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Giovanni Cavagna
Milano State University
Milan, Italy

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To my students

Foreword

In the fall of 1989, as a third-year medical student, I was preparing to enroll in a human physiology course at the University of Milan. Several professors offered that course and a lottery mechanism matched students with a professor. If your grades were high enough, though, and you were not happy with the results of the lottery, you had the option to petition for enrollment with a professor who had a reputation for being quite lenient. When the lottery assigned me to Prof. Cavagna, known for being particularly demanding, I heeded peer pressure and petitioned, and obtained, to be switched to the more lenient professor's course. Nonetheless, I remained intrigued by the exacting reputation that surrounded Cavagna, so I decided that, for the first week, I would attend classes of both professors. Attending those first few classes from Cavagna convinced me that his (deserved) reputation was a reflection of the quality, dedication, and commitment to teaching, and I re-petitioned to be switched back to where destiny had originally placed me. While, admittedly, I did not have the time to study any subject other than physiology for the entire academic year, I now look back at that course 30 years later and recognize that it was one of the best professional investments for my career. It is thus particularly precious that Cavagna has collected and structured the teaching material from 40-plus years of didactics to medical students in the current volume.

When approaching this book, one recognizes fundamental themes that transcend individual topics and chapters because they form the conceptual underpinning of physiology as one of the foundational disciplines of medicine: the concept of functions of organs and systems as transformations of energy, the quantitative approach to measuring such functions, the energy economy of such transformations, the integration of the components of a system across scales, from micro to macro, and the concept of homeostasis are all examples of those themes.

Chapter 1 deals with the statics and dynamics of the systemic and pulmonary circulations. Several physiologic concepts are introduced in the context of their clinical correlate, which will make the reading of this volume enticing for medical students. For example, the hydrostatic indifferent point is discussed in the context of the genesis of orthopnea in congestive heart failure, laminar and turbulent flow in relation to murmurs, the sphygmic waveform in relation to aortic valve disease, and the critical closing pressure in the setting of reduced flow states such as hypovolemic shock and atherosclerosis. In addition, the rationale for proper clinical measurement of physiological variables, such as invasive blood pressure monitoring with intravascular catheters, is presented, and common missteps are discussed.

Chapter 2 treats the physiology of muscle, both skeletal and cardiac, and locomotion. While the heart is more commonly treated in conjunction with the circulatory system, the organization that Cavagna provides enables an immediate and informative parallelism of similarities and differences between the two types of striated muscle. This is the chapter in which the integration of molecular and systems physiology is most apparent, reflecting Cavagna's decades of seminal contributions to the physiology of the musculoskeletal system, from isolated muscle fibers to elephants.

Chapter 3 pertains to the ventilatory function and metabolism. Having pursued a career in the field of anesthesiology and critical care, it is enlightening for me to see how concepts such as the alveolar opening pressure during re-expansion from a collapsed state and the relaxation curve of the respiratory system have represented the conceptual foundation for the improvement in mechanical ventilator management of patients with acute respiratory distress syndrome that has led to improved outcomes over the past decade. The next frontier in this field is the development of personalized mechanical ventilation through, among other means, measurement of esophageal pressure to differentiate the relative contributions of the lung and chest wall to the impairment of respiratory mechanics in the individual patient. Consequently, the discussion of esophageal pressure measurements to tease apart the lung and chest wall curves is particularly timely. In addition, topics such as acid–base equilibrium and related disturbances are of the utmost clinical relevance as virtually any physician will have to interpret a patient's blood gas report at some point in their career.

Chapter 4 is on renal physiology, which is treated with an emphasis on the same overarching themes of the entire book: work (osmotic in the case of the kidney), homeostasis, and the functional unit (the nephron in the kidney). In addition, concepts that clinicians will encounter daily in their profession, such as the renal clearance of solutes, are explained in detail.

Five years after my physiology course, I went back to Prof. Cavagna and joined his laboratory as a part-time research fellow for a couple of years, before emigrating to the USA. I thus had the opportunity to learn from Cavagna the researcher, rather than the professor. The obsessive compulsive nature of his data checking, the attention to detail in experimental setup and conditions, and the importance of always asking "why" (i.e., intellectual curiosity) and of stripping away the irrelevant to get to fundamental principles for how things work (i.e., theory) are all things that I learned in those later years. These teachings have been invaluable in my career and clearly transpire from this book.

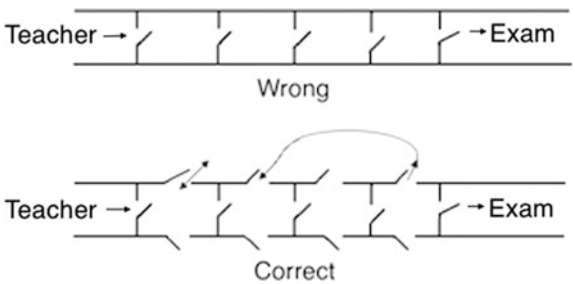
Saint Louis, MO, USA Guido Musch

Preface

In my frequent visits to Milan hospitals, I met several old students of mine who warmly told me that my lessons are still useful for their work. Since my last lessons on circulation, muscle, respiration, and kidney were filmed, I decided to publish them in the hope to help a larger number of students.

In my opinion, a physiological mechanism can be fully understood and more easily retained when it is developed from and through physics (when possible). This is what I did in my lessons assuming an elementary knowledge of mathematics and physics.

A problem in teaching is the separation between lessons content in student memory and his outside world experience. Often, the different topics are stored sequentially in the memory of the student, as in closed wagons of a train, to be "expectorated" at the examination (first figure below). This leads to two problems: (i) It becomes difficult for the student to explain an outside condition on the basis of the mechanisms learned during the course, and (ii) it becomes difficult to connect between them arguments taught in subsequent order. To prevent these inconveniences, it is necessary to open the doors of the train of student memory toward its daily external world and to associate items taught in a different order (second schema below). This is a task of both teacher and student. I did my best here.



I reproduced the slides and my drawings on the blackboard as figures in the text. In the legend of the figure taken from several books and articles, I referenced the original source for further reading.

I wish to thank Dr. Mario Legramandi for his help in recovering original literature sources and his accurate revision of the manuscript.

Milan, Italy Giovanni Cavagna

Contents

Chapter 1
Circulation of Blood

Abstract Definition of absolute, relative and transmural pressures. Manometers. Mechanical energy of a fluid. Statics of circulation: effect of height, acceleration and immersion in water on blood pressure and distribution within the body. Dynamics of circulation. Laminar motion: derivation of the parabolic profile of blood velocity within a vessel, the law of Poiseuille and its consequences. Axial accumulation of red cells: effect of vessel dimensions and the Fahraeus-Lindqvist effect. Flowmeter. Turbulent motion: derivation of the critical velocity and of the Reynolds Number. Incidence of kinetic energy in circulation: downstream pressure, side pressure and end pressure in different parts of the circulation. The sphygmic wave. Measurement of blood pressure. Organization of systemic and pulmonary circulation. Equilibrium conditions of blood vessels: definition of tension and the Law of Laplace. Elastic, active and mixed tensions in vessels walls. Critical closing pressure. The capillaries. Function of capillaries. Factors affecting production of the interstitial fluid and edema. Venous circle. Pulmonary circle from top to bottom of lung zones in the erect position: waterfall effect. Coronary flow: effect of heart beats frequency. Fetal circle.

1.1 Introduction

Physiology: a study of the functions of a living organism. What is a 'function'? A function consists in a transformation of energy. All the functions of our organism consist in a transformation of chemical energy into another form of energy. For example in the nervous system chemical energy is transformed in a difference of electrical potential across the neurons membrane (the action potential), in the muscular system chemical energy is transformed in a very different kind of energy: the mechanical energy (mechanical work done by muscle), the kidney transforms chemical energy in a difference of osmotic potential (when concentrating urine), the liver and other tissues transform chemical energy into different forms of chemical energy. A 'motor' is a transformer of energy: a living organism is an ensemble of small motors. These motors, in order to continue their function, require a *constant surrounding*. For example, they cannot work properly when the temperature increases above 45 °C, when

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osmolarity deviates appreciably from 0.3, the pH from 7 or toxic molecules are produced by the metabolism. In conclusion, a constant internal surrounding is necessary.

The problem is that a motor pollutes its surrounding. For example consider the oxidation of a mole of glucose:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 686 \text{ kcal}$$

It requires oxygen and produces carbon dioxide, water and heat, i.e. per se the reaction implies a modification of its surrounding. Then what?

If you want to maintain constant an inanimate object, for example a picture, you put it in a closed container. On the contrary if you want to maintain constant the surrounding within the living body, you, cannot close its communication with the external ambient. In fact, as shown in the example above, a closed system would be polluted by an increase in carbon dioxide, water and heat. In conclusion: a function requires a constant internal surrounding, but when it occurs, it pollutes it. The solution of this problem is to open the system towards the external environment. For example, in the example above, the function to go on must absorb oxygen from outside, and eliminate carbon dioxide, water and heat into the external surrounding. In other words in order to perform work a function requires both an input and an output. This means that all the cells functioning in our body, for example in the liver, must communicate with the external environment in spite of the distance between internal and external ambient. How this is done?

Two ways: one way appropriate for large distances, the second for small distances. The first one is the *circulation* of the blood. In the example above, the blood of the capillaries near the cells releases oxygen and takes away carbon dioxide, water and heat to large distances. However as in a bus network, the bus does not arrive within your home and you must walk from the bus stop to your apartment by walking, i.e. from the capillary to the working cell. In our body system this walking mechanism corresponds to *diffusion*, a mechanism useful for small distances only, operating in all tissues of our body to allow communication of the internal surrounding with the external environment.

The entire circulation of blood is at the service of the capillaries: blood flows one-way only contrary to respiration where air flows two-ways. As you know from anatomy blood flows from the left ventricle, into aorta, arteries, arterioles, capillaries, cava veins, right atrium (systemic circulation), right ventricle, pulmonary artery, pulmonary capillaries, pulmonary veins, left atrium (pulmonary circulation) (Fig. 1.1).