Screening for Coronary Artery Disease in Asymptomatic Pilots with Diabetes Mellitus

Meryem Zerrik; Amal Moumen; Mouna El Ghazi; Fahd Bennani Smiress; Zakaria Iloughmane; Choukri El M'hadi; Mohamed Chemsi

INTRODUCTION: Coronary artery disease (CAD) is a cause of death in 75% of patients with diabetes. Its often asymptomatic nature delays diagnosis. In aeronautics, it can cause in-flight incapacitation, beyond which it represents a major fear for the medical expert. Screening for CAD is still a topical subject with the advent of new cardiovascular (CV) risk biomarkers and more effective screening tests. We report the experience of the Aeromedical Expertise Center of Rabat in this screening of diabetic pilots, with a recommendations review.

METHODS: A prospective study over 1 yr included diabetic pilots who benefited from systematic screening for CAD after a CV risk stratification. Coronary angiography is performed if a screening test is positive. Subsequent follow-up is carried out in consultation with the attending physician with regular evaluation in our center.

RESULTS: There were 38 pilots included in our study. The average age was 55 ± 4.19 yr and about 73% had a high CV risk. CAD was detected in 4 cases (10.52%) who had abnormal resting electrocardiograms and required revascularization with the placement of active stents. Approximately 75% of pilots with CAD returned to fly through a waiver with restrictions.

DISCUSSION: Screening for coronary disease in diabetics is controversial, and current recommendations are not unanimous. In our study, the screening did not identify coronary diabetic pilots who could benefit from bypass surgery. Nevertheless, coronary disease was diagnosed, justifying grounding to preserve flight safety, which is an absolute priority in aviation medicine.

KEYWORDS: in-flight incapacitation, silent myocardial ischemia, flight safety, coronary artery disease, diabetes mellitus.

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Diabetes mellitus (DM) is one of the fastest growing global health emergencies of the 21st century.[11] An estimated 463 million people are living with DM, a number that has doubled over the past 20–30 yr. Diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries.[18] Stepwise's Moroccan survey observed an increasing prevalence of diabetes from 6.6–10.6% between 2000–2017.[13]

Over time, DM leads to target organ damages with cardiovascular (CV) complications, diabetic retinopathy, nephropathy, and neuropathy. The incidence of CV events is greater in people with diabetes. Diabetes confers a twofold excess risk for coronary heart disease, the main cause of mortality and morbidity in these patients.[7] In aircrew, the Federal Aviation Administration declared that diabetes prevalence in U.S. civil pilots increased from the mid-1990s through 2005 (i.e., 1.57%),[15] thus pilots are not spared from this pandemic and its coronary risk. Unfortunately, in diabetic patients, coronary artery disease (CAD) is often asymptomatic until the onset of an acute coronary event. This event can occur in pilots with diabetes and cause in-flight incapacitation or sudden death. Moreover, the International Air Transport Association found acute coronary syndromes to be the leading cause of sudden incapacitation during either military or civilian flight operations resulting in

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aircraft accidents and fatalities.[2] Even if silent coronary disease is frequent in patients with diabetes, its detection in primary prevention is still debated.[16]

Several noninvasive screening tools have been proposed to detect CAD, and new screening methods with greater performance are now available. However, their prognosis value, cost-benefit ratio, and the potential harms of such approaches must be carefully evaluated, mainly in aircrew members. This paper aimed to evaluate the efficiency of a systematic silent myocardial ischemia (SMI) screening in asymptomatic diabetic pilots.

METHODS

Subjects

In a retrospective cross-sectional study, we enrolled pilots presenting themselves for a Class 1 medical examination performed in the Aeromedical Expertise Center of the Military Teaching Hospital Mohamed V of Rabat, Morocco, from January 1 to December 31, 2020. We included in the present study all civilian airline pilots having established type 2 diabetes, who performed a periodical visit examination during the period of study. For pilots requiring more than one medical examination during the study period, only their first examination was included in the study. Patients included had to be under antidiabetic therapy, have a waiver for diabetes, and be asymptomatic from any typical or atypical symptoms of CAD. Military pilots were excluded because we aimed to have a homogenous population to evaluate in the present study.

Pilots were informed about the study and agreed to participate, without any objections, to achieve their health benefits and to enhance scientific goals. The Scientific Research Committee of the Mohamed V Military Hospital determined that this study was exempt from Institutional Review Board approval because the goal of the study is to evaluate the efficiency of our screening strategy, as we do for all diabetes aircrew (as described in the Moroccan rules), and they gave permission to publish the results in the national and international communities. An additional consideration was that the population included in the study would have to undergo the same evaluation and the same decision regardless of inclusion in the study, meaning there were no new experiences or examinations required of them specifically for the study.

Materials

Data on patient demographics, medical history, comorbidities, laboratory and vital status measurements, micro- and macrovascular complications, medications, and total flight hours (TFH) were collected from pilots' medical records at the airline's medical center in an anonymous format. In order to assess CV risk factors, anthropometric data and CV risk factors were compiled from participants' medical records.

Hypertension was diagnosed if subjects were on drug treatment for hypertension or had a systolic blood pressure of ≥130 mmHg and/or diastolic blood pressure of ≥80 mmHg. Obesity was diagnosed if the patient had a body mass index ≥30 kg · m^{-2}. Smoking was defined as active smoking or smoking cessation of fewer than 3 yr.

Lipid anomalies assessment was based on enzymatic measurement of total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol after 12 h of fasting. Dyslipidemia was defined by total cholesterol >200 mg · dL^{-1} (5.1 mmol · L^{-1}), LDL cholesterol >160 mg · dL^{-1} (4.13 mmol · L^{-1}), and/or HDL cholesterol <40 mg · dL^{-1} (1.03 mmol · L^{-1}) for men and <50 mg · dL^{-1} (1.29 mmol · L^{-1}) for women, and/or triglycerides >1.5 g · L^{-1} or use of lipid-lowering drugs.

The assessment of CV risk was based on CV risk categories developed by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2019 recommendations in the guidelines on diabetes, prediabetes, and cardiovascular diseases (CVD).[5] Individuals with DM and CVD or DM with target organ damage, such as proteinuria or kidney failure (estimated glomerular filtration rate [eGFR] <30 mL · min^{-1} · 1.73 m^{-2}), are at very high risk (10-yr risk of CVD death >10%). Patients with DM with three or more major risk factors, or with a DM duration of >20 yr, are also at very high risk. Patients with DM duration >10 yr without target organ damage plus any other additional risk factors are at high risk. Young patients (with type 2 DM and aged <50 yr) with DM duration <10 yr without other risk factors are at moderate risk.[5]

Carotid atherosclerosis and lower limb diabetic arteritis were assessed by Doppler ultrasonography. Microalbuminuria was defined as a urine albumin excretion rate of 30–300 mg per 24 h for 24 h of urine collection (or 20–200 μg · min^{-1} or 30–300 μg · mg^{-1} creatinine on two of three urine collections). The eGFR was calculated using the "modification of diet in renal disease" equation, and chronic kidney failure was defined by eGFR <60 ml · min^{-1} · 1.73 m^{-2}. A detailed neurological exam and a dilated fundus oculi examination were performed on all patients. ST segment and T-wave changes on previous resting electrocardiogram (ECG) were evaluated.

Procedure

Then we proceeded to a systematic screening based on resting ECG, echocardiography, and ECG exercise tests, which were conducted using the Bruce protocol. Patients with a positive treadmill test underwent coronary angiography. Patients with a borderline exercise test underwent a functional test imaging myocardial perfusion scintigraphy (MPS), stress echocardiography, or stress MRI. Functional test imaging was chosen according to cardiologist advice, patient preference, and test availability in our center.

Statistical Analysis

Statistical analysis was performed with SPSS 18 software. The number of patients and the corresponding percentages were given for categorical variables, mean ± SD was reported to describe the normally distributed continuous variables, and medians with interquartile ranges were reported for continuous variables with skewed distributions. The Kolmogorov-Smirnov test was performed on all measures to assess data normality. Chi-square or Fisher's exact test was used to compare the categorical variables as appropriate. Means were compared using the Student's *t*-test and medians were compared using the Mann-Whitney test. A *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 38 diabetic pilots were eligible for CAD screening in this study. The age distribution ranged from 46–62 yr old, with a mean (SD) of 55 (±4.19) years. All were men, with a median flight time of 6785 h. Diabetes duration varied between 8–13 yr, averaging 8 yr (±4.1). Patients were treated with metformin or dipeptidyl peptidase-4 (DPP-4) inhibitors, or a combination of these two therapies. The average HbA1c was 6.76% (50 mmol · mol^{-1}) (±0.7). Degenerative complications were established: two patients had asymptomatic carotid atherosclerosis in supra-aortic trunk ultrasonography; two patients had microalbuminuria; one case of asymptomatic atherosclerosis in the lower limb arteries; and one case of diabetic retinopathy. The CV risk factors characteristic of diabetic pilots are presented in **Fig. 1**. Hyperlipidemia with or without treatment was present in 42.9% of cases, which was the most represented CV risk factor, and 5.26% of cases presented microalbuminuria, which was the least represented factor. We did not have any cases of associated comorbidities or disorders like obstructive sleep apnea syndrome, nonalcoholic fatty liver disease, or erectile dysfunction. Concerning the CV risk stratification according to the ESC/EAS 2019 recommendations, 74% of our pilots were at a high risk, 21% were at a very high risk, and only 5% were at a moderate risk.

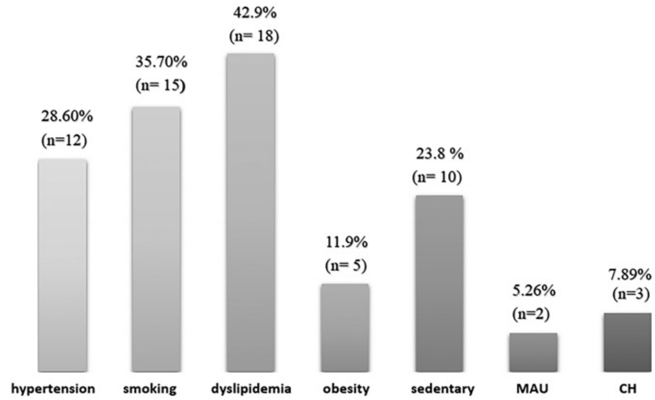

Fig. 1. Cardiovascular risk factors among the studied population out of gender and age. CH = coronary heredity; MAU = microalbuminuria.

An algorithm illustrating the result of the cardiac investigations of our pilots is presented in **Fig. 2**. There were four abnormal resting ECG results observed in the diabetes pilot group (10.52%). T-wave abnormalities were present in two pilots, ventricular extrasystoles were present in one pilot, and left ventricular hypertrophy by voltage criteria was present in one pilot. The ECGs were all normal and all pilots performed exercise stress ECGs. These tests were negative in 32 cases and those patients did not undergo any further testing.

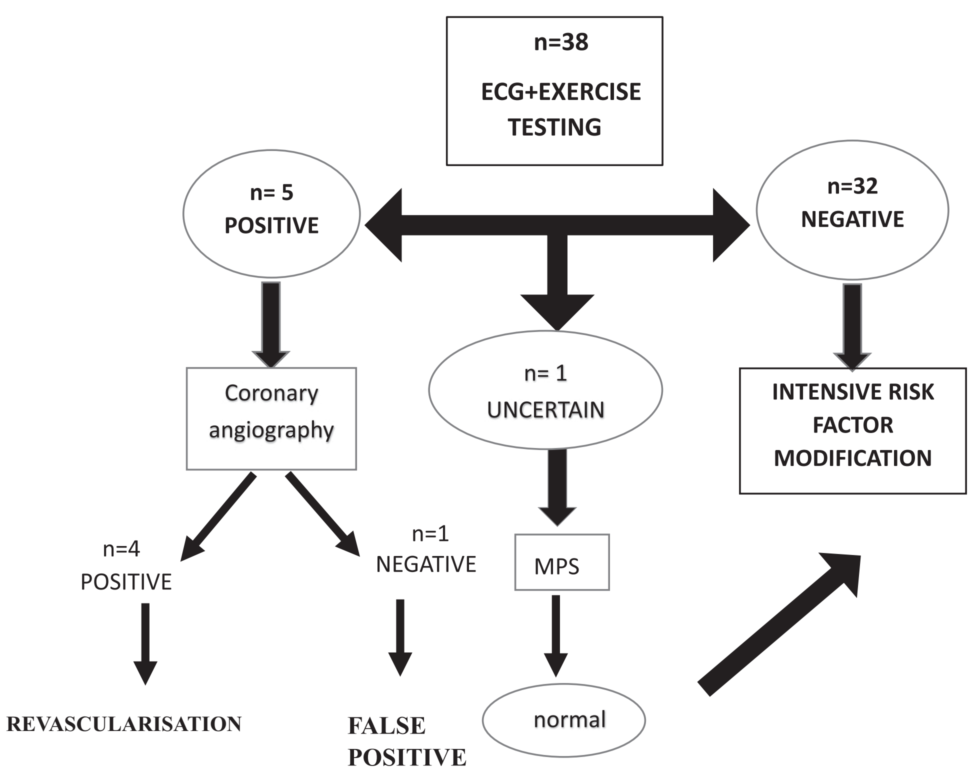

Fig. 2. Algorithm illustrating the result of the screening process.

In five cases, the exercise stress ECG was judged to be positive. In four patients, the ECG showed 1–2.5 mm ST-segment depression, and these patients were referred for coronary angiography. One pilot was found to have severe circumflex branch stenosis, three pilots had anterior interventricular branch stenosis, and one pilot had normal coronary arteries. One pilot presented with borderline ECG results that showed <1-mm ST segment depression and was referred for an MPS, which was normal and showed no myocardial perfusion defect. This patient was not then referred for coronary angiography.

We found four patients who had significant lesions, characterized by more than 70% artery stenosis, and these patients underwent successful percutaneous coronary intervention. Three pilots with CAD returned to flight through a waiver, two pilots after 6 mo and 1 pilot after 1 yr, with some restrictions: there must be a second pilot on-board and they must have a follow up examination every 3 mo. One pilot was declared definitively unfit for Class 1 certification. **Table I** describes the comparison of epidemiological aspects and CV risk factors among subjects with and without SMI.

DISCUSSION

For the first time in our aeromedical expertise center, a systematic screening of SMI was applied to commercial pilots with diabetes and asymptomatic from any typical or atypical symptoms of CAD. For diabetic patients, there are 12 prediction models specifically designed to calculate future CV risk. The risk-prediction model used in this study is the set of CV risk categories according to ESC/EAS 2019 recommendations. The advantage of the model used in this paper is that it requires data to be routinely established at each medical examination.

During recent decades, the risk of CV events has markedly decreased in patients with diabetes through multifaceted improvements in diabetes care, risk factor management, self-management education and support, and better integration of care.[9] However, this risk remains higher than in the general population. CV risk associated with diabetes is heterogeneous.

The prevalence of SMI in randomized clinical trials varies between 5.6–21.1%, depending on the screening strategy.[4] In our study of 38 screened pilots, 4 of them had an SMI, resulting in a prevalence of 10.52%. This exceeded the 1% rule, which is the risk threshold applied to the medical fitness of pilots.

Even if silent coronary disease is frequent in patients with diabetes, its detection in primary prevention is still debated. Up to 50% of SMI cases are not detected at the time of onset but are instead detected later during routine care when CV symptoms occur, or by cardiac imaging.

Indeed, regarding the screening of asymptomatic patients, the recommendations of several societies are not unanimous. The latest French guidelines, published in 2004, limited the assessment of myocardial ischemia to selected patients.[14] The American Diabetes Association guidelines, released in 2022, recommend not screening asymptomatic diabetes patients for silent CAD, because it does not improve outcomes as long as atherosclerotic CVD risk factors are treated.[1] A risk stratification approach has recently been developed by the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes.[5] This approach starts with a risk stratification that includes: age, type, and duration of diabetes; the number of associated risk factors; and target organ damage. Indeed, carotid or limb arterial ultrasound study, coronary artery calcium (CAC) score, and coronary computed tomography angiography (CCTA) can be used to better assess CV risk. Recently, the French Society of Cardiology and the French-speaking Society of Diabetology proposed a consensus strategy defined by diabetologists, cardiologists, and CV imagers in order to more precisely evaluate coronary risk and propose an algorithm for screening according to risk levels in asymptomatic diabetes patients in primary prevention.

Obviously, aircrew represent a particular group among high-CVD-risk individuals. In addition to common life strain and on-duty factors like hypobaria, pressurization, sedentariness, jet lag, high-caloric foods, etc., aircrew face typical stress such as repeated proficiency simulator checks, intermittent medical exams and total flight hours obligations, employer pressure, responsibility, and scheduled accomplishment. These factors may lead to CVD, either directly or indirectly. They interact with traditional risk factors, behavioral risk factors, and emerging CV risk factors.[3]

The Moroccan aeromedical standards refer to the Equipment and Transport Administration Order No. 1209-09, relating to aircrew members' physical and mental fitness conditions, the accreditation of centers of expertise in aeronautical medicine, and the appointment of medical examiners. They suggest using the treadmill test, MPS, stress echocardiogram, and possible coronary angiography if an asymptomatic CAD is suspected during the aeromedical examination. Furthermore, the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes recommend (for medicolegal reasons) screening for CAD in asymptomatic subjects whose occupations involve public safety (e.g., airline pilots, or lorry or bus drivers), who must also commonly undergo periodic testing for the assessment of exercise capacity and evaluation of possible heart disease, including CAD.[12] In 2019, the NATO Cardiology Working Group published a consensus for screening and investigation of aircrew for asymptomatic coronary disease, based on

Table I. Comparison of Epidemiological Aspects and Cardiovascular Risk Factors Between Subjects With and Without Silent Myocardial Ischemia.

PILOTS	SMI (*N* = 4)	NO SMI (*N* = 34)	*P*
Age	55.00	55.53	0.813
HbgA1c	7.02%	6.73%	0.44
BMI	26.89	26.79	0.93
Hypertension	25% (*N* = 1)	32.4% (*N* = 11)	1
Dyslipidemia	50% (*N* = 2)	47.1% (*N* = 16)	1
Smoking	75% (*N* = 3)	25.3% (*N* = 12)	0.28
Sedentary	50% (*N* = 2)	23.5% (*N* = 8)	0.27
Family History of CHD	100 (*N* = 4)	52.9% (*N* = 18)	0.12
Obesity	25% (*N* = 1)	11.8% (*N* = 4)	0.44

BMI = body mass index; CHD = coronary heart disease; SMI = silent myocardial ischemia a three-phase approach beginning with initial risk stratification using a population-appropriate risk calculator that includes family history and nonfatal and fatal endpoints, like the Reynolds risk equation and a resting ECG. Enhanced screening is recommended for aircrew identified as being at increased risk, by means of CAC Score alone or combined with a CCTA. Additional screening may include exercise testing and vascular ultrasound imaging. Aircrew identified as being at high risk based on enhanced screening require secondary investigations, which may include functional ischemia testing and potentially invasive coronary angiography. Functional stress testing as a stand-alone investigation for significant CAD in aircrew is not recommended.[8]

Exercise stress tests are limited in detecting potentially flow-limiting CAD and predicting future CV events.[17] Despite its low sensibility and specificity in screening for atherosclerosis, exercise test ECG has detected 4 pilots with SMI in our study of 38 pilots with diabetes, which amounts to a prevalence of 10%, with 1 pilot definitively unfit for a Class 1 certification. Exercise stress test remains simple; it has a low cost and is widely available in our center. That's why we chose to include it in our screening strategy. However, it is overtaken by CCTA and CACs, which are more recommended in aircrew with increased risk of CAD; unfortunately, neither test was used in our study due to being both expensive and not yet included in our current national aeromedical recommendations.

CAC score is a rapid, safe, and inexpensive method for detecting coronary atherosclerosis. It is associated with low radiation. The CAC score assesses the volume of coronary calcifications and assumes that each calcification corresponds to an atherosclerotic plaque. Patients are stratified according to the Agatston Score.[6] CAC score has a higher sensitivity and specificity with a positive predictive value for detecting severe lesions (>70%). Nevertheless, the prevalence of a high CAC score is >20% among asymptomatic patients with diabetes, greater than in the elderly and in those without diabetes.[10]

Unlike CACS, CCTA provides information about luminal stenosis's number, extent, and location. It additionally has the advantage of imaging and characterizing plaque (into calcified, noncalcified, or mixed plaque morphology). In asymptomatic patients with diabetes, anatomical analysis of plaques can help to detect future vulnerable plaques at risk of acute future events.[10] Most coronary events that occur in younger individuals are caused by the rupture of non-flow-limiting coronary plaques or superficial erosion-remodeled plaques. However, CCTA is more radiant (2–4 MSV) and has some limitations in the case of obesity or kidney failure. In addition, when the CAC score is high, CCTA analysis becomes difficult due to the blooming effect linked to the presence of calcifications and may overestimate luminal encroachment in CACs of >1000.[5,8]

A cardiac computed tomography protocol that provides CCTA and CACS information may be the preferred modality for aircrew identified as being at increased risk based on enhanced screening. The presence of an obstructive lesion greater than 50% is a reasonable aeromedical threshold for grounding and further investigation.[8]

Finally, the results of our study could be different if we had a larger sample size, including military pilots with diabetes who had specific constraints that could increase CV risk. The results would also be more effective if we had used a more efficient test like CCTA in our screening strategy, which is not widely available in our center.

Despite advances in prevention and early disease intervention, CAD is still the most incapacitating cause in military or civilian aviation, resulting in aircraft accidents and fatalities. DM is a major risk factor for the development of CAD and the aircrew population with diabetes is growing in number worldwide. Many CV risk scores are available that can be applied to patients with type 2 diabetes, but the validity and transportability of such a model to assess aircrew may need to be evaluated in future studies.

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