CURRENT PERSPECTIVES

The contribution of the giraffe to hemodynamic knowledge: a unified physical principle for the circulation

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Hemodynamics stands on three main physical principles: the hydrostatic pressure, firstly described by Stevino, the viscous flow pressure, described by Poiseuille and the total hydraulic energy, or Bernoulli's equation.

However, neither of these physical principles gives a comprehensive description of the single pressure measurement in the cardiovascular system. Hence, all these principles should be used together to fully describe the physical forces acting in the circulation of blood.

Experiments that measured the hydrostatic pressure in the jugular vein of the giraffe have shown that a few guidelines need to be followed to measure it correctly. Following these guidelines, it can be seen that hydrostatic and viscous flow pressures are strictly related to one another, and that this relationship is described in mathematical terms. In addition, it has been shown that hydrostatic and viscous pressures should be included in Bernoulli's principle, to give the combined Bernoulli-Poiseuille equation.

This unified principle is helpful not only to measure correctly the pressure with a catheter connected to a pressure transducer, but also to give to the pressure measured in a patient with the mercury manometer, a strong connection with the description of the pressure as a physical force acting inside the circulation. In addition it provides a comprehensive view of the cardiovascular system as a closed hydrodynamic system, in which the heart is a pump, that does not normally work to overcome the force of gravity.

The question at this point is: are there any pathophysiological conditions in which the heart needs to be confronted with the sudden appearance of the force of gravity inside the cardiovascular system?

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Key words: **Hydrostatic pressure; Viscous flow pressure; Total hydraulic energy; Hydrodynamic closed system; Gravity, Combined Bernoulli-Poiseuille equation.**

Introduction

Under the present conditions of our knowledge, medical science is still based on a method, the experimental method of Bernard[1]. As a scientific method it refers to and borrows theories and principles from the so-called "true" sciences, such as mathematics, physics, chemistry, etc[2].

Hemodynamics stands on three main physical principles: the principle of Stevino (S) on hydrostatic pressure (P_{hyd}), of Poiseuille (P) on hydrodynamics of a viscous fluid, and on the Bernoulli's principle (B) on the total hydraulic energy of an ideal fluid[3-5].

In medicine textbooks and in teaching courses, these three theories are classically considered as separate from one another to take advantage of the different aspects of hydrodynamics that they describe.

This way of presentation does not overcome perplexity, however, because it is difficult, mainly for medical students, to find a connection between these physical principles and the concrete measurement of an arterial or venous pressure.

In the following discussion, after a brief description of the main characteristics of the physical principles under consideration, I synthetically report the experimental data obtained from the giraffe. On the basis of these data a unifying hypothesis has been proposed about the physics of the circulation: the so-called combined Bernoulli-Poiseuille (BP) equation in which the S is also included[6]. This extension of B was for the first time proposed, to my knowledge, by Synolakis and Badeer[7]. It has the great advantage to be comprehensible, complete and applicable, not only to theoretical, but also to practical situations.

I then underline the fact that this proposal will consistently reduce the existing gap between the pressure measured in our patients and the description of pressure as a physical force.

Finally, I briefly mention the possible implications and future perspectives of this hypothesis, mainly focused on the description of a model of a hydrodynamic system and on the question whether the heart does or does not work against the force of gravity.

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The physical principles under consideration

Stevino. When P_{hyd} is measured, the physical law which describes the forces involved in the S is usually written as:

$$P_{hyd} = \rho gh \quad (1)$$

where ρ = density, g = acceleration of gravity, and h = height.

Its practical application requires first of all a clear definition of a zero reference level, then a right assignment of the signs plus (+) or minus (–) to the factor h. As I have recently described[8], if the pressure existing at the level of reference (P_0) is taken into consideration, the S is written as:

$$P_{hyd} = P_0 - \rho g (\pm h) \quad (2)$$

and, if one assumes P_0 as equal to zero, then:

$$P_{hyd} = - \rho g (\pm h) \quad (3)$$

The reason why P_{hyd} needs to be written as a negative factor to be correctly calculated lies in the convention regarding the element h, which designates h as positive above the zero level, and negative below.

Since P_{hyd} positively increases below the zero level, while the h factor becomes negative, a minus sign should always precede the product ρgh to reestablish it as positive, as it naturally is[8].

For S the shape of the conduit and its dimensions are irrelevant, provided that there is a continuous column of fluid[4,5].

For the heart and the circulation, the zero level of reference is the pressure existing in the right atrium, which is conventionally taken as equal to zero pressure.

The hydrostatic indifferent point, which is the point where P_{hyd} is always constant, independently of the orientation of the major axis of the body with respect to the gravitational field, is fairly near the right atrium, immediately below the heart, thus confirming the previous assumption[9,10].

In the following discussion P_{hyd} shall be distinguished from a different but similar factor, which is the gravitational potential energy. P_{hyd} shall then be written, when appropriate, without signs and with a subscript α, following a nomenclature already described[6], as:

$$P_{hyd} = \rho gh = (\rho gh)_\alpha \quad (4)$$

Poiseuille. When measuring blood pressure in a patient with a mercury manometer from the brachial artery using the Korotkoff's sounds and keeping the arm at the heart level (while, as it is known, the air manometer may be positioned anywhere) the physical law of reference is the P law.

The pressure force, described by P, is the force generated by the cardiac pump, and is a physical force necessary to overcome resistances to flow, i.e. the viscous flow pressure (P_v)[4,5].

In its simplest form the P is written as:

$$P_1 - P_2 = \frac{8L\eta}{\pi r^4} \Delta V \quad (5)$$

which is to say that the pressure difference ($P_1 - P_2$) or the pressure drop, between two distant points, is directly proportional to the distance (L), the viscosity of the fluid (η), the existing flow rate (ΔV in the unit of time) and inversely proportional to the radius of the conduit (πr^4).

The factor $8L\eta/\pi r^4$ represents the resistances to flow (R). Hence, by considering $P_1 - P_2 = \Delta P = P$ and ΔV in the unit of time as flow (Q), the P may be rewritten as:

$$P = RQ \quad (6)$$

or:

$$Q = P/R \quad (7)$$

Equation 7 describes, in the most general form, the acting forces and their interactions in the circulation of blood.

At this point I wish to underline that no correlation exists between S and P.

In equations 1, 2, 3 and 4 no mention is made to P_v nor to flow, and in equations 5, 6 and 7, no reference is reported to P_{hyd}. Hence both S and P are valid and applicable, but we still do not know which relations hold between the two.

Bernoulli. The B law was for the first time proposed to our attention, as applied to the hemodynamics, by Burton with his textbook "*Physiology and Biophysics of the Circulation*"[3]. Burton described that the flow of blood is due to a difference in the total hydraulic energy between two points, rather than to a pressure difference. He also described that the absence of flow in a test tube, in which there is always a P_{hyd} gradient between the fluid's free surface and its depth, is due to the absence of a total hydraulic energy gradient[3].

The B is the physical principle of reference for the energetics of the circulation and it describes the interrelationship between the pressure, velocity and gravity effects of an ideal, incompressible and inviscid (non-viscous) flow. In its simplest notation it is written as:

$$E_{tot} = E_P + E_K + E_{GP} = \text{constant} \qquad (8)$$

where E_{tot} = total hydraulic energy, E_P = pressure energy, E_K = kinetic energy, and E_{GP} = gravitational potential energy.

Each of these terms is in the dimensional units of energy, i.e. $M\,L^2T^{-2}$, where M = mass, L = length and T = time.

In this equation, viscous forces are usually not taken into consideration, thus no energy is lost in frictions, heat is not generated, and the total energy is preserved and constant in different sections of a flow[4,5].

By dividing each term of equation 8 by the volume, the B equation is obtained in the form of "pressure equivalent". This means that each term of equation 8 is written in dimensional units of pressure ($M\,L^{-1}T^{-2}$), rather than in energy dimensional units[4].

Equation 8 written in terms of "pressure equivalents" becomes:

$$P + 1/2\rho v^2 + (\rho g h)_\beta = \text{constant} \qquad (9)$$

When the B is transformed in "pressure equivalent" units, the term E_{GP} becomes quantitatively identical to P_{hyd} (ρgh). To distinguish it from P_{hyd} (see equation 4) it is therefore indicated with the subscript β.

This way of writing B underlines the fact that both E_{GP} and E_K may convert into pressure and vice versa, i.e. any term may be "equivalent" to pressure[4].

The two terms P_{hyd} and E_{GP} are quantitatively identical and mathematically of opposite sign: while P_{hyd} increases with deepness (i.e. with – h), E_{GP} increases in the opposite direction, above the zero level (i.e. with + h).

P_{hyd} and E_{GP} must always be separately considered because, although they both originate in the relationship between the acceleration of gravity and the weight of a fluid element, they bear a different physical meaning. The E_{GP} term is actually the gravitational potential energy of a fluid element in relation to its position.

The term E_P may also be written as "pressure equivalent" (i.e. in dimensional units of pressure). In this case it simply becomes pressure, P. This pressure is nothing else than the effective measurable pressure in a section of flow (P_{eff}).

Since there is no actual way to describe different pressure sources with just one physical relationship, P_{eff} may be described as the result of interactions of many different pressures, such as ambient pressure (P_0), P_{hyd}, and pressure due to flow (P). Therefore, P_{eff} is mathematically a function (f) of different pressure sources, such as:

$$P_{eff} = f\,(P_0, P_{hyd}, P) \qquad (10)$$

Then, equation 9 becomes:

$$P_{eff} + 1/2\rho v^2 + (\rho g h)_\beta = \text{constant} \qquad (11)$$

Among all these different pressure terms, the P_v does still not appear. As a matter of fact, in its usual form, the B law does not take into consideration viscous forces[3].

From the classical point of view we have therefore three discrete descriptions of separate forces: the hydrostatic, the viscous and the total hydraulic energy of an ideal fluid. We know, however, that these forces are simultaneously present in the flow of blood and that the resulting pressure measurements takes into account their interactions.

At this point many interesting questions may be asked: if P does not consider P_{hyd} which relation exists between P_v and P_{hyd}? Is it possible to distinguish between the two, for example, in orthostasis? What is the hemodynamic meaning of the B law? What is the usefulness of B if it does not consider P_v?

The giraffe's contribution

Answers to our questions come from the studies done on the jugular vein of the giraffe. The first measurements of P_{hyd} in the giraffe's neck gave unexpected results[11]. A pressure gradient from the giraffe's head to the heart was actually found, but it was in the opposite direction of that predicted by gravity, which is to say that jugular venous pressure was higher at the cranial end rather than at the bottom of the neck (Fig 1)[11].

A first line of interpretation of these data was that a compartmentalization of the blood might have occurred due to the action of venous valves[11].

To verify this hypothesis and these measurements, a vertical hydrodynamic closed loop system was built in the laboratory by Hicks and Badeer[6]. This system allowed to study the pressures in the system, either with or without a flow generated by a constant flow pump (Fig 2)[12].

The correct measurement of the pressure in the descending limb of this system was not an easy task to accomplish. The following three methods should be

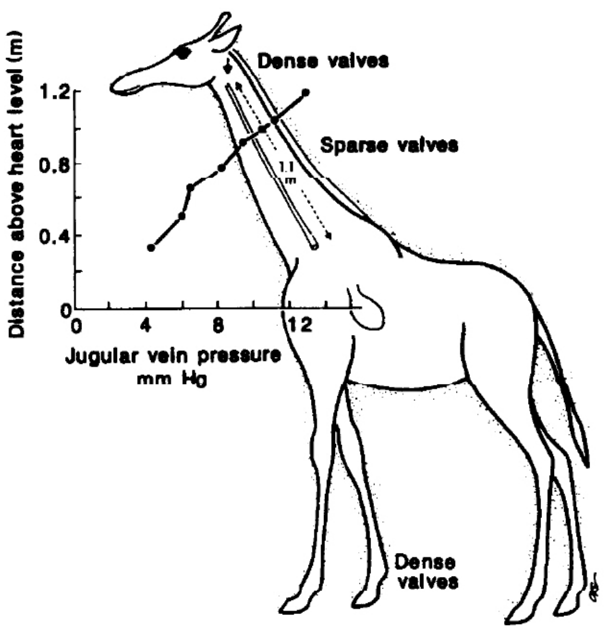

Figure 1. - Pressure as a function of hydrostatic height in the jugular vein and intervalve spacing in the giraffe's neck. *Solid arrow:* catheter insertion point; *dotted arrows:* maximum extension of Millar tip. In one giraffe the jugular vein pressure gradient was ~ 9 mmHg per 90 cm of vertical distance or 0.14 cm H_2O per cm of vertical distance ... Unfortunately, the Millar transducer was insufficiently long to measure intrathoracic venous pressure. These data indicate that viscous flow pressure in the jugular vein is opposite to that predicted by gravity and may suggest compartmentalization of the blood column. From Hargens et al[11], with permission from Nature.

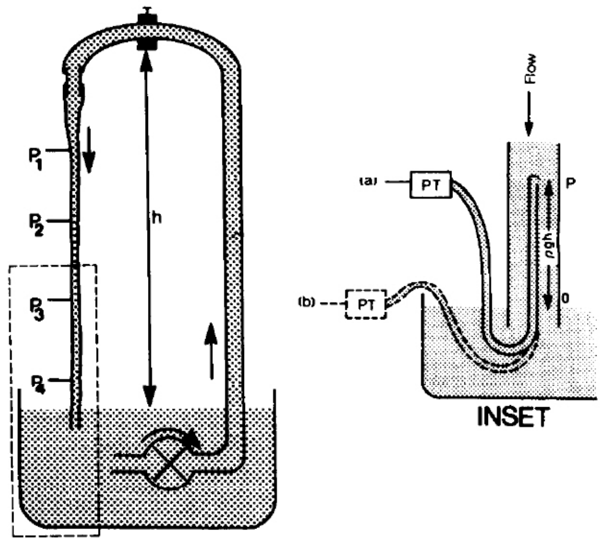

Figure 2. - Schematic model to record pressures in collapsible descending limb of a siphon loop. The degree of collapse in the descending limb was determined by adjusting the flow rate of pump and resistance with screw clamp positioned at the top of loop. P_1-P_4: relative levels at which pressure was measured in the descending limb. Inset: details of methods used for determining pressures with liquid-filled catheters. Pressure transducer (PT) at position *a* measures sum of viscous flow pressure and gravitational pressure. When the transducer is lowered to position *b*, gravitational pressure (ρgh) of liquid column within the catheter will counterbalance gravitational pressure of moving fluid within the descending limb. Resulting pressure measurement is viscous flow pressure. h: height. From Hicks and Badeer[12], with permission from the American Journal of Physiology.

strictly adhered to obtain correct pressure measurements.

Method 1: system without a flow. In this system, P_{hyd} is the only pressure present. If a liquid-filled catheter connected to a pressure transducer is used, then the transducer needs to be calibrated at zero pressure before the catheter is inserted in the system where pressure has to be measured. Then, in order to correctly measure P_{hyd}, the transducer should be positioned at the same height of the catheter's tip (Fig 3), which is to say that if the tip of the catheter, for instance, is moved upwards, the pressure transducer should also be raised and vice versa[6,8].

Method 2: constant flow in the system. By switching on the pump, flow starts in the system. In the descending limb of the vertical loop, in addition to P_{hyd}, there is now also a pressure due to viscous forces, i.e. a P_v. The P_{eff} measured at any point in the descending limb will result from the interactions between P_{hyd} and P_v.

But, how do we measure P_v and P_{eff}?

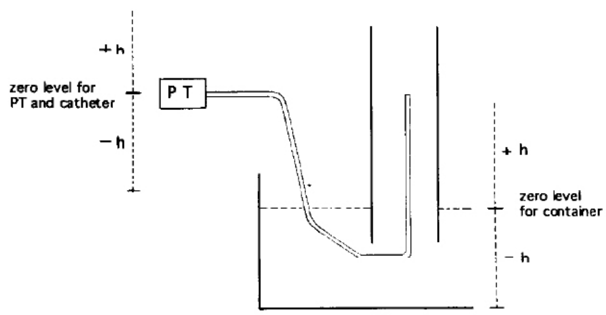

Figure 3. - Scheme of a part of the descending limb of an inverted U tube, filled with fluid and immersed inside a liquid container. The PT and the liquid-filled catheter at the position shown in the figure measure the hydrostatic pressure present in the descending limb of the U tube, when no flow is present in the system (method 1 in the text). Abbreviations as in figure 2.

To measure P_{eff}, the total pressure present in the system at that point, the position of the transducer with respect to the catheter's tip should be as described in method 1, i.e. at the level of the catheter's tip (Fig 2, inset: position a)[12].

To measure P_v only, the transducer should be positioned at the level of free surface of the fluid. This in order to cancel the effect of P_{hyd} (Fig 2, inset: position b)[12].

Following these methods, the pressures shown in figure 4[12] were recorded: P_{eff} was measured with method 2a, P_v with method 2b and P_{hyd} was calculated using equation 3.

It was then seen that P_{hyd} calculated by equation 3 precisely agreed with P_{hyd} calculated by the following equation:

$$P_{eff} = P_v + P_{hyd} \qquad (12)$$

which, of course, may also be written as:

$$P_{hyd} = P_{eff} - P_v \qquad (13)$$

Hence, from these experiments Hicks and Badeer concluded that the effective pressure at any point in the descending limb of a vertically oriented hydrodynamic system is the result of the algebraic sum of P_{hyd} and P_v, i.e. equations 12 and 13.

As shown in figure 5[13], this conclusion is, of course, true for the jugular vein of the giraffe. The first pressure measured in the giraffe's neck (Fig 1)[11], which was against the predicted P_{hyd} gradient, was the P_{eff} and not the true P_{hyd} only.

By taking into consideration the different pressure components and plotting them in a single graph, figure 5 is obtained. This figure shows exactly the development of the different pressure forces from the upper neck to the thoracic outlet in the jugular vein of the giraffe.

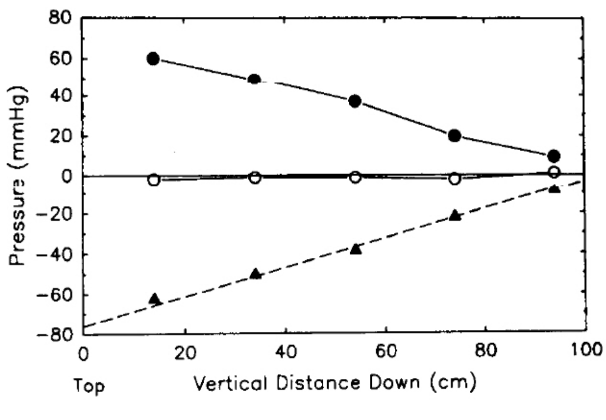

Figure 4. - Plot of pressure components in partially collapsed descending limb of a vertically oriented loop (see figure 2). •: viscous flow pressure; o: actual pressure; ▲: gravitational pressure; - - -: gravitational pressure calculated from ρgh. Actual pressure was determined by maintaining the transducer at the level of the catheter's tip (position *a* in figure 2, inset). Viscous flow pressure was determined by lowering the transducer to the reference level (position *b* in figure 2, inset). Gravitational pressure at each level was determined from viscous flow pressure and actual pressure (equation 13 in the text). Note agreement between gravitational pressure determined from equation 13 and gravitational pressure calculated from ρgh (- - - -). From Hicks and Badeer[12], with permission from the American Journal of Physiology.

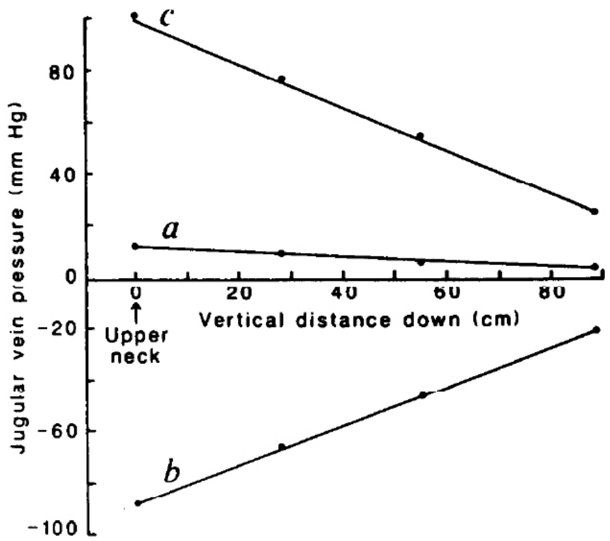

Figure 5. - Plot of pressure components in the jugular vein of the standing, sedated giraffe based on data from Hargens et al[11]. Note the increase in the gravitational component of pressure down the vein (b) and the decrease in pressure due to viscous resistance to flow (c). The actual pressure existing in the vein (a) is equal to the sum of viscous flow and gravitational pressures. Because the drop in viscous flow pressure is greater than the rise of gravitational pressure, the actual pressure gradient down the vein shows a slight decrease. From Badeer[13], with permission from Nature.

Hence, we are now able to establish a precise and definite relationship between P_{hyd} and P_v. This relationship, although measured in the venous part of the circulation, holds true for the arterial circulation as well, and it can be extended to the totality of the circulatory tree.

The combined version of the Bernoulli-Poiseuille equation. In addition, to clarify the difference between P_{eff}, P_v and P_{hyd}, Hicks and Badeer confirmed the already formulated hypothesis of a combined version of the pressure forces we are taking into consideration[6,7].

These Authors proposed to include the factors P_v and P_{hyd} into the B equation, to have the so-called BP unified law of hydrodynamics.

To insert P_v and P_{hyd} in the B, the factor E_P, and therefore P_{eff}, is described as follows:

$$E_P = f\,(P_0, P_v, P_{hyd}) \qquad (14)$$

Hence, on the basis of equation 12, if one regards P_0 as equal to zero, equation 11 may be written as:

$$[(P_v + P_{hyd}) + (^1/_2 \rho v^2) + (\rho gh)_\beta] = \text{constant} \quad (15)$$

where $$P_v = 8L\eta/\pi r^4$$

$$P_{hyd} = [-\rho g(\pm h)] = (\rho gh)_\alpha$$

Equation 15 is the combined, unified BP equation which, as can be seen, is also comprehensive of the S equation.

I would like to underline that in this combined equation, the terms P_v and P_{hyd} are the true P and S equations, previously described in equations 5 and 3. Hence the term P_{eff} of equation 15 may also be written as:

$$P_{eff} = P_v + P_{hyd} = (8L\eta/\pi r^4) + [-\rho g(\pm h)] \quad (16)$$

or, with the introduction of flow:

$$P_{eff} = (RQ) + [-\rho g(\pm h)] \quad (17)$$

Therefore we finally know that there is a strong relationship between the pressure we measure, which is the P_{eff}, and the physical description of the forces acting in the cardiovascular system, as described by equations 12 and 15.

To complete at least superficially the physicist point of view, two notes should at this point be added.

The first one refers to an element of accelerative pressure (P_{acc}) that the already quoted Authors include in the factor E_P. In this way E_P becomes a function of four different pressure sources, P_0, P_v, P_{hyd}, and P_{acc}[6]. However, this does not modify in any way what we have seen so far.

The second note refers to the combined BP equation. If viscous forces are introduced, we are not dealing with ideal fluids any longer. Thus some of the E_{tot} would be lost in frictions and finally dissipated as heat. To have the B law in syntony with the law of conservation of mechanical energy (as it was originally written), once the P_v term is introduced, another term, which corresponds to the energy dissipated as heat, needs to be added, as clearly reported in the already referenced work[6]. Again, this would not modify the reported discussion and the following conclusions.

Perspectives and conclusions

Our discussion of the physical principles that determine pressure within the circulation yields the following inside.

First of all, the method to precisely measure P_{hyd}, P_v and P_{eff} with a catheter connected to a pressure transducer. Then, that the P_v and P_{hyd} relationship is precisely quantifiable, as has been experimentally proven, and that it corresponds to what we measure in the clinical practice on the arterial side of the circulation. Finally that the combined BP equation would no longer be restricted to the ideal fluids, but it would be also applicable to viscous flow.

The BP equation describes the total hydraulic energy of the circulation and energy is, broadly speaking, the capacity to do work. Hence BP would be an additional way to describe the ability of the heart to work as a pump, as judged from the point of view of the circulation.

This point is not esoteric and is critical to a complete understanding of the effects of gravity on pressure within the circulation and on the heart.

As Burton already said many years ago, because of the B principle, the heart, normally, does not have to work to raise blood up to the head: hence the heart does not normally work against gravity[6] (this conclusion, however, is still regarded as debatable by others[14]).

As a consequence, the cardiovascular system, in its physiological state, may be regarded as a "closed" hydrodynamic system. A closed hydrodynamic system is defined "as one in which liquid in a container is driven and returned to its original level through a tube system (rigid or collapsible) without being exposed to the ambient atmosphere above the original level"[6]. If derangements of the venous circulation occur, however, such as compartmentalization of the venous flow, the heart's work would be immediately affected, not only because of a decrease in preload, but also because of changes in physical forces present in the system. In these pathophysiological conditions the system will behave as an "open" rather than a "closed" hydrodynamic system.

A hydrodynamic system is defined as "open", if the liquid is raised (or lowered) from a given position to a higher (or lower) gravitational potential energy and is discharged in the environment or stored at this new potential[6] (the terms "closed" and "open" systems are also used by thermodynamics, although with a different meaning[2,15]).

Due to the obvious limitations of space and time, the topic of a hydrodynamic system and its possible application to some discrete clinical settings, such as, for example, the syncope of vaso-vagal syndrome[16] and the high-altitude pulmonary edema[17], should be matter for future analysis and investigations.

What I would like to stress at the end is that a model of reference, such as that of a hydrodynamic closed and open system, might be very useful for the analysis of many circulatory conditions, both in health and in disease states. If reference is made to the possible alterations occurring in a hydrodynamic system, and to the forces acting inside it, as described by the combined BP equation, this will facilitate and improve our hemodynamic understanding.

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References

1. Bernard C: Introduction à l'étude de la médecine expérimentale. 2nd edition. Milan: Feltrinelli, 1973.
2. Recordati G: Determinismo, indeterminismo, omeostasi ed organizzazione funzionale del sistema nervoso viscerale. Cardiologia 1990; 35: 9-24.
3. Burton AC: Fisiologia e biofisica della circolazione. I edizione. Roma: Il Pensiero Scientifico Editore, 1969.
4. Milnor WR: Hemodynamics. Baltimore, MD: Williams & Wilkins, 1989.
5. Caro CG, Pedley TJ, Schroter RC, Seed WA: The mechanics of the circulation. New York, NY: Oxford University Press, 1978.
6. Hicks JW, Badeer HS: Gravity and circulation: "open" vs "closed" systems. Am J Physiol 1992; 262: R725-R732.
7. Synolakis CE, Badeer HS: On combining the Bernoulli and Poiseuille equation. A plea to authors of college physics text. American Journal of Physics 1989; 57: 1013-1019.
8. Recordati G: Alcune precisazioni sulla definizione, formulazione e misurazione della pressione idrostatica. Ipertensione e Prevenzione Cardiovascolare 1997; 4: 142-148.
9. Blomqvist CG, Stone HL: Cardiovascular adjustments to gravitational stress. In: Shepherd JT, Abboud FM, eds. Handbook of physiology. Vol III, Part 2. Bethesda, MD: American Physiological Society, 1983: 1025-1063.
10. Rowell LB: Human cardiovascular control. New York, NY: Oxford University Press, 1993.
11. Hargens AR, Millar RW, Pettersson K, Johansen K: Gravitational haemodynamics and oedema prevention in the giraffe. Nature 1987; 329: 59-60.
12. Hicks JW, Badeer HS: Siphon mechanism in collapsible tubes: application to circulation of the giraffe head. Am J Physiol 1989; 256: R567-R571.
13. Badeer HS: Haemodynamic of the jugular vein in the giraffe. Nature 1988; 332: 788-789.
14. Seymour RS, Hargens AR, Pedley TJ: The heart works against gravity. Am J Physiol 1993; 265: R715-R720.
15. Nicolis G, Prigogine I: Self-organization in nonequilibrium systems. From dissipative structures to orders through fluctuations. New York, NY: John Wiley & Sons, 1977: 19-25.
16. Mosqueda-Garcia R, Fernandez-Violante R, Tank J, Snell M, Cunningham G, Furlan R: Yohimbine in neurally mediated syncope. J Clin Invest 1998; 102: 1824-1830.
17. Sartori C, Trueb L, Scherrer U: High-altitude pulmonary edema. Mechanisms and management. Cardiologia 1997; 42: 559-567.