Chapter 6

CARDIOVASCULAR AND RESPIRATORY SYSTEMS

Åsa Tivesten and Jörgen Isgaard
Research Center for Endocrinology and Metabolism, Department of Internal Medicine, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden

Key words: Cardiac output; cardiomyocytes; myocardium; peripheral resistance; sleep disorders

1. STRUCTURAL AND FUNCTIONAL ASPECTS OF THE CARDIOVASCULAR SYSTEM

1.1 The myocardium and cardiac hypertrophy

The myocardium is the muscle layer of the wall of the heart. It consists of cardiac muscle fibres (cardiomyocytes), connective tissue (connective tissue cells and extracellular matrix), and blood vessels in the capillary microcirculation. Approximately 90% of left ventricular tissue volume in small rodents is occupied by cardiomyocytes, while 85% of the cells are interstitial cells. The interstitium is comprised of more than 95% of type I and type III collagens.

The term hypertrophy defines an increase in cellular size based on a concordant increase in all of the cellular constituents. Cardiac hypertrophy is an important compensatory mechanism in left ventricular pressure or volume overload states. The hypertrophy is then induced locally, triggered by the increased wall tension. Besides increased load, extrinsic trophic hormonal or neurogenic factors may trigger cardiac hypertrophy. Load-dependent and load-independent hypertrophy share some common
intracellular as well as autocrine-paracrine mediators. Moreover, there are common transcriptional regulatory pathways during cardiac hypertrophy, including re-expression of protein isoforms normally expressed in the developing heart (such as skeletal α-actin, atrial and brain natriuretic factor, and β-isoform of myosin heavy chain), as well as immediate-early proto-oncogenes. Besides control of gene transcription, increased translation efficiency represents a means of initiating the hypertrophic response.

1.2 Calcium in the contractile process and in hypertrophy-signaling

Calcium ions (Ca\(^{2+}\)) have multiple functions within the cardiomyocyte, although the most well-studied is their role in the contractile process. Following a membrane potential, Ca\(^{2+}\) enter the cardiomyocyte through the L-type Ca\(^{2+}\) channels and this Ca\(^{2+}\) influx in turn triggers release of Ca\(^{2+}\) from the sarcoplasmic reticulum through the ryanodine receptor. The Ca\(^{2+}\) then bind to troponin C and the contractile elements are activated. The sarcoplasmic reticulum ATPase (SERCA) then rapidly pumps back Ca\(^{2+}\) into the sarcoplasmic reticulum. Ca\(^{2+}\) are also excreted from the cell, mainly through the Na\(^{+}/Ca^{2+}\)-Exchanger, which is driven by the electrochemical gradients for Na\(^{+}\) and Ca\(^{2+}\).

Na\(^{+}/K^{+}\)-ATPase has a key role in the active transport of Na\(^{+}\) and K\(^{+}\) across the cell membrane and establishing a negative electrical potential inside cells. Cardiac glycosides, e.g. digoxin, increase cardiac contractility by an inhibition of Na\(^{+}/K^{+}\)-ATPase, which results in an increased intracellular concentration of Na\(^{+}\) ions. As the Na\(^{+}/Ca^{2+}\)-Exchanger transports Na\(^{+}\) and Ca\(^{2+}\) in both directions, increased Na\(^{+}\) levels are followed by increased Ca\(^{2+}\) levels within the cell and thereby contractility is enhanced.

Besides being involved in the contractile process, Ca\(^{2+}\) acts as an activator of signal transduction pathways responsible for hypertrophic cardiac growth. Proteins involved in Ca\(^{2+}\) handling, such as calmodulin and calsequestrin, seem to play important roles as overexpression of these proteins may cause cardiac hypertrophy. Recent studies have reported increased expression and/or activity of the Na\(^{+}/Ca^{2+}\)-Exchanger in experimental models of hypertrophy, and inhibition of Na\(^{+}/K^{+}\)-ATPase has also been linked to cardiac hypertrophy.

1.3 Peripheral resistance and vascular endothelial function

Arterial blood pressure is determined by two prime factors: cardiac output and peripheral resistance. Cardiac output is almost exclusively regulated by changes in total peripheral resistance, and is adjusted in order to