLAF are required to undergo a aeromedical examinations in the Center for Man in Aviation (CMA).[5] This includes a medical and family history, assessment of cardiac risk factors using Reynold's Risk Score, physical examination, resting ECG and blood and urine tests (Table 2).[18] In addition, a standardized bicycle exercise test is performed every 5 years after the age of 40 and every two years after the age of 50. If significant abnormalities occur, the subject is referred to the cardiologist for further diagnostic work-up.[19]

Table 2: Laboratory examinations performed during routine aeromedical examinations in the RNLAF.

Laboratory examinations	
Venous blood	Glucose, creatinine, total cholesterol, triglycerides, high density lipoprotein (HDL), high sensitivity C-reactive protein, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin, amylase, white blood cell count, red blood cell count, hematocrit, hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets.
Urine	Specific gravity, pH, leukocytes, nitrite, proteins, glucose, ketones, urobilinogen, bilirubin, erythrocytes.
Calculated	Low density lipoprotein (LDL) and estimated glomerular filtration rate (eGFR).

Study proceedings

Subjects will undergo cardiac CT (Brilliance iCT or dual-detector spectral CT 7500, Philips Healthcare, Best, The Netherlands) using prospective ECG-triggering in a diastolic phase (78%) and 0.4 mg sublingual nitroglycerin spray. A beta blocker (metoprolol) is administered if the heart rate is >65 beats per minute. Scan parameters are adjusted to weight < or ≥80 kg. A non-contrast cardiac scan (120 kV and 50-60 mAs) is performed to calculate CACS. Scanning parameters for CCTA are as follows:70-80 ml contrast (Iopromide 300 I/mg, Bayer Healthcare, Berlin, Germany) injected intravenously followed by 50 ml 50% contrast / 50% saline mix and a 30-40 ml saline flush at 6-6.7 ml/sec; 80/128×0.625 collimation; 0.9 mm reconstructed slice thickness; 0.27 s gantry rotation-time, 100-120 kV and 210-300 mAs.

The CT scans are sent to a workstation (IntelliSpace, Philips Healthcare, Best, the Netherlands) to calculate CACS using the Agatston method and use CCTA to make centre-line multi-planar-reconstructions of the coronary arteries.[20] All CT scans are assessed by an experienced cardiovascular radiologist. Presence, type of coronary artery atherosclerotic plaque (non-calcified, calcified or partially calcified) and degree of luminal stenosis is graded according to the modified 17-segment American Heart Association coronary model using the CAD-RADS system: no plaque and no stenosis (CAD-RADS 0); minimal stenosis (1-24%, CAD-RADS 1); mild stenosis (25-49%, CAD-RADS 2); moderate stenosis (50-69%, CAD-RADS 3), severe stenosis (70-99% in 1 or 2 vessels (CAD-RADS 4A); >50% stenosis in left main or ≥70% in 3 vessels (CAD-RADS 4B); and total occlusion (CAD-RADS 5).[21,22] Additionally, all segments with more than 30% stenosis are counted towards aggregate stenosis[3] High risk plaque features (positive remodeling, low attenuation plaque (<30 HU), spotty calcification and napkin ring sign) are used to label a vulnerable plaque with an additional CAD-RADS V modifier label if a single coronary plaque has ≥two high risk plaque features**.**[21, 23]

Study results are discussed by the SUSPECT working group, consisting of four cardiologists, one cardiovascular radiologist and a senior military flight surgeon. Participants are informed about the findings. Treatment is based on best clinical judgement by the SUSPECT study group and is follows (a) CACS ≥400 AU, Left main >30%, or any stenosis ≥50%: referral to cardiologist for further evaluation; (b) CACS 100-399 AU, a single luminal stenosis 25-49% (CAD-RADS 2), or vulnerable plaque (≥2 features): lipid lowering therapy (e.g. statins) and life style advice; (c) CACS 1-99 AU or single luminal stenosis <25%: lifestyle advice. Statins were only initiated if indicated by additional risk factors; and (d) aeromedically relevant CAD: lipid lowering therapy (e.g. statins) and life style advice. Referral to a cardiologist was not routinely performed, but results were discussed with the Aeromedical Specialist (AMS) of the Military Aviation Authority of the RNLAF.

Outcomes

The primary endpoint is CAD, defined as a composite of a coronary stenosis ≥50% and/or CACS ≥100. The secondary endpoint is 'aeromedically significant CAD', as defined by national military regulations as a left main stenosis of >30%, any luminal stenosis ≥50%, or an aggregate coronary stenosis of ≥120%. This is of particular interest in our population, because of potential flight safety implications.

Sample size calculation

Prevalence of CAD is highly variable in asymptomatic persons.[24] In the MARC study, performing cardiac CT in 318 asymptomatic sportsmen aged ≥45 years, 16% had a CACS ≥100 and 5% had a ≥50% luminal stenosis on CCTA.[7,25] In the SCAPIS study of 25.182 Swedish individuals (51% women, age 50-64 years) without known CAD, 12% had a CACS ≥100, and 5% had a ≥50% coronary stenosis on CCTA.[11] Only one aviation medicine study has been performed using CT as a secondary screening tool for CAD, and showed that 13 of 44 (30%) aircrew had a ≥50% coronary stenosis.[26]

We determined the expected population proportion (p) for CAD (defined as any luminal stenosis ≥50% and/or CACS ≥100 AU) as approximately 20%. The sample size (N) was calculated with the formula

$$n = \frac{z^2 * p * (1-p)}{e^2}$$

where z=1.96 using a confidence level (α) of 95%, and a margin of error (e) of 0.05. Based on these numbers, the calculated sample size (n) was 246 subjects.

Statistical analysis

Continuous variables are reported as mean±SD when normally distributed or as median (interquartile range), if not normally distributed. Categorical variables are presented as proportions. We use t-tests to compare continuous variables when data were normally distributed, and Mann-Whitney U in case of a non-normally distribution. Categorical variables are analyzed using chi square or Fisher's exact test, where appropriate. After univariable analysis regarding baseline characteristics and presence of CAD, a multivariable analysis is preformed using stepwise logistic regression. In order to assess the added value of screening using cardiac CT in this population, a number needed to screen (NNS) and net reclassification improvement (NRI) are provided. All statistical analyses are performed using IBM SPSS® Version 27 software. A p value of <0.05 is considered statistically significant.

DISCUSSION

The SUSPECT study assesses the value of cardiac CT for clinically and 'aeromedically' relevant CAD in asymptomatic Dutch military aircrew aged ≥ 40 years in comparison to standard cardiac screening. The main benefit is early recognition of subclinical CAD, which provides the opportunity for early intervention to improve prognosis and flight safety. Furthermore, this study will give additional information on the ongoing question whether coronary CT scanning improves cardiovascular risk stratification in asymptomatic people with high-hazard occupations. The study results will be compared to similar studies in other populations, such as the MARC study that assessed the additional value of cardiac CT above a normal sport medical examination (including a bicycle exercise test) for relevant CAD in asymptomatic, middle-aged male athletes.[7] We postulate that primary screening with cardiac CT in military aircrew, will outperform current screening protocols using exercise ECG. However, some concerns regarding this primary screening have to be acknowledged.

First, cardiac CT requires radiation exposure and intravenous contrast material injection. Radiation is around 3-5 mSv, which is similar to a normal yearly 'background' radiation exposure in the Netherlands (2.5mSv). Non-ionic contrast material has a low risk of contrast-induced nephropathy or allergic reactions, which are usually mild and self-limiting.[27]

Second, finding subclinical CAD with primary screening using cardiac CT may lead to flight restrictions. The MAR regulations are based on a luminal stenosis on conventional coronary angiography, and findings may be different on CT. CACS and calcified plaque can also be increased in case of long-term intense exercise, which may apply to some aircrew.[28] Consequently, some aircrew may be unnecessarily grounded until a cardiologist has performed a full assessment. The number of aircrew that are unnecessarily referred to a cardiologist may be significantly lower than by screening for CAD using exercise ECG, which suffers from a suboptimal positive and negative predictive value.[7,8]

Third, is extra costs of cardiac CT. It is possible that a primary screening protocol using cardiac CT could increase or prevent unnecessary and expensive referral to a cardiologist. Additionally, absence of CAD on CT could motivate a longer interval between required cardiac screening moments and improve cost-effectiveness, a subject of continuing debate among (military) organizations.[3,29,30]

CONCLUSION

The results of the SUSPECT study will provide insight in the added value of cardiac CT in routine aeromedical screening of military aircrew. In addition, we expect that this study will provide guidance in the ongoing debate how to screen asymptomatic people with high-risk occupations for relevant coronary artery disease.

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