

CORRESPONDENCE

Letters to the Editor

Importance of Local Hemodynamic Conditions in the Atherosclerotic Effect of Increased Heart Rate

We congratulate Custodis et al. (1) on their review regarding the role of increased heart rate (HR) in vascular pathophysiology. We would like to underscore the importance of local hemodynamic conditions on the atherosclerotic effect of increased HR and to expand on the pathophysiological mechanisms involved in this effect.

Elevated HR appears to promote atherosclerosis by modulating the local hemodynamic environment (2). Low and oscillatory endothelial shear stress (ESS), which plays a critical role in the pathogenesis of atherosclerosis (3), occurs in geometrically irregular regions of the coronary arteries during systole, whereas in the same regions, ESS increases to more physiologic levels during diastole (2). As HR increases, the fraction of the cardiac cycle corresponding to diastole decreases, thereby increasing the exposure of endothelium to the atherogenic effect of systolic low ESS and attenuating the atheroprotective effect of diastolic ESS (2). Moreover, moderately elevated HR increases the frequency of ESS oscillations between systole and diastole in atherosclerosis-prone regions, further enhancing the local atherogenic environment (2).

Also, high HR may increase the cardiac output, increasing the blood pressure and subsequently the local tensile stress, which also plays a critical role in atherosclerosis (2,4). In addition to the magnitude of tensile stress, elevated HR may also increase the frequency of the periodic tensile stress fluctuations between systole and diastole, resulting in a cumulative "fatigue effect" on the coronary endothelium (2,4).

By increasing tensile stress, increased HR may alter the structure and organization of the extracellular matrix within the coronary wall, thereby promoting stiffening of the wall. Within stiff coronary arteries, the proatherogenic local hemodynamic environment may be enhanced (2,5).

The pulsatile motion of the heart during the cardiac cycle induces periodic changes in the geometry of the coronary arteries, which in turn influence the local hemodynamic environment. By increasing the frequency of the pulsatile heart motion, high HR enhances the periodic geometric changes of the coronary arteries, accelerating the atherosclerotic process (2).

Further experimental and clinical studies are warranted to elucidate the underlying molecular mechanisms implicating increased HR in coronary atherosclerosis. Slowing HR could potentially decrease the progression of atherosclerosis by reducing the local atherogenic vascular environment. This effect may be involved in any beneficial role of HR-lowering agents in preventing coronary artery disease.

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REFERENCES

1. Custodis F, Schirmer SH, Baumhäkel M, et al. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol* 2010;56:1973–83.
2. Giannoglou GD, Chatzizisis YS, Zamboulis C, et al. Elevated heart rate and atherosclerosis: An overview of the pathogenetic mechanisms. *Int J Cardiol* 2008;126:302–12.
3. Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. *J Am Coll Cardiol* 2007;49:2379–93.
4. Thubrikar MJ, Robicsek F. Pressure-induced arterial wall stress and atherosclerosis. *Ann Thorac Surg* 1995;59:1594–603.
5. Chatzizisis YS, Giannoglou GD. Coronary hemodynamics and atherosclerotic wall stiffness: a vicious cycle. *Med Hypotheses* 2007;69:349–55.

Reply

We thank Drs. Chatzizisis and Giannoglou for their response to our paper (1). We fully agree that local hemodynamic characteristics, such as shear and tensile stress, as well as spatial deformation are closely affected by heart rate and may therefore determine vascular function and fate. As an integral component of cyclic stress (pulse pressure times heart rate), heart rate closely controls vascular integrity and defines transmural force imposed by pulsatile blood flow. Increasing evidence establishes a role for heart rate as a risk factor, and experimental studies support the hypothesis of a direct mechanistic link between heart rate and atherogenesis. However, experimental evidence on the exact rate-dependent changes of the local hemodynamic environment and the subsequent molecular signalling is still sparse. In vitro studies (e.g., characterizing different frequencies of shear or cyclic strain) provide very important insight but model only part of the hemodynamic effects of heart rate in vivo. We therefore believe that the comment of Chatzizisis and Giannoglou outlines important areas of future research.

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REFERENCE

1. Custodis F, Schirmer SH, Baumhäkel M, et al. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol* 2010;56:1973–83.