Chronotropic incompetence: are the carotid arteries to blame?

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This editorial refers to 'Chronotropic response to exercise testing is associated with carotid atherosclerosis in healthy middle-aged men¹' by S.Y. Jae et al., on page 954.

Jae et al.¹ report on the association between the chronotropic response during exercise testing and carotid atherosclerosis in a large cohort of 8959 healthy middle-aged men. Importantly, the association between an attenuated heart rate (HR) response to exercise and a measurement of sub-clinical atherosclerosis by ultrasonography was independent of age, conventional cardiac risk factors, and parameters of inflammation.

The HR response to exercise is related to several parameters including age, resting HR, functional capacity, cardiac function, extent of coronary artery disease, and the autonomic nervous system. A common definition of an abnormal HR response during exercise is the failure to achieve 85% of the age-predicted maximal HR (defined by 220 bpm minus the patient’s age). This method may, however, be confounded by the resting HR and functional capacity. Therefore, the concept of HR reserve was introduced. The HR reserve is defined as the difference between maximal predicted HR (or 220 bpm minus the patient’s age) and resting HR. Failure to use 80% of HR reserve is considered as chronotropic incompetence. To take into account the functional capacity, the chronotropic index can be calculated as HR reserve/metabolic reserve percentage, with metabolic reserve measured by gas analysis. A marker of abnormal HR response during exercise is then defined as a chronotropic index <0.8 in the absence of beta-blocker therapy.²

In most laboratories, failure to reach 85% of age-predicted maximum HR during exercise is considered as a sub-maximal response that is associated with a decreased sensitivity to detect coronary artery disease. Thus, studies have shown that an abnormal HR reserve is not diagnostic for coronary artery disease.³ Therefore, in the clinical setting, abnormal HR responses should not be used to establish a diagnosis of coronary artery disease. However, the HR information obtained during the test can further help in the risk stratification of an individual patient. Recent large-scale studies have found that an abnormal chronotropic index or HR reserve <80% is associated with increased long-term mortality in asymptomatic subjects and in lower and higher risk patients referred for exercise testing. Most importantly, the prognostic information obtained from HR during exercise appears to be incremental to pre-test information, such as the Framingham risk score, and to post-test information, such as functional capacity or information obtained from nuclear perfusion imaging, treadmill exercise echocardiography, or coronary angiography.³⁻⁴ Recently, Khan et al. reported in a series of 3736 patients referred for symptom-limited exercise testing and taking either metoprolol tartrate or atenolol that chronotropic incompetence remained an independent predictor of death. Of note, Khan et al.⁹ defined a cut-off of HR reserve ≤62% to define chronotropic incompetence in patients taking beta-blockers.

Although several large-scale studies have established the prognostic value of the chronotropic response during exercise, the underlying mechanisms are not very clear. Chronotropic incompetence is generally believed to reflect an underlying autonomic nervous system imbalance. Individuals with dysfunctional autonomic HR responses may be more predisposed to lethal cardiac arrhythmias and thus increased mortality regardless of the presence or extent of coronary artery disease.

A possible explanation for the association between chronotropic incompetence and carotid artery atherosclerosis as documented by Jae et al.¹ can be found in the area where the common carotid artery bifurcates. Pioneer work by Hering and Heyman¹⁰ has shown that the carotid sinuses and the walls of the large arteries arising from the carotid artery contain receptors that, by a reflex mechanism, act upon and regulate the activity of the cardiovascular and respiratory centres. Arterial blood pressure is constantly monitored by baroreceptor nerve endings that are sensitive to stretching of the vessel wall and are connected with the central nervous system through the glossopharyngeal nerve. Under normal physiological conditions, baroreceptor firing exerts a tonic inhibitory influence on sympathetic outflow from the medulla. Hypotension results in a disinhibition of the medullary centres, leading...
to an increasing sympathetic outflow and a decreasing para-
sympathetic outflow. These autonomic changes cause vaso-
constriction (increase in total peripheral resistance),
tachycardia, and positive inotropy, thus restoring arterial
blood pressure.

The role of the carotid baroreceptors on the exercise HR
response is far more complex, involving resetting of the
arterial baroreflex to a higher operating point and inter-
action with muscle chemoreceptors and baroreceptors.11
As the carotid sinus baroreceptors are ‘stretch’ receptors,
increased stiffness of the vessel wall associated with
arotic artery atherosclerosis will most likely affect the
ability of the receptors to respond to pressure changes.
Other baroreceptors are located in the aortic arch, operat-
ing at pressure levels ~30 mmHg higher. As atherosclerosis
of the carotid arteries is often associated with aortic
atherosclerosis and reduced aortic compliance, the sensi-
tivity of aortic baroreceptors may also be influenced. Jae
et al.1 demonstrated nicely that the presence of carotid
atherosclerosis was associated with chronotropic incompe-
tence, but the conclusion would have been stronger if the
analysis of the carotid arteries had included an evaluation
of the vessel wall elasticity. Wall tracking techniques can
be easily combined with carotid artery intima-media thick-
ness measurements and allow a non-invasive evaluation of
arterial compliance.12 Also, as no outcome data were
available, the independent prognostic information of
carotid artery atherosclerosis vs. chronotropic incompe-
tence in a population of healthy individuals remains
unclear.

In conclusion, the authors have to be congratulated for
this well-documented and large-scale study on chronotropic
incompetence. Further studies are now needed to unravel
the pathophysiological mechanisms that produce the abnor-
mal response in individual patients, including down-regu-
lation of beta-adrenergic receptors, central nervous
system effects, and baroreflex abnormalities, with their
potential relationship to carotid atherosclerosis.13 Also,
additional studies on how to modulate chronotropic incom-
petence by interventions are awaited. In the meantime,
the HR response during exercise can be easily measured
during exercise testing and can help, based on a large
amount of clinical data, in the risk stratification of
asymptomatic individuals as well as patients with estab-
lished coronary artery disease.

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