Homeostasis in dynamic self-regulatory physiological systems

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Abstract

Understanding the general principles of homeostasis and its regulation in health and disease is key to managing patients in intensive care units and operating theatres. In these environments, it is crucial to realize that physiological control is a dynamic process aimed at achieving a balance between two opposing sets of factors. Whereas one set of factors (e.g. the sympathetic nervous system) attempt to increase a physiological variable of interest at any given time, opposing forces acting almost concurrently, (e.g. the parasympathetic nervous system) will result in the reduction in the value of this variable. The human body is a self-adapting system and as a result of its ability to adapt, new physiological 'steady states' will be reached and maintained even in diseases. This review will explore some of the concepts and pathways involved in the regulation of homeostasis in the immediate, intermediate and delayed time scales following an initial perturbation, emphasizing the dynamic nature of this regulation.

Keywords Homeostasis; milieu-interieur; neural and hormonal control; physiological steady state; regulation; self-regulatory systems

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should be able to:

- understand the physiological regulatory processes contributing to the maintenance of homeostasis at steady state
- recognize the immediate, intermediate and delayed responses that maintain homeostasis
- describe the role of the cardiovascular system (cardiac output and venous return) and the Starling forces in maintaining homeostasis
- understand the complex neuro-hormonal interplay underpinning the maintenance of the composition of the 'milieu-interieur' and the dynamic nature of balance in steady physiological states

Historical perspectives

The concept of normal human physiology being a dynamic balance between two sets of opposing forces is certainly not new. The ancient Chinese philosophers described these opposing sets forces as '*Yin*' and '*Yang*' and this approach was integral to the Taoistic worldview. The Taoists further went on to characterize any deviation in this dynamic balance between the opposing sets forces as a state of '*dis-ease*'. In contemporary terms, these ancient concepts can be extrapolated as normal physiological variables being the product of a dynamic balance between factors that act to increase the value of that variable and the opposing factors that tend to decrease it — both sets of factors acting concurrently. For example, normal blood pressure (BP) or heart rate (HR) is always a dynamic balance between sympathetic activity (and/or circulating levels of catecholamines) that tend to increase HR/BP and parasympathetic activity (and or acetylcholine/endogenous opiates) that decreases HR/BP. The regulation of all physiological variables follows this general paradigm of two opposing sets of factors acting in harmony to achieve 'normality' or 'health'. More recent references to self-adjusting systems as a fundamental requirement of normal human physiology or health may be found in the writings of several European Physiologists. In 1877 the German Physiologist Eduard Friedrich Wilhelm Pflüger recognized these interactions as necessary for maintaining a steady state as exemplified in the following comments '*The cause of every need of a living being is also the cause of the satisfaction of the need to maintain a steady state*.' The Belgian Physiologist Fredericq in 1885 wrote, '*The living being is an agency of such sort that each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance. The higher in the scale of living beings, the more numerous, the more perfect and the more complicated do these regulatory agencies become. They tend to free the organism completely from the unfavourable influences and changes occurring in the environment*.' These generic ideas that had existed from antiquity were synthesized by Claude Bernard in 1877 through more precise quantitative analyses of these factors, leading to the coining of the term '*homeostasis*' and giving greater emphasis for these concepts as the very foundations of modern physiology. Claude Bernard pointed out that all living cells and tissues are surrounded by a fluid medium, which surrounds and bathes these tissues and cells. Maintaining the chemical and electrical properties of this surrounding fluid medium is a fundamental property of all life forms, irrespective of their level of complexity and sophistication. The composition of this fluid matrix or the '*milieu interieur*' is maintained constant within a narrow range through a sophisticated system of neurohumoral regulatory processes. The importance of this regulation was further highlighted by Claude Bernard when he wrote '*It is the fixity of the milieu interieur which is the condition of free and independent life*,' … and … '*all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment* …'. Although the influence of Clause Bernard has led to a greater emphasis on the composition of the extracellular fluid (ECF) when the concept of homeostasis is discussed, it is important to

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realize that these generic concepts apply to virtually all cells, tissues and systems and understanding the dynamic interaction at all levels of organization is key to understanding physiology and disease. This present review, however, will focus only on aspects of the control systems involved in maintaining homeostasis, broadly classifying them into immediate, intermediate and delayed control systems for convenience. In reality however, all the regulatory pathways, despite falling within these broad temporal categories, co-exist with considerable overlap. In order to consider the systems that regulate the composition of this fluid matrix, it is first necessary to review the formation and circulation of this fluid matrix under normal conditions.

Starling's forces and the formation of ECF

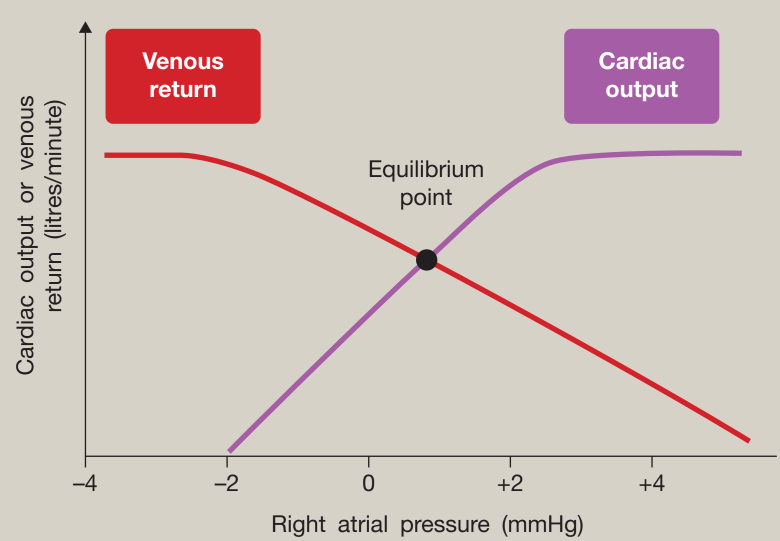
As a result of the pressure gradients across the capillary beds in the body, there is continuous extravasation of serum at the arterial end of the capillary beds through ultrafiltration. The ultra-filtrate is re-absorbed at the venous end of the capillary bed as the gradients are reversed. The excess fluid formed through this process permeates through the body and it is within this interstitial fluid compartment all cells and tissues are 'suspended'. As the pressure gradients at the arterial end of the capillary bed is greater than the corresponding reverse gradient at the venous end, the volume of fluid filtered out is greater than the corresponding volume that is re-absorbed at the venous end. This surplus volume is therefore available to 'circulate' within the body and provide the fluid medium or matrix within which exchange of ions, nutrients, oxygen and CO_2 between the cells and the ECF are enabled. This excess fluid will be ultimately returned to the central circulation *via* the lymphatic system and the thoracic duct. If the ultra-filtrate formed at the capillary beds is an important component of the milieu-interieur, the rate of its formation, re-absorption and circulation must be an important determinant of its composition. For example, a faster rate of renewal of this circulating medium will tend to counterbalance any changes in composition arising through metabolic activity or other extraneous factors. When viewed in this light, one of the most important regulators of the composition of the interstitial fluid compartment has to be the cardiovascular system — the cardiac output, its distribution between the various vascular beds, the perfusion pressures and the differential regulation of the hydrostatic pressure at the arterial and venous ends of the capillary beds.

Regulation of cardiac output

The term cardiac output refers to the volume of blood pumped out by the left ventricle each minute. Under stable conditions this will also be the same volume ejected by the right ventricle each minute and is the product of stroke volume and heart rate. At steady states, the volume of blood ejected by the left ventricle must equal the amount of blood returning to the right atrium. In other words, in health, cardiac output is equal to venous return. It is frequently schematically represented as in Figure 1.

The heart is capable of increasing or decreasing the amount of ejected blood, based on the amount of stretch the myocardium is subjected to as a result of changes in venous return (Frank—Starling's law). When viewed in this light, it becomes immediately apparent that the single most important factor regulating cardiac output is, in fact, venous return, which in turn is determined by the metabolic requirements of the body. This raises the question of how changes in the composition of the ECF

Cardiac output and venous return curves



These concepts have been reviewed very extensively and readers are referred to standard textbooks for a better understanding of how these curves are altered by sympathetic activity, changes in circulating volume and systemic vasoconstriction/dilatation.

Figure 1

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