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EDITORIAL

Risk of Sudden Cardiac Death in Patients with Angina with no Evidence of Cardiac or Other Diseases: Need Special Attention

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Angina is a symptom of coronary artery disease (CAD), developed due to myocardial ischemia. Myocardial ischemia is a life-threatening disease because it is found to be associated with myocardial infarction (MI), ventricular tachycardia, ventricular arrhythmia, and sudden cardiac death. According to the WHO report, cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 19.8 million people died from CVDs in 2022, representing approximately 32% of all global deaths. Among deaths, 85% were due to heart attack and stroke. Out of the 18 million premature deaths (under the age of 70) due to non-communicable diseases in 2021, about 38% were caused by CVDs [1].

Not all patients with angina have obstructive CAD. Thus, a set of investigations is performed to diagnose CAD in patients with angina following American Heart Association (AHA)/ American College of Cardiology (ACC) practice guidelines, [2] which include blood investigations, 12-lead Electrocardiogram (ECG), treadmill test, thallium-201 myocardial perfusion SPECT imaging (Tl-201 MPI), and coronary angiography. The coronary angiography allows visualization of the site and extent of occlusion. It is an invasive procedure, whereas the Tl-201 MPI is non-invasive. The Tl-201 MPI demonstrates a high degree of accuracy in determining the presence, location, and extent of ischemic heart disease (IHD). The Tl-201 MPI is also found to be sensitive for detecting microvascular abnormalities in patients with transient ST-segment elevation on treadmill testing and normal coronary angiography.

More than half of all patients with angina undergoing elective invasive angiography have no obstructive CAD [3]. Further investigation with Coronary thermodilution, acetylcholine response test, and other tests performed [4] revealed an interesting finding that in patients with symptoms of ischemia with no obstructive coronary artery disease (INOCA), 52% of patients had isolated microvascular angina, 17% had isolated vasospastic angina, 20% had both, and 11% had noncardiac chest pain. Over three-quarters of patients with INOCA had comparable angina burden but reduced quality of life compared to patients with obstructive CAD.

It is evidenced by studies that there are certain percentages of patients

Declarations

The author declares that she has no conflict of interest.

who clinically present with angina; however, they do not have any evidence of myocardial ischemia. Clinically, they are considered patients with non-cardiac chest pain with symptomatic angina. They undergo symptomatic treatment.

The moot question remains, "whether they have any cardiac autonomic modulation derangement?" Surprisingly, assessment of cardiac autonomic tone/modulation using heart rate variability (HRV) showed reduced HRV in these patients with angina with no evidence of myocardial perfusion defects (MPD), as compared to both patients presenting with angina with MPD and healthy subjects. These patients had no evidences of hypertension, diabetes mellitus, chronic kidney diseases, chronic respiratory diseases, thyroid dysfunction, and gastrointestinal disorder. All patients were male and they were non-smokers and non-alcoholics, and not taking drugs other than conventional cardiac drugs. Patients were followed up for one year. During follow-up, the risk of sudden death was also seen in this group of patients [5].

Even an adult male patient, aged 35 years, clinically presenting with angina, with no evidence of CAD or any other diseases, showed markedly reduced HRV and baroreflex sensitivity (BRS). Unexpectedly, the patient had a sudden death within six months of follow-up [6].

Several studies have reported reduced HRV in patients with CAD. A reduced HRV is also reported in patients with microvascular angina. It reveals that patients clinically presenting with angina, whether they have myocardial ischemia, MI, or microvascular angina, show reduced HRV. Markedly reduced HRV has been reported as one of the independent predictors of sudden death in patients with MI.

In summary, there are several patients who present with angina clinically; however, they do not have any evidence of CAD or other systemic diseases. They are considered normal, having symptomatic angina. However, evidence suggests that they have reduced cardiac autonomic tone/modulation, as assessed with HRV, compared to patients with angina with IHD, and they also have a risk of sudden death. It needs special attention to bring this fact to light for further investigation and management of the quality of life of these patients. Further studies are needed to explore other underlying mechanisms and the management of these cases.

Possible mechanisms for angina and sudden cardiac death in patients with no CAD or other diseases

Basically, angina is due to myocardial ischemia, a condition in which oxygen supply to the cardiac muscle is reduced, which leads to the release of adenosine, lactic acid, and other ischemia-induced metabolites in the myocardium. These metabolites stimulate pain receptors present in the cardiac afferent sympathetic nerve fibers [7, 8], which carry pain sensation to the central pain-processing area of the brain for perception and to the autonomic center of the brain for autonomic responses. Activation of sympathetic efferent nerve fibers leads to changes in the electrical activity of the heart, i.e., an increase in heart rate, changes in ECG, or arrhythmia, based on the degree of myocardial ischemia. Generalized sympathetic activation from the autonomic center of the brain can alter blood pressure by changing myocardial contractility and vascular responses. It can also alter other visceral functions.

However, in patients with angina with no CAD and any other diseases, the scenario seems different. In such patients, HRV is reduced in the absence of any diseases, i.e., cardiac autonomic modulation is itself reduced. It is well known that the regulation of cardiovascular function is under the control of the autonomic nervous system. Thus, it may directly affect the cardiovascular compensatory mechanisms and cardiovascular reserve. It may directly lead to reduced coronary blood flow reserve. Therefore, the demand for coronary blood flow during activity and stress is not appropriately met. This may cause accumulation of adenosine and other metabolites in the myocardium during stress and activity. These accumulated metabolites stimulate cardiac afferent sympathetic fibers [7, 8], causing angina in patients with no CAD/IHD. In response to angina, reflex activation of efferent sympathetic and parasympathetic outflow to the heart is reduced, as evidenced by reduced HRV [5, 6], thus, unable to activate compensatory mechanisms. Markedly, reduced autonomic outflow to the heart may cause a marked reduction in coronary flow reserve. As a result, there may be more and more accumulation of metabolites in the myocardium. Possibly, the accumulation of increased levels of metabolites causes cardiac electrical activity and myocardial dysfunction, leading to sudden death.

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