Chapter

Risk Factors for Cardiovascular Diseases in Aircrew

Nathan B. Buila, Gilbert K. Kabanda, Elysee M-C. Munyoka, Jean-Marc B. Bantu and Jean René M'Buyamba-Kabangu

Abstract

The relation of atherosclerotic cardiovascular disease (ASCVD) to not only traditional but also new and emergent risk factors has been assessed in aircrew. Total flight hours (TFH), high altitude and weightlessness exposure have been accounted among traditional risk factors for CVD among the aircrew. The risk factors do not perform in loneliness. To predict the 10 years global CV risk, several scores are being applied either based on traditional CVD risk factors only or also including new and emergent risk factors. To prevent aircrew from developing CVD, one should focus on the control of behavioral and metabolic risks as well as the polymorphe treatment of high CV risk individuals.

Keywords: Cardiovascular risk factors, Screening, Aircre

1. Introduction

Aircrew represent a particular group among " high cardiovascular disease (CVD) risk individuals". In addition to common life strain, aircrew face typical stress such as repeatedly proficiency simulator checks, intermittent medical exams and total flight hour obligations, employer pressure, responsibility, and scheduled accomplishment. These factors may lead to CVD, either directly or indirectly. They interact with traditional risk factors (genetic risk factors: aging, gender, ethnicity, chromosomes, HLA, genes, inflight incapacitation) and behavioral risk factors (inactivity, alcohol drinking, smoking, unhealthy diet) and emerging cardiovascular risk factors. The consequence is cardiovascular remodeling triggered by oxidative stress, inflammation and endothelial dysfunction. Unexpected in-flight medical incapacitation or distraction of a pilot may result in aviation accident, which is of public interest, harming himself, aircrafts, passengers and environment. Notwithstanding progress in prevention and early disease intervention, ischemic events secondary to coronary artery disease (CAD) remains among the commonest causes of unheralded acute incapacitation in the Western population. Thus, aeromedical providers should help aircrew to prevent CVD. It is essential to assess and stabilize the patient, control risk factors and optimize pharmacological treatments. Controlling weight and managing obesity, providing healthy diet and promoting physical activity, and educating aircrew and instituting home-based care monitoring is an important tool to preventing CVD. Aircrew with CVD are at high-risk and require a multifaceted and multidisciplinary intervention that should be started as soon as possible.

The health of aircrew is an imperative requirement for safe travels of millions of people worldwide. The presence or development of CVD in aircrew, with the risk of potential clinical manifestations, continues to be a major concern to aviation medical practitioners. Despite the rigorously medical screen of pilots compared with several other professions, the presence of multi-crew environment, and the cockpit resource management with incapacitation training, acute coronary artery events remain an important cause of in-flight incapacitation or distraction ending in aircraft accidents and fatalities [1]. Few, if any, aircrew involved in accidents and incidents suffer from antecedent symptomatic coronary disease. Cardiovascular incapacitation of a pilot though rare event represents a seriously potential threat for flight safety [2]. In addition, CVDs linked to unexpected in-flight medical incapacitation or impairment account for half of human factor-related causes of aviation accidents [1]. In military operation, using single-pilot, high-performance aircraft, and even in dual-pilot, cardiac events were found to be second cause of aircraft accidents due to acute incapacitation [3].

From 1962 to 2015, Gray et al. listed 10 accidents and incidents in commercial passenger flights related to coronary artery events which concerned either the commandant or the first officer and resulted in 240 fatalities [4]. Moreover, 10 out of the 98 in-flight medical events addressed by the Australian Transport Safety Bureau (ATSB) between 1 January 1975 and 31 March 2006, consisted of heart attack explaining the high-observed mortality rate [5]. Autopsy studies of young military personnel and aircrew have demonstrated atherosclerosis as a common finding, including cases of severe disease and aeromedically disqualifying findings [6–8].

2. Epidemiology of risk factors for cardiovascular disease in aircrew

2.1 Traditional risk factors for cardiovascular disease in aircrew

Several studies mentioned the established risk factors for CVD continuum including hypertension, type-2 diabetes, dyslipidemia, smoking, overweight and mainly abdominal adiposity, physical inactivity and Mets [9]. Recent data suggest disturbing increases in the prevalence of these risk factors for CVD (**Figure 1**) [10].

2.1.1 Hypertension

Worldwide, hypertension is the leading etiology of morbidity and mortality [11, 12]. Hypertension is the first issue for pilots to secure their medical certificate [1, 13]. Through complications such as myocardial infarction, stroke, renal failure and death, hypertension constitutes a risk of in-flight incapacitation. In-flight CV events are believed to be scarce although allegation of in-flight CV incapacitation misdiagnosis has once been put forth [14]. Exposure to flight stress could be listed as a plausible explanation as weighted by total flight time at baseline. Indeed, considering the responsibility to fly the plane, flight crew is exposed to chronic stress that might trigger both hypothalamo-pituitary- adrenocortical and sympatho-adreno-medullary pathways to raise arterial blood pressure. In addition, it has been reported that chronic stress could lead to hypertension, which is triggered by angiotensin II through either lymphocyte T activation or vascular inflammation.

2.1.2 Types-2 diabetes

Type-2 diabetes either through chronic complications (heart disease, hypertension, and stroke) or acute complications (hypoglycemia or hyperglycemia episodes)

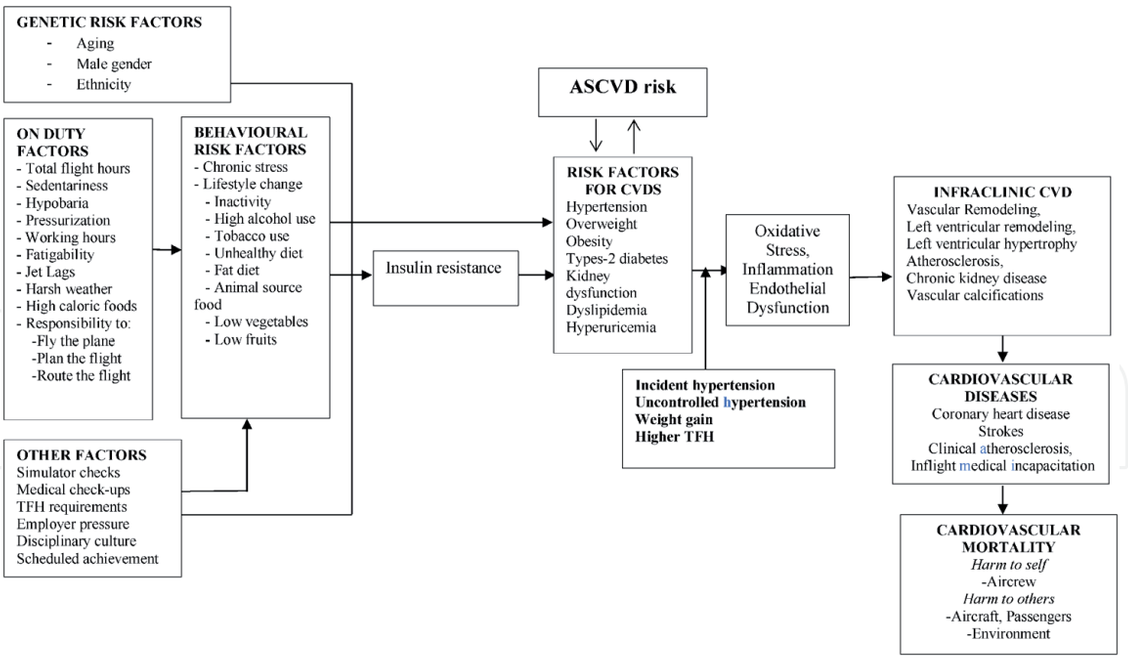

Figure 1.
Relationship between risk factors and CVD among aircrew. ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease; TFH: total flight hours.

can grievously compromise flight safety and harm not only the aircrew himself but also the passengers, the aircraft, and the environment [15]. The relationship between blood glucose control and the establishment of CVD in diabetes remains a matter of controversy. Whilst several glucose-lowering trials in diabetes showed significant reduction in microvascular complications, they systematically failed to achieve significantly in macrovascular complications. Still, it should be mentioned that some systematic reviews and meta-analysis have recommended that efforts to improve blood glucose lower the incidence of CVD [16].

2.1.3 Smoking

Smoking has long been considered as the major risk factor for the establishment of CVD. Tobacco use, the single largest preventable cause of CV morbidity, is responsible for 10% of all of CVDs and doubles the 10-y mortality rate [17]. Worldwide, nearly a billion people are smokers and newly smokers are men from low- and middle-income countries (LMICs). Smoking delirious effect is dose related with no safe limit observed. It has been shown that passive smoking produces noticeable interferences in the normal autonomic nervous system functioning characterized by increased sympathetic drive and reduced HR variability (HRV) and parasympathetic modulation.

2.1.4 Overweight/obesity

Obesity, a significant determinant of CVDs, is extensively related to hypertension even if the exact mechanisms remain not totally unraveled [18]. This relation should now focus on weight variation across time along with visceral or intra-abdominal fat that is likely linked to the insulin resistance syndrome, an indicator of generalized metabolic disorder [18]. Obesity interacts with aviation duties. In fact, not only does obesity increase the risk of sudden CV incapacitation, but the risk of sudden and subtle incapacitation consequential to sleep apnea and the risk of pulmonary embolus do [19]. On the other hand, obesity can jeopardize the egress of

aircraft in emergency [19]. The current results demonstrated that short term commercial flying significantly altered cardiovascular function including the reduction of parasympathetic modulations. Further, greater physical fitness and lower body fat composition were associated with greater cardiac autonomic control for passengers during flights. Enhanced physical fitness and leaner body composition may enable passengers to cope better with the cardiovascular stress and high allostatic load associated with air travel for enhanced passenger well-being [20]. In an observational cross-sectional study among Brazilian pilots, Palmeira found that more than half of and nearly a quart pilots were overweighed and obese, respectively. These authors concluded that overweight and obesity among the commercial airline pilots was high and represents a serious health problem in this population [21].

2.1.5 Physical inactivity

The lack of physical activity has contributed increasingly to overweight and obesity in young persons and adults. Physical activity is significant for primary and secondary prevention as well notwithstanding of BMI. Aircrew have little physical activity and eat higher caloric foods away from home at unscheduled time intervals [21]. Physical inactivity and unhealthy diet are responsible of raised BP, increased blood glucose, increased blood lipids, and overweight and obesity.

2.1.6 Total flight hours

The relationship between higher TFH and ASCVD risk in pilots have been established [22] as well as how TFH expresses the likelihood of crash involvement significantly compared with aging, which encompasses a conflict between decreasing cognitive functions that jeopardizes flight safety and increasing flying expertise that enhances fight safety [23]. Similarly, having 5,000 tfh or more protects against crash involvement but this protection levels off at a threshold of 10,000 tfh [23]. Likewise, inverse nonlinear relationship has been found between crash involvement and total flight time [23].

2.1.7 High altitude exposure

Pilots have to cope with stress due to 6,000 to 8,000 feet pressurized environment, and working hours [21]. It is known that the increase of BP with high altitude exposure 3000 m above sea level (asl) [24]. The explanation among several is the sympathetic activation (increased BP, HR, cardiac output, myocardial twist) through peripheral chemoreceptor [24]. Individuals with grade 2 hypertension and increased ASCVD risk should check their BP values before and during HA (>2500 m) exposure. Individuals with grade 1 hypertension may reach very HA (>4000 m) with adequate medical therapy; uncontrolled severe hypertensive individuals (grade 3) should avoid exposure to very HA [24]. At HA, left ventricular experiences changes such as an increase of systolic function with elevated sphericity index, but a decrease of diastolic function [25, 26]. Moreover, HA exposure may increase risk of cerebral ischemia for individuals with antecedent of ischemic stroke [26–28]. Background contributors are increased hematocrit and greater blood viscosity. HA exposure increases risk of hemorrhagic stroke in those with cerebral aneurysms and arterial/venous malformation [29]. HA may be at benefit for arrhythmia [24]. High altitude less than 4000 m does not affect pacing and implantable cardioverter devices [30].

At sea level, barometric pressure is 760 mmHg, and air has a partial pressure of oxygen (PO_2) of 160 mmHg. Airline flight usually cruises at altitudes

of 9,150–13,000 m (30–40,000 feet) asl where the atmospheric PO_2 is usually ≤38 mmHg, which would normally result in a lethal level of airway (alveolar) hypoxia. Aircraft cabins are therefore environmentally modified (pressurized) to atmospheric pressures of 1,530–2,440 m (5,000–8,000 feet) asl [24].

2.1.8 Weightlessness exposure

Microgravity is a concern as it affects the entire body's systems, especially the cardiovascular system. Even with very short-duration exposure to microgravity, the cardiovascular system meets the return to gravity with CV deconditioning [24].

2.2 New and emergent risk factors for cardiovascular in aircrew

Atherosclerotic cardiovascular disease (ASCVD) starts at a very young age and progresses over time allowing sufficient time for screening and early detection of the condition. Because CVD often appears in individuals with lower CVD risk, some other markers should be able to provide added information about individual's risk, above and beyond the traditional risk factors at baseline. Among them are hs-CRP, intima-media thickness (CIMT), LVH, faster HR, kidney dysfunction, carotid ankle-brachial index (ABI), coronary artery calcium (CAC) score, cardio-respiratory fitness, apolipoprotein B (ApoB), micro-albuminuria, and genetic risk markers.

2.2.1 Fast resting heart rate

Several clinical and epidemiological reports have suggested that fast resting HR, as a marker of sympathetic nervous system and RAS overactivity, not only is a powerful independent predictor of CVD, but also of all-cause mortality. Resting faster HR could be associated, through oxidative stress and subsequent inflammation, with development of atherosclerosis, progression of heart failure, and enhancement of myocardial ischemia or infarction [31]. In a cross-sectional study of Congolese aircrew from both African and Caucasian origin, the proportion of subjects with a faster resting HR was of the same magnitude as the 6.8% observed in a normative sample from the First U.S. National Health and Nutrition Examination Survey (NHANES) I data [32]. It was nearly five times more frequent in flight than in cabin crew.

2.2.2 Left ventricular hypertrophy

LVH is an independent predictor of morbidity and mortality including disabling events such as sudden death, myocardial infarction and stroke. Echo-based LVH is a well-established predictor of CV morbidity and mortality in either the general population or high-risk groups. LVH has been found to be the most powerful risk factor for sudden death, ventricular arrhythmias, myocardial ischemia, CHD, and congestive heart failure. LVH regression due to treatment of hypertension predicts an improved prognosis. Abnormal LV geometry in hypertensive patients is frequently associated with diastolic dysfunction, which can be further evaluated, by a combination of transmitral flow and tissue Doppler studies. Aging–associated vascular remodeling and insulin resistance with subsequent constellation of multiple CVD risk factors might have led to LVH [33] with elevated 10-year global cardiovascular risk as observed in our airmen. Insulin resistance and subsequent hyperinsulinemia have been reported to activate the sympathetic nervous and the renin angiotensin systems resulting in endothelial dysfunction. With reference to

Laplace's law, high blood pressure and obesity could trigger cardiac remodeling through hemodynamic and humoral mechanisms and the thickening of cardiac wall may occur through collagen deposits. It has been reported that moderate to severe LVH, of mainly concentric geometric subtype is a common finding among aircrew with age, subclinical atherosclerosis and components of the MetS as its main associated CV risk factors [34].

2.2.3 Intima media thickness

The determination of cIMT in individual CV risk stratification and target organ appears in recent hypertension guidelines because of pathological IMT consistency related to future cardiovascular events.

2.2.4 Kidney dysfunction

Chronic kidney disease (CKD) stands as a global public health problem in HICs as well as in LMICs. In the USA, the third National Health and Nutrition Examination Survey (NHANES III) estimated that the prevalence of CKD has risen from 11% between 1988 and 1994 up to 13% between 1999 and 2004 [35, 36]. In a systematic review and a meta-analysis from 21 medium- and high-quality studies, Stanifer found 13.9% overall prevalence of CKD in SSA [37].

2.2.5 High sensitivity C-reactive protein

Hs-CRP is a marker of inflammation and endothelial dysfunction and subsequent atherosclerosis. It is produced by hepatocytes in response to circulating cytokines, particularly IL-6.18. It is also a robust downstream marker of inflammation, although unlikely to have a causative role in CVD. Consequently, the relationship between elevated hs-CRP and ASCVD risk remains a matter of controversy. The merit of hs-CRP use is because it does require neither sophisticated equipment nor particular operator skills, especially in developing countries. The hs-CRP, which is incorporated in the Reynolds score, may provide supplemental predictive capacity compared with the FRS [38]. Moreover, the 2013 ACC/AHA guidelines on the assessment of CV risk recommend hs-PCR in men (>50 y) and in women (>60 y) at intermediate risk, which are qualified for lipid lowering drugs [39]. In this regard, many studies reported a robust association of hs-CRP with numerous traditional risk factors for CHD such as obesity, diabetes, physical inactivity, smoking, and alcohol use [40–42]. Other studies highlighted the modest relationship between hs-CRP and CVD, because of its variability among age, gender (higher magnitude in men), and ethnicity (higher magnitude in African Americans vs. Caucasians) [43, 44]. A study comprised of aircrew from both African and Caucasian origin reported a net reclassified global ASCVD risk based on 2018 ESC/ESH guidelines chiefly in intermediate risk hypertensive individuals [40].

2.2.6 Coronary artery calcium

Coronary artery calcium (CAC) a powerful novel risk indicator for ASCVD risk. It is linked with an enhanced risk to develop harmful cardiovascular events independently of clinical markers and inflammatory biomarkers [45]. Conversely, a calcium artery score of 0 has a strong negative predictive value for the development of coronary artery diseases (CAD).

2.2.7 Genetic risk scores

Genetic risk scores have been proposed because of the association between loci or genes and higher ASCVD risk. The advantage of genetic biomarkers on other biomarkers is that they exist at birth and can be determined even in antenatal period. But, gene–environment interactions can sometimes be responsible for development of disease states. Furthermore, using new variables such as genetic markers may enhance CV prediction even if this possibility remains questionable [46]. In a post-hoc meta-analyze of six systematic reviews on effect of ASCVD risk estimate in primary prevention, Collins et al. reported that there was no evidence that the potential use of ASCVD risk estimate leads to decreasing in CVD morbidity and mortality due to the deficient quality of systematic reviews.

3. Global cardiovascular risk estimate in aircrew

3.1 Global cardiovascular risk estimate using traditional risk factors

Given that risk factors for CVDs do not act in isolation, quantification of risk is an important part of the risk stratification process. The prediction of an individual's ASCVD risk over a one 10-y period traditionally involves assessment of CVD risk factors such as age, gender, baseline levels of systolic and diastolic BP, serum cholesterol, smoking status and history of diabetes. Published in 1998 [47] and modified in 2002 [48], the Framingham risk score (FRS) derived from the Framingham Heart Study (FHS) which is broadly granted as the pioneering longitudinal cohort study [49, 50]. FHS chart, a risk prediction model, assigns weight (points) to traditional risk factors for ASCVD such as age, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), treated or untreated SBP (yes or no), smoking status (yes or no), and type-2 diabetes (yes or no). This FHS chart produces an estimate (or risk) of developing CVD or a component of CVD (such as stroke, peripheral vascular disease, or heart failure) over a fixed time, for example, the next 10 years [50]. Also, Framingham investigators presented heart /vascular age which is the age that corresponds to a person with normal risk factors and the same 10-year CV risk stating that low 10-year risk can cohabit with a vascular age higher than the chronological one [51]. FHS chart has been broadly utilized for clinical guidelines [52], transported, and validated in several non-Framingham settings [53].

Besides the Framingham estimate functions, other significant risk functions such as the European Systematic Coronary Risk Evaluation (SCORE) function, the Prospective Cardiovascular Münster (PROCAM) function [53], the QRISK [54, 55] algorithms, the Reynolds risk score [56, 57], the Multi Ethnic Study of Atherosclerosis (MESA) algorithms may be used [58]. The final objective of all these ASCVD risk prediction models should be to improve clinical guidelines in detecting silent and undiagnosed CVD. Nevertheless, there are some caveats to using these risk factors alone in a model as prognostic tools for CVD risk prediction. Most of these risk equations have been constructed with data from Western populations, are generally population-specific, and may not be safely extrapolated to other populations. One must consider the fact that the calculated risk does not mean the occurrence of event in any specific individual but rather in 100 individuals with identical features.

For aviation personnel, rigorous medical scrutiny leads to the exclusion of those with evident CVDs at either initial or renewal of their medical licenses [2]. CVD events are often silent or may present without warning. All the licensed

aviation personnel undergo CV assessment including electrocardiogram (ECG), echocardiography, and lipid profile at initial. An ECG can be done at renewal as appropriate.

Several Civil Aviation Authorities (CAA) highly recommend aircrew, chiefly those aged 40 years or more, to periodically be screened for cardiovascular risk using suitable risk investigative tools that comprise family history and non-fatal and fatal end points, and a resting ECG. For most aircrew, the Reynold's risk equation provides a reasonably well-calibrated risk estimate, which includes family history [57]. The assessment and management of aeromedical risk continue to be a balancing act between practicality, risk tolerance and the advances of diagnostic medicine. The risk, which can be considered as a minimum objective for a large public transport aircraft due to medical causes, lies in the region of 10^{-8} and 10^{-9} per hour or per flight as appropriate.

A single risk matrix cannot reflect the operational impact of a medical event for all aircrew roles. To reflect the operational impact of a medical event incorporating aircrew role, a series of risk matrices that reflect the varying operational risk pertinent to specific aircrew role (the third dimension) is required. This led Gray et al. to develop a three-sized risk matrix, which embodies discrete aircrew duties: (i) aircrew with direct control over the aircraft (ie, pilot, copilot), (ii) aircrew personnel with input to navigation or engine/mechanical systems (ie, navigator, FEs), and (iii) aircrew responsible for passenger or cargo (ie, loadmasters, cabin crew) [4]. Although technically, air traffic controllers (ATCs) are not considered crews, they are considered to have an attributable risk similar to that of pilots.

Thus, ICAO asks stakeholder countries to use ASCVD estimate scores in aeromedical risk assessment to help alleviating morbidity and mortality in aeronautical setting. For example, the New Zealand Guideline Group (NZGG) adjusted [59], updated [60], and even assessed [61] the Framingham ASCVD estimate tools. In a matched case–control study accounting Oceania- based airline pilots using the NZGG adjusted Framingham score, Wirawan posited the NZGG score had low sensitivity and thus missed to predict 47% of the CV events [62].

3.2 Global cardiovascular risk estimate using new and emergent risk factors

Risk in CVD is still assessed chiefly by clinical features such as age, hypertension, diabetes mellitus, hyperlipidemia, and family history. Nonetheless, biochemical, cellular, and imaging frameworks are firmly allowing for increasingly improved risk assessment.

Aircrew undergo various investigations to assess cardiovascular risk that are anatomical (Cardiac CT, cardiac MR or invasive coronary angiography, transthoracic and transesophageal echocardiography), physiological (Myocardial perfusion imaging, including perfusion MRI, myocardial perfusion scintigraphy [MPS], both single photon emission CT [SPECT] and positron emission tomography [PET]), stress echocardiogram (with either physiological or pharmacological stress) and fractional flow reserve (FFR) and Clinical (Exercise stress ECG test, CAC scoring). Exercise stress ECG test is not recommended as a solely investigative tool for assessment of significant CAD in aircrew [63]. It is relevant to note that the negative predictive value (NPV) of the CCT for the detection of CHD is almost 100%, which implies that a negative scanner is very reassuring at least for the next 35 years [64].

To comply with the approach of the ICAO, it is recommended to CAAs to hold an inventory of the effective of aircrew to monitor their careers and health, their accidents and impairments [65]. Even for private aircrew, there are concerns, which imply that some degree of restriction must be applied. On the other hand, several CAAs prohibit pilots aged 65y or older from flying on commercial flight operations

even if this remains debatable [63]. The so-called "age-65 rule" is of concerns about the potential deleterious effects of aging on pilots' safety performance [66].

Aircrew with elevated cardiovascular risk established on inceptive screening should go through intensified screening that includes ancillary, to name but a few, stress ECG, CAC scoring solely, or combined with a CT coronary angiogram (CTCA) investigation, and vascular ultrasound imaging (VUI). Second-line investigative risk tools for CAD assessment comprise functional imaging, and invasive coronary angiography (ICA). Emerging technologies comprise CMR for plaque imaging and FFR that is a technique traditionally used as an adjunct to ICA to measure pressure differences across coronary stenosis.

Exercise stress ECG provides useful risk-stratification information including aerobic fitness, BP response and arrhythmia assessment, which may be incorporated in intensified screening. The use of routine exercise stress testing as a sole screening tool for CAD is not supported by evidence and is not recommended. Exercise stress tests are limited in their ability to detect potentially flow-limiting CAD and to predict future cardiovascular events. Because of its restricted sensitivity and specificity, exercise stress ECG has a flaw as screening test for coronary atherosclerosis. Moreover, because of its very low PPV for future coronary events, stress ECG should be discouraged as a stand-alone tool to determine aeromedically significant CAD.

The Astro-CHARM tool is the first integrated ASCVD risk calculator to incorporate risk factors, including hs-CRP, family history, and CAC data. It improves risk prediction in comparison with traditional risk factor equations and could be useful in risk-based decision making for cardiovascular disease prevention in the middle-aged general population.

Ultrasound imaging of the carotid and femoral arteries provides easily accessible visualization of vascular anatomy without radiation. cIMT and carotid and femoral artery plaque, have been evaluated as markers for cardiac disease and stroke risk. Several prospective studies have shown that the presence of carotid and femoral bifurcation plaques is associated with future cardiovascular events, independent of other risk factors. Guidelines support the use of carotid artery ultrasound in the cardiovascular risk assessment of asymptomatic aircrew at intermediate risk.

To identify aeromedically significant CAD, physiological imaging such as stress echo, perfusion MRI or myocardial perfusion scintigraphy (MPS) has limited utility and is not recommended as the sole secondary investigation for aircrew considered to be at high cardiovascular risk as it may overlook aeromedically significant (aggregate) stenosis. ICA should be reserved for those aircrew who are deemed at high risk for significant CAD or where accurate delineation of percentage coronary stenosis is required. ICA currently remains the gold standard for anatomical imaging of coronary arteries. This is because the spatial resolution of ICA is superior to that of CTCA. CTCA is less accurate than ICA for quantifying luminal stenosis. The threshold for initiating enhanced screening of aircrew with increased estimated risk for a coronary event is an organizational decision.

4. Preventing cardiovascular disease

Aircrew retirement age is increasing and the burden of subclinical, but potentially significant, coronary artery atherosclerosis is unknown in pilots above age 40 [20]. Prevention of CVD in aircrew may be even more problematic than in the general population. The control of CVD should focus on the reduction of behavioral risks (salt, tobacco, alcohol, physical inactivity) and metabolic risks (high BP, diabetes mellitus, and obesity), and on multidrug therapy for treatment of individuals

at high risk of heart attack and stroke based on these risks. Preventive initiatives should make it easier for healthy aircrew to stay healthy, and for those with established CVD or at high risk for CVD to modify their behavior [67]. To prevent the onset of CVD in aircrew, many avenues including healthier lifestyle such as regular physical activity, healthier diet, weight loss, moderate alcohol consumption, and smoking cessation, and the control risk factors can be considered.

Regular physical activity lowers the risk of CVD, improves endothelial and platelet function, and diminishes insulin resistance [68]. In fact, regular physical activity corrects raised BP and lipid profile, increases the level of HDL but lowers that of TC and LDL-c [68–70]. NICE guidelines recommend 150 minutes of moderate intensity aerobic activity per week, or 75 minutes of vigorous aerobic activity. Whilst NICE give only a consensus recommendation regarding the utility of exercise as primary prevention, guidelines from the AHA and ESC give class 1A recommendations with almost identical prescriptions, referring to a solid and consensual body of evidence [17, 71]. It has been reported in a recent cross-sectional study including 22 physically active men, exempt from CVD, that particular features of physical fitness such as aerobic capacity were associated with better cardiovascular control (HRV and BP) during flights. These authors encouraged future studies to investigate the role of physical fitness in reducing the flight-induced stress and related cardiac autonomic alterations for the general population [20].

Diet represents the most significant modifiable factor in the primary prevention of CVD. There is evidence that eating fruit and vegetables have been found to have compelling cardiovascular effects [69]. Epidemiological evidence shows that a diet low in fruits is the third most important risk factor of CVDs following high BP and cigarette smoking, accounting for more than 5 million deaths worldwide in 2010 [72]. The mechanisms of action mainly included the modulation of molecular events and signaling pathways associated with correcting endothelial dysfunction, reducing disorders in lipids metabolism, anti-hypertension, suppressing platelet's function, alleviating I/R injury, inhibiting thrombosis, reducing oxidative stress, and inhibiting inflammation responses [73]. Several studies have highlighted the impact of high-potassium diet on high BP, singularly in the presence of high dietary sodium, using the inward-rectifying potassium (K_{ir}) [74].

There is evidence that modest weight loss (e.g., 5–10%) can reduce CVD risk profile even when the patient remains in the obese range [75, 76]. Modest weight loss has been linked with an improvement in fasting glycaemia, glycosylated hemoglobin (HBA1c), and systolic and diastolic BP and plasma lipid profile (TG, TC, and LDL-c) [77]. Moreover, weight loss can also improve the efficacy of antihypertensive medications. Weight loss should employ a multidisciplinary approach that includes dietary advice, regular exercise, and motivational counseling [17, 78]. Weight loss can also be promoted by anti-obesity drugs and, to a greater degree, bariatric surgery, which appears to decrease CV risk in severely obese patients [79]. There are moves to suggest that, alongside reduction in BMI, reduction in WC as a proxy for reductions in visceral adiposity should become an important target for amelioration of CVD risk.

Four decades ago, epidemiological studies showed the historically J-shaped curve between alcohol consumption and cardiovascular risk [80, 81]. Recently, both cohort studies and meta-analyses corroborated the robustness of the mentioned relationship [82]. These authors argued that abstinence is associated with an increase in cardiovascular risk compared to light drinking and low levels of alcohol consumption associated with a lower level of CHD. Similarly, INTERHEART, NICE, and ACC studies showed moderate to light alcohol use was linked with preventing CVD. Contrastingly, through a large mendelian randomization meta-analysis, Holmes et al. showed that reduction in alcohol intake is linked with reduction

in CVD risk even in light-moderate drinkers [83]. It is on this basis that the ESC guidelines recommend no safe level of alcohol intake [84].

Smoking cessation is strongly recommended by all guidelines and smoker is likely to use nicotine replacement therapy (NRT), bupropion (a norepinephrine dopamine reuptake inhibitor) and particularly varenicline (a partial nicotine receptor agonist). Evidence suggests the use of NRT outweigh its cardiovascular risks whilst the use of E-cigarettes are still controversial [85].

Lowering BP to an optimal level (<130/80 mmHg) has been found to significantly reduce the risk of CVD [86]. Best proven non pharmacologic Interventions for prevention and treatment of hypertension that are weight loss, health diet, lower intake of dietary Na+, enhanced intake of dietary K+, physical exercise, and moderate alcohol intake approximately impact on SBP by 5, 11, 6, 5, 5, and 4 mmHg, respectively. Specific BP lowering drugs include calcium blockers, diuretics, ACEI, ARBS, and beta-blockers [84]. Medical practitioners are advised to avoid pharmacological inertia characterized by negligence of medical providers to initiate or intensify pharmacological therapy as stated by guidelines [84].

The overall strategy toward risk management for type-2 diabetes patients should focus on BP and lipid control to lower the leading complications of diabetes. Diabetes is treated with diet, exercise, and some antidiabetic medications [87]. Lowering cholesterol by means of drugs such as statins alone or associated with either ezetimibe or anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), has been found to reduce ASCVD risk; however, lipid-lowering diet and physical exercise are also important [88].

In aircrew with heart failure, medications should include B-adrenergic blockers, ACEIs, and more recently Ivabradine and/or sacubitril/ valsartan combination, when appropriate. Implantable cardioverter defibrillators and/or resynchronization should be associated. Exercise training is usually indicated based on the patient response to applied exercise protocols. In patients with CKD, risk factors such as hypertension, type-2 diabetes, and obesity should be controlled [89].

Traditional herbal remedies should be avoided for numerous riveting studies showed their toxicity even if histological and toxicological studies are needed to validate this causal relationship [89]. Antihypertensive treatment reverses myocardial hypertrophy, and additionally reduces repolarization time and its dispersion, the incidence and the severity of ventricular arrhythmia, and the risk of cardiovascular events.

Flight crew represent a high CVD risk subgroup requiring development of a comprehensive prevention and care program to mitigate the elevated risk and improve their quality of life and performance.

Author details

Nathan B. Buila[1*], Gilbert K. Kabanda[2], Elysee M-C. Munyoka[3], Jean-Marc B. Bantu[4] and Jean René M'Buyamba-Kabangu[2]

1 Cardiology Division, Department of Internal Medicine, University of Kinshasa Hospital, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

2 Hypertension Unit, Cardiology Division, Department of Internal Medicine, University of Kinshasa Hospital, University of Kinshasa, Kinshasa, Democratic Republic of the Congo

3 Papavest Medical, Brussels, Belgium

4 Free University of Brussels, Brussels, Belgium

*Address all correspondence to: drnathanbuila@gmail.com

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