Heterozygous Familial Hyperlipidemia in a Fighter Pilot

Lori C. Gatzke

BACKGROUND: Heterozygous familial hypercholesterolemia (HeFH) is an autosomal dominant disease characterized by elevated low-density lipoprotein cholesterol (LDL-C) that increases risk for clinically significant atherosclerotic cardiovascular disease (ASCVD). This common (1:220) disease is present within the fighter pilot community and hesitation to treat this condition at younger ages results in a higher risk for coronary artery disease (CAD), the presence of which can be catastrophic for flying safety.

CASE REPORT: A 40-yr-old asymptomatic F-15 pilot presented with persistently elevated LDL-C levels > 190 mg · dL^{-1} and a significant family history of CAD. Coronary artery calcium, CT angiography, and finally, invasive angiography were used to further stratify him as having mild CAD. Initiation of statin therapy significantly lowered his LDL and subsequent risk for disease progression, allowing him to return to flying.

DISCUSSION: Early recognition and treatment of HeFH is imperative for lowering the risk of ASCVD. Often the medical community supporting flyers is hesitant to diagnose or treat this condition, due to nonrecognition, the young age of presentation, or reluctance to potentially ground a flyer. By intervening earlier, rather than waiting, aviators can remain on flying status longer with lower risk to themselves and their aircrew.

KEYWORDS: coronary artery disease, atherosclerotic cardiovascular disease, preventative medicine, aviation medical standards, high performance aircraft.

Gatzke LC. *Heterozygous familial hyperlipidemia in a fighter pilot*. Aerosp Med Hum Perform. 2021; 92(10):835–837.

In 2020, over 1 million Americans had a myocardial infarction (MI) and more than 16 million Americans were estimated to live with coronary artery disease (CAD).[13] The recognized risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) include increasing age, male sex, and a number of modifiable risk factors: smoking status, physical activity, blood pressure, blood glucose, body weight, and diet.[13] Elevated cholesterol is another established risk factor for the development of clinically significant CAD with an estimated doubling of the risk of CAD for adults with hyperlipidemia.[5]

Heterozygous familial hypercholesterolemia (HeFH) is a common disease, occurring in as many as 1 in 200 people.[9] It is a genetic, autosomal dominant condition that causes lifelong elevated low-density lipoprotein cholesterol (LDL-C) levels, and if not found and treated from an early age, untreated men are at a 50% risk for a coronary event by age 50 (untreated women 30% risk by age 60).[10] As many as 20% of MIs in younger men (<45 yr of age) are attributed to HeFH.[7] Underdiagnosis and inadequate treatment are significant problems for patients with HeFH, with greater than 1 million in the United States underdiagnosed, and only half of those carrying a diagnosis treated to goal.[10] According to the Familial Hyperlipidemia Foundation's CASCADE-FH registry data, the mean age of familial hypercholesterolemia diagnosis was 50 yr, by which age more than one-third had already suffered an ASCVD event.[7] Early diagnosis and adequate treatment of HeFH in childhood and young adulthood lowers the incidence of ASCVD to the same risk level as those without HeFH.[10]

From the U.S. Air Force Medical Service, Peterson-Schriever Garrison, Colorado Springs, CO, USA.

This manuscript was received for review in April 2021. It was accepted for publication in June 2021.

Address correspondence to: Lori C. Gatzke, M.D., 559 Vincent St., Peterson AFB, CO 80914, USA; lorigatzke.md@gmail.com.

Reprint and copyright © by the Aerospace Medical Association, Alexandria, VA.

DOI: https://doi.org/10.3357/AMHP.5906.2021

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

CASE REPORT

In June 2020, a 40-yr-old F-15 pilot presented to the Flight Medicine clinic for his yearly Periodic Health Assessment, an annual physical for aviators. He described his health and fitness level as excellent, enjoying the benefits of regular physical activity and lifelong abstinence from alcohol and tobacco. His BMI was 26 and blood pressure readings at that appointment and historically were less than 130/80. His past medical history was significant for some high-frequency hearing loss and laser eye surgery, and he took no medications or supplements daily. Upon questioning him about his family history, however, a red flag became apparent: his father also enjoyed excellent physical health until his "sudden" myocardial infarction and subsequent multivessel coronary artery bypass surgery in his early 60s.

The patient experienced no cardiac symptoms at rest or during exercise. Labs drawn revealed an elevated LDL-C of 208 mg · dL^{-1} and total cholesterol of 262 mg · dL^{-1}. Fasting blood sugar was 86 and he had normal renal and hepatic function. After receiving this abnormal lipid panel, he was immediately started on a high-dose, high-intensity statin and was referred for coronary calcium CT.

A review of his records showed an LDL-C of 192 mg · dL^{-1} and total cholesterol of 258 mg · dL^{-1} as early as 2009 (patient age was 29 yr), which was then checked intermittently until it was checked yearly after 2018. He noted that his doctors always commented that it was high, but as he was young they did not recommend starting a medication and instead encouraged routine checks and to continue his healthy lifestyle.

The coronary artery calcium score was 120 Agatston units in the left main coronary artery, placing him above the 90th percentile for men between the ages of 40 to 45, suggesting a high likelihood of mild coronary artery disease with significant narrowing possible. He went to a cardiologist who confirmed the presence of familial hyperlipidemia and referred him for echocardiography (normal) and CT angiography which showed nonocclusive focal calcific atherosclerotic plaque in the proximal and mid left anterior descending arteries, including the distal right coronary artery, resulting in mild stenosis (25–49%) and minimal stenosis (< 25%), respectively. He was categorized as CAD-RADS 2, indicating mild nonobstructive coronary artery disease that merited aggressive medical therapy. As coronary artery disease is disqualifying for all flying classes in the Air Force, he was referred to the Aeromedical Consultation Service at Wright-Patterson AFB for further evaluation. He underwent coronary angiography, which demonstrated mild nonobstructive calcifications in the left anterior descending arteries not requiring stent placement and, thus, he continued with medical management.

During this evaluation period, his LDL-C dropped to 49 mg · dL^{-1} and total cholesterol decreased to 96 mg · dL^{-1} on the maximum dose of a high-intensity statin, which he tolerated well. He was returned to flying status and allowed to continue flying high-performance aircraft. His children were referred to their pediatrician for testing for familial hypercholesterolemia.

DISCUSSION

In the United States, the commonly accepted diagnostic criteria for HeFH include: LDL-C ≥ 160 mg · dL^{-1} for children, LDL-C ≥ 190 mg · dL^{-1} for adults plus one first-degree relative similarly affected or with premature CAD or positive genetic testing for an LDL-C raising gene defect (LDL receptor, ApoB, or PCSK9).[7] Patients with negative test results for the three genes yet who still have the typical familial hypercholesterolemia phenotype may have other genetic variation contributing to high LDL-C levels. Performing genetic testing allows for more refined genetic counseling of relatives, however.[10] In a study of 20,485 CAD-free control and prospective cohorts, individuals with an LDL-C level ≥ 190 mg · dL^{-1} and no familial hypercholesterolemia mutation (6.7%) were at a 6-fold increased risk of CAD than the reference group with an LDL-C ≤ 130 mg · dL^{-1}. In contrast, subjects with an LDL-C level ≥ 190 mg · dL^{-1} and a familial hypercholesterolemia mutation (1.7%) were at a 22-fold increased risk than the reference group.[6] Once identified in a patient, both LDL-C and familial hypercholesterolemia mutation testing (cascade screening) should be performed to screen for at-risk first-degree relatives.[6]

There is controversy on when to initiate lipid screening, with the U.S. Preventative Services Task Force (USPSTF) recommendation for initiation at 35 for men and 45 for women. The American Heart Association (AHA), American College of Cardiology (ACC), and the National Lipid Association give a grade 1 Class of Recommendation for a fasting or nonfasting plasma lipid profile in adults who are 20 yr of age or older.[4] The USPSTF awards a grade I for insufficient evidence to screen children and adolescents 20 yr or younger, though the American Academy of Pediatrics, AHA, ACC, and National Lipid Association recommend universal lipid screening in children between the ages of 9 to 11 yr.[7] For adults ages 40 to 75, risk can be calculated using race- and sex-specific pooled cohort equations, most commonly the 10-yr ASCVD risk calculator developed by the AHA/ACC. For patients ages 20 to 39, lipids should be measured and assessed with other risk factors every 4 to 6 yr, though the utility of the 10-yr ASCVD risk calculator is limited in this population.[1] Notably, patients with familial hypercholesterolemia are at significant risk of having an early ASCVD event, and the use of risk calculators is not applicable to this group.[1]

The treatment of HeFH is less controversial: the first-line medication is statin therapy. In a 1995 randomized controlled trial, placebo-controlled statin trials of pravastatin 40 mg in patients with LDL-C ≥ 190 mg · dL^{-1} showed a reduction in MI and cardiovascular death, with the benefits extending in a 20-yr observational follow-up study.[12] Additionally, as high-intensity statins provide greater risk reduction than moderate-intensity statins or placebo, patients with HeFH should receive high-intensity statins at the highest tolerated dose.[4] Given that many patients with FH will have at least a mild CAD at diagnosis, placing them at very high risk for future cardiac events, the goal for statin therapy should be an LDL-C of 70 mg · dL^{-1} or less. If unable to reach this goal on maximally tolerated statin therapy,

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05

the addition of nonstatins (ezetimibe, PCSK9 inhibitors, or in more severe cases lipoprotein apheresis) is indicated.[7]

Approved statins for U.S. Air Force air crew include simvastatin, pravastatin, lovastatin, atorvastatin up to 80 mg · d^{-1} and rosuvastatin up to 40 mg · d^{-1}.[11] A higher dosage or combination medication requires an aeromedical waiver. An aviator should be grounded for 5 d when starting a statin or after any dose adjustment to monitor for side effects.[11] Second line medications or combination therapies include ezetimibe and fenofibrate, both of which require a 3- and 5-d grounding period, respectively, for side effects, and both require an aeromedical waiver.[11]

In the civil aviation world there are considerable differences in the methods of measuring and addressing elevated cholesterol panels in aviators. The UK Civil Aviation Authority requires lipid screening of all initial pilot applicants and a repeat screen after the pilot turns 40 yr of age.[2] Both the International Civil Aviation Organization and the U.S. Federal Aviation Administration (FAA) do not routinely screen aviators for elevated cholesterol. The FAA considered a mandatory screening of pilots, followed by in-depth cardiovascular examination if their total cholesterol levels were greater than 300 mg · dL^{-1}, but this policy change was rejected in 1996. Most reportable cardiovascular conditions include further evaluation with a lipid panel.[2] The FAA does not restrict statin or other cholesterol-lowering medication classes due to favorable side effect profiles and demonstrated overall safety.[2]

In the flying environment, unique conditions such as hypobaric pressure, hypoxia, heat stress, catecholamine surges, and high $+G_z$ maneuvers reduce oxygen supply to the myocardium, exacerbating ischemia in individuals with existing CAD. When this ischemia presents symptomatically, it carries the risk of sudden incapacitation and inability to maintain control of the aircraft, a catastrophic scenario.[3] For this reason, CAD is the leading cause of disqualification for aviators and, if returned to flying status, individuals are often restricted to non-high-performance aircraft (<2.5 G_z with another qualified pilot).[8] The relatively common condition of HeFH leads to an earlier onset and higher risk CAD, and aviation medical providers should seek to identify and treat this condition as early as possible to prevent, most importantly, death and disability associated with the disease. If identified and treated at younger ages, aircrew are more likely to remain qualified for flying high-performance aircraft safely.

ACKNOWLEDGMENTS

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Air Force, Department of Defense, or the U.S. Government.

Financial Disclosure Statement: The author has no competing interests to declare.

Authors and Affiliations: Lori C. Gatzke, M.D., 21st Medical Group, Peterson-Schriever Garrison, Colorado Springs, CO, USA.

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019; 74(10):e177–e232. Errata in: J Am Coll Cardiol. 2019; 74(10):1429–1430; and J Am Coll Cardiol. 2020; 75(7):840.
2. FSF Editorial Staff. Elevated cholesterol levels present major risk for cardiovascular disease. Human Factors and Aviation Medicine. 2001; 48(3): 1–8. Alexandria (VA): Flight Safety Foundation; 2001.
3. Green N, Gaydos S, Hutchison E, Nicol E. Handbook of aviation and space medicine, Ch. 49. London: CRC Press; 2019.
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019; 139(25): e1082–e1143.
5. Karr S. Epidemiology and management of hyperlipidemia. Am J Manag Care. 2017; 23(9, Suppl.):S139–S148.
6. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016; 67(22):2578–2589.
7. McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc. 2019; 8(24):e013225.
8. Nicol ED, Rienks R, Gray G, Guettler NJ, Manen O, et al. An introduction to aviation cardiology. Heart. 2019; 105(Suppl. 1):s3–s8.
9. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol. 2016; 4(10):850–861.
10. Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018; 72(6):662–680.
11. U.S. Air Force. Category: Gen, Medication: Atorvastatin. Official Air Force Aerospace Medicine Approved Medications. Washington (DC): U.S. Air Force; 2021. Report No.: AF/SG3P.
12. Vallejo-Vaz AJ, Robertson M, Catapano AL, Watts GF, Kastelein JJ, et al. Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men with Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up. Circulation. 2017; 136(20):1878–1891.
13. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics – 2020 update: A report from the American Heart Association. Circulation. 2020; 141(9):e139–e596.

http://prime-pdf-watermark.prime-prod.pubfactory.com/ | 2025-02-05