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Differential Pressure, P_D, Capital Parameter in the Determination of Cardiac Health and Prominent Kinetic Indicator of Drugs in the Blood

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Authors' contributions

This work was carried out in collaboration between both authors. Author ABK designed and supervised the study, wrote the protocol, performed compartmental analysis of this paper, and wrote the manuscript. Author PLK discussed the results of the study, managed the proof reading, he did the references and correction of manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Background: this work is a suite of previous articles where it has been demonstrated that if the differential pressure remains constant, it allows when it is multiplied by cardiac frequency to determine the volumic cardiac power (KUNYIMA equation). Also it has afforded to calculate differential enthalpy (ΔH_D) that is exothermic energy in ejection fraction. In KUNYIMA Formula the differential pressure has allowed to assess in satisfactory way one part of total energy from cellular metabolism (Keith-Flack node) which enable the heart blood to circulate in the organism. In KUNYIMA relations, P_D made possible the calculation of cardiac exergetic yield nowadays unrecognized by researchers, different from volumic yield defined by ejection fraction. This cardiac exergetic yield has been assimilated to the heart longevity.
Aim and objective: this work gives in detail mathematical useful expressions, rational approaches to be followed when differential pressure substantially changes, for example when the blood

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contains an injected drug at c_0 initial concentration and when the kinetic of this drug should be followed.
Methodology: Calculations have been our methodology using compartmental analysis.
Results: It is shown hereby the use of differential equations in the determination of kinetic parameters
Conclusion: Physical Cardiochemistry is improved with new theory.

Keywords: KUNYIMA equation; KUNYIMA Formula; KUNYIMA relations; differential enthalpy; cardiac frequency; volumic cardiac power; Physical Cardiochemistry.

1. INTRODUCTION

The currents of action originate at the level of the cellular membrane which is covered with positive ions on its external face and negative ions on its intracellular face. When two microelectrodes are placed, one intracellular, the other extracellular, potential differences can be recorded on the galvanometer, these are the membrane potentials. These potentials are of two types:

Rest potential: This is the potential difference that is recorded when a microelectrode crosses a cellular membrane, it is about 90 mV [1-5]. The interior of the cell is negative compared to the exterior. This potential would be produced by the arrangement of K^+ ions. The cellular membrane is in fact comparable to a semi-permeable membrane through which ionic exchanges take place. At rest, the intracellular proteins which have an electronegative charge therefore attract the K^+ and Na^+ ions which are positively charged. But, while the K^+ ions are retained inside the cell by these negative charges, the Na^+ ions, for which it should be the same, mostly remain extracellular. This therefore means that there are active exchanges; they are done in part thanks to the energy supplied by ATP and this is what is known as the "Sodium Pump".

However, the K^+ ions diffuse because of their high intracellular concentration, but being always attracted by intracellular protein, they remain stuck to the external face of the membrane, and therefore produce positive charges there. Intracellular negative charges are produced by free proteins.

Action potential: By stimulating a cellular membrane, variations in the membrane potential are observed which correspond to depolarization and then to repolarization. Indeed, when the fiber is stimulated, this has the effect of a tiny depolarization of the membrane, which increases its permeability to the Na^+ ion. This then enters the cell in a massive way and causes very significant depolarization. It is the sequence of these phenomena which is the basis of the action potential.

Electrical variations are then recorded which always take place in the same way for the same fiber. The curve obtained has the appearance of a monophasic wave. This wave is conventionally broken down into 5 parts: 1) sudden depolarization, 2) rapid initial repolarization, 3) slow repolarization, 4) the membrane potential returns to its resting value and 5) resting potential.

In fact, at the level of the heart, this potential can affect certain variations of shape according to the group of fibers considered. The membrane of the muscular fiber, like all cellular membranes, is surrounded by an infinity of positive and negative charges distributed symmetrically on two sides. During an excitation at a point, there is a loss of polarization for a very short time, and therefore between this point and the next a potential difference is established which produces a dipole. On the other hand, the activation propagating very quickly, this causes the appearance of a multitude of small dipoles. All of these dipoles can finally be assimilated to a single dipole. During depolarization, this dipole will have its positive pole forward and its negative pole behind.

Immediately after the depolarization takes place the repolarization, which will also be equivalent to a single dipole which follows the depolarization dipole, but whose electric charges are arranged in the opposite direction, that is to say: the positive pole will be behind and the negative pole forward.

During depolarization, the exploration electrode which is located at a point downstream of the path of the dipole will therefore be on the positivities side; it will therefore see a positive field and the recording will give a positive variation. Then the depolarization reaches the

end of the fiber, there is disappearance of the dipole and the electric field therefore becomes zero, which is visualized on the recording by a return to the isoelectric line. But immediately after, repolarization occurs, so the electrode will only see negative charges this time, which will result in the recording as a negative wave; at the end of the repolarization the dipole disappears again and there is once again a return to the isoelectric line. These phenomena which are practically the same in the opposite direction, have, however a very different duration from one another. The depolarization is extremely short, of the order of 0.02 of a second; while the repolarization has a duration which can go up to 0.08 of a second.

The heart is made up of multiple muscular fibers, and the path of excitation through the heart muscle is determined by the structure of that muscle. In the embryo, the myocardium has contractile activity without there being any nerve stimulation. In humans, this automatism is localized to a region of the modified myocardial fibers which form the nodal tissue. It is formed of fibers rich in sarcoplasm and containing a lot of glycogen. It is in this tissue that the rhythmic contractions, characteristic of cardiac activity, are born and it is thanks to it that they are routed into the ordinary myocardium, which can therefore contract spontaneously without control of the cardiac nerves. The constant disposition of nodal tissue and its acting has been described elsewhere [6-9] *where it has been noted that the heart rhythm is under the control of nodal tissue which encompasses Keith and Flack node, Aschoff-Tawara node, His bundle and Purkinje network through which the nodal influx spreads from Keith Flack node (right auricle) to His bundle to entail ventricles contractions.*

It should be noted here that nodal tissue gives rise to contraction wave and it accelerates the conduction of this wave.

2. MATERIALS AND METHODS

2.1 Materials

Under this rubric fig.1, main foundation of our philosophy, is the schematic representation of the cardiac system in a plane and shows clearly the blood flow in the hearth (small circulation). Blue color is the blood charged of CO_2 and red color is the blood charged of oxygen. The blood flow from blue color to red color takes place within alveoli (Lungs).

2.2 Methods

Compartmental analysis has been used [10-11] and performed through a simple pattern of three compartments such as alimentary canal (or general circulation blood of upper vena cava or lower vena cava before entering in small circulation), blood of small circulation and the heart.

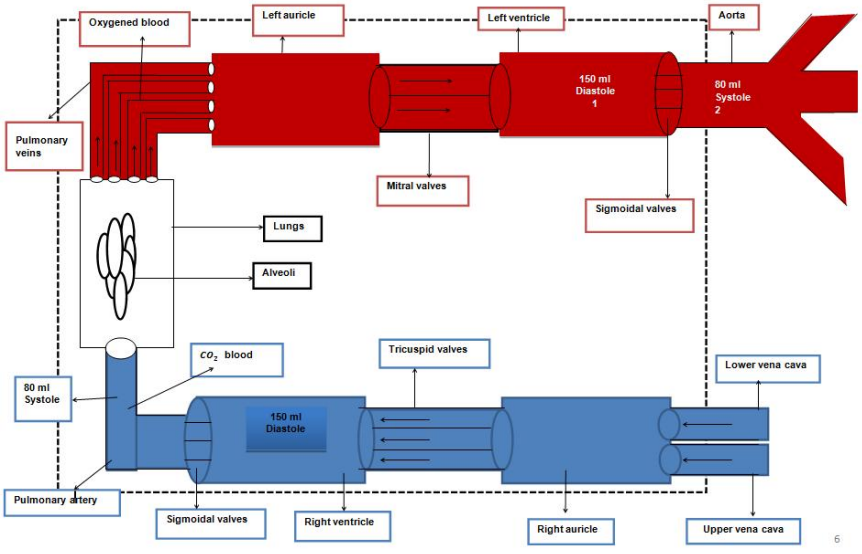
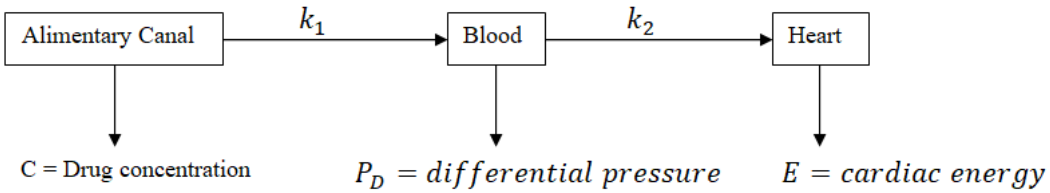


Fig. 1. Kunyima chart (Schematic representation of the cardiac system in a plane). Made in LACOPA/UNIKIN, DRC

Whether a drug in the alimentary canal (or in blood of general circulation) at C concentration arriving in the blood of small circulation with a kinetic constant k_1. This blood of differential pressure P_D circulates in the heart with a kinetic constant k_2. The energy of the heart E will be certainly affected.



C, P_D and E are state variables which can be described by the following equations in this above mentioned system. The circulation of drug in the blood depend only on time (not on space) and it should exist a cause to effect relation between its concentration, differential pressure and energy of heart (hypothesis).

$$\dot{C} = -k_1 C \quad (1)$$

$$\dot{P_D} = k_1 C - k_2 P_D \quad (2)$$

$$\dot{E} = k_2 P_D \quad (3)$$

The effect of disturbance of k_1 on these state variables C, P_D, E has been established in differentiating the above equations relative to k_1.

$$\frac{\partial^2 C}{\partial t \partial k_1} = -k_1 \frac{\partial C}{\partial k_1} - C \quad (4)$$

$$\frac{\partial^2 P_D}{\partial t \partial k_1} = k_1 \frac{\partial C}{\partial k_1} + C - k_2 \frac{\partial P_D}{\partial k_1} \quad (5)$$

$$\frac{\partial^2 E}{\partial t \partial k_1} = k_2 \frac{\partial P_D}{\partial k_1} \Longrightarrow \frac{\partial}{\partial k_1} \frac{\partial E}{\partial t} = \frac{\partial \dot{E}}{\partial k_1} = k_2 \frac{\partial P_D}{\partial k_1} \quad (6)$$

$$\int \partial \dot{E} = \int k_2 \, \partial P_D$$
$$\dot{E} = k_2 P_D$$
$$\int dE = \int k_2 P_D dt$$

$E = k_2 P_D t$ The integration constant has been neglected for simplification reason.

$$\frac{E}{t} = k_2 P_D \quad (7)$$

It has been demonstrated that to have a correct unit for k_2, $\frac{E}{t}$ should be volumic cardiac power (P_v) [7].

$$P_v = k_2 P_D \quad (8)$$

k_2 has been baptized KUNYIMA constant [7] k_k to remember Dr Anaclet KUNYIMA BADIBANGA, ordinary Professor and founder of KUNYIMA equation (8). It has been shown in the same work that KUNYIMA constant was exactly the cardiac frequency.

The differential pressure $P_D = P_{systolic} - P_{diastolic}$ is an important parameter because it enables to calculate many other physical sizes namely cardiac exergetic yield different from ejection fraction used by physician to define volumic yield. Cardiac exergetic yield is a measure of cardiac longevity [12-14]. The calculation of this parameter has been made possible by assuming P_D constant.

As a precondition $\frac{\partial C}{\partial k_1} = x$, $\frac{\partial P_D}{\partial k_1} = y$ and $\frac{\partial E}{\partial k_1} = z$,

The equations (4), (5) and (6) become

$$\dot{x} = -k_1 x - C \quad (9)$$

$$\dot{y} = -k_1 x + C - k_2 y \quad (10)$$

$$\dot{z} = k_2 y \quad (11)$$

These are sensitivity equations we will talk about in next paper. It should be announced that this research lead to the proposition of manufacturing of a new Sphygmomanometer (KUNYIMETER) where in addition to traditional parameters (systolic pressure, diastolic pressure, cardiac frequency) will appear new parameters (cardiac volumic power, cardiac exergetic yield,…)

A differential pressure, P_D, can not be zero. It has a positive initial value P_D^0, for a normal person. This initial value can increase or decrease with the presence of foreign body of C_0 concentration in blood circulation, for example a drug, cholesterol, stress, toxic compounds….In absence of all disturbance capable to change

substantially differential pressure, it can be said in first approximation that the differential pressure is constant for an individual in a given environment. If this differential pressure changes here is the solution. Equations (1), (2) and (3) can be written:

$$\dot{C} = -k_1 C \implies C = C_0\, e^{-k_1 t} \quad (12)$$

$$\dot{P_D} = k_1 C - k_2 P_D \quad (13)$$

$$\dot{E} = k_2 P_D \implies E = k_2 \int P_D dt \quad (14)$$

$$(13) \implies \frac{dP_D}{dt} = k_1 C - k_2 P_D$$

$$\frac{dP_D}{dt} + k_2 P_D = k_1 C \quad (15)$$

This differential equation admits homogeneous solution and particular solution.

Homogeneous solution:

$$\frac{dP_D}{dt} + k_2 P_D = 0$$

$$\int \frac{dP_D}{P_D} = \int -k_2 dt$$

$$P_D = Ae^{-k_2 t} = P_D^0\, e^{-k_2 t} = Y_h \quad (16)$$

Particular Solution (Y_p):

$$P_D = A(t)\, e^{-k_2 t} \quad (17)$$

$$\frac{dP_D}{dt} = P_D^{'} = A^{'}(t)\, e^{-k_2 t} - A(t) k_2\, e^{-k_2 t} \quad (18)$$

(18) in (15) :

$$A^{'}(t)\, e^{-k_2 t} - k_2 A(t)\, e^{-k_2 t} + k_2 P_D = k_1 C \quad (19)$$

$$A^{'}(t)\, e^{-k_2 t} - k_2 A(t)\, e^{-k_2 t} + k_2 A(t)\, e^{-k_2 t} = k_1 C_0\, e^{-k_1 t} \quad (20)$$

$$A^{'}(t)\, e^{-k_2 t} = k_1 C_0\, e^{-k_1 t} \quad (21)$$

$$A^{'}(t) = k_1 C_0\, e^{-k_1 t}\, e^{+k_2 t} \quad (22)$$

$$A(t) = k_1 C_0 \int e^{(k_2 - k_1)t}\, dt \quad (23)$$

$$A(t) = \frac{k_1 C_0}{k_2 - k_1}\, e^{(k_2 - k_1)t} + D \quad (24)$$

(24) in (17)

$$P_D = \left[\frac{k_1 C_0}{k_2 - k_1}\, e^{(k_2 - k_1)t} + D\right] e^{-k_2 t} \quad (25)$$

$$P_D = \frac{k_1 C_0}{k_2 - k_1}\, e^{k_2 t}\, e^{-k_1 t}\, e^{-k_2 t} + D\, e^{-k_2 t} \quad (26)$$

$$P_D = \frac{k_1 C_0}{k_2 - k_1}\, e^{-k_1 t} + \mathrm{D}\, e^{-k_2 t} \quad (27)$$

For $t = 0 \Rightarrow \quad P_D = P_D^0$ (28)

$$P_D^0 = \frac{k_1 C_0}{k_2 - k_1} + D \quad (29)$$

$$D = P_D^0 - \frac{k_1 C_0}{k_2 - k_1} \quad (30)$$

(30) in (27)

$$P_D = \frac{k_1 C_0\, e^{-k_1 t}}{k_2 - k_1} + P_D^0\, e^{-k_2 t} - \frac{k_1 C_0}{k_2 - k_1}\, e^{-k_2 t} \quad (31)$$

$$P_D = Y_p = P_D^0\, e^{-k_2 t} + \frac{k_1 C_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \quad (32)$$

Total solution = $Y_h + Y_p = \ (16) + (32)$

$$P_D = P_D^0\, e^{-k_2 t} + P_D^0\, e^{-k_2 t} + \frac{k_1 C_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k2t}\right) \quad (33)$$

$$P_D = 2\, P_D^0\, e^{-k_2 t} + \frac{k_1 C_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \quad (34)$$

Calculation of E

$$\mathrm{E} = k_2 \int P_D dt \quad (35)$$

$$E = k_2 \left\{\int \left[2\, P_D^0\, e^{-k_2 t} + \frac{k_1 C_0}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)\right] dt\right\} \quad (36)$$

$$E = k22\, PD0\, e{-}k2t dt + k1C0k2{-}k1\ \ e{-}k1t{-}\ e{-}k2t dt \quad (37)$$

$$E = k_2 \left\{2\, P_D^0 \int e^{-k_2 t} dt + \frac{k_1 C_0}{k_2 - k_1}\int e^{-k_1 t} dt - \frac{k_1 C_0}{k_2 - k_1}\int e^{-k_2 t}\, dt\right\} \quad (38)$$

$$E = k_2 \left\{-\frac{2\, P_D^0}{k_2}\, e^{-k_2 t} - \frac{k_1 C_0}{k_1(k_2 - k_1)}\, e^{-k_1 t} + \frac{k_1 C_0}{k_2(k_2 - k_1)}\, e^{-k_2 t} + F\right\} \quad (39)$$

$$E = -2\ P_D^0\ e^{-k_2 t} - \frac{k_2 k_1 C_0}{k_1(k_2 - k_1)}\ e^{-k_1 t} + \frac{k_2 k_1 C_0}{k_2(k_2 - k_1)}\ e^{-k_2 t} + \mathrm{F} \quad (40)$$

$$E = -2\ P_D^0\ e^{-k_2 t} - \frac{k_2 C_0}{k_2 - k_1}\ e^{-k_1 t} + \frac{k_1 C_0}{k_2 - k_1}\ e^{-k_2 t} + \mathrm{F} \quad (41)$$

$at \quad t = 0 \Rightarrow E = E_0$

$$E_0 = -2P_D^0 - \frac{k_2 C_0}{k_2 - k_1} + \frac{k_1 C_0}{k_2 - k_1} + F \quad (42)$$

$$F = E_0 + 2P_D^0 + \frac{C_0(k_2 - k_1)}{(k_2 - k_1)} \quad (43)$$

$$F = E_0 + 2P_D^0 + C_0 \quad (44)$$

(44) in (41)

$$E = -2\ P_D^0\ e^{-k_2 t} - \frac{k_2 C_0}{k_2 - k_1}\ e^{-k_1 t} + \frac{k_1 C_0}{k_2 - k_1}\ e^{-k_2 t} + E_0 + 2P_D^0 + C_0 \quad (45)$$

$$E = \left(\frac{k_1 C_0}{k_2 - k_1} - 2\ P_D^0\right)\ e^{-k_2 t} - \frac{k_2 C_0}{k_2 - k_1}\ e^{-k_1 t} + E_0 + 2P_D^0 + C_0 \quad (46)$$

In the case where P_D is constant it leads to k_1 determination.

Indeed, $\dot{P_D} = k_1 C - k_2 P_D \quad (47)$

$k_2 P_D = k_1 C$ and $\dot{E} = k_2 P_D = k_1 C \quad (48)$

$$\frac{dE}{dt} = k_1 C \quad (49)$$

$$\int dE = \int k_1 C\ dt = \int k_1 C_0 e^{-k_1 t}\ dt \quad (50)$$

$$E = k_1 C_0 \int e^{-k_1 t}\ dt = \frac{-k_1 C_0\ e^{-k_1 t}}{k_1} + R_0 \quad (51)$$

$$E = -C_0\ e^{-k_1 t} + R_0 \quad (52)$$

$$at\ t = 0 \Longrightarrow E_0 = R_0 - C_0 \quad (53)$$

$$R_0 = E_0 + C_0 \quad (54)$$

$$E = -C_0\ e^{-k_1 t} + E_0 + C_0 \quad (55)$$

$$E = C_0\ (1 - e^{-k_1 t}) + E_0 \quad (56)$$

It has been seen that

$$E = k_2 P_D t + E_0 \quad (57)$$

(56 = 57)

$$C_0\ (1 - e^{-k_1 t}) + E_0 = k_2 P_D t + E_0 \quad (58)$$

$$k_2 P_D t = C_0\ (1 - e^{-k_1 t}) \quad (59)$$

$$k_2 P_D t = C_0 - C_0 e^{-k_1 t} \quad (60)$$

$$k_2 P_D t - C_0 = -C_0 e^{-k_1 t} \quad (61)$$

$$\frac{C_0}{C_0} - \frac{k_2 P_D t}{C_0} = \frac{C_0}{C_0} e^{-k_1 t} \quad (62)$$

$$1 - \frac{k_2 P_D t}{C_0} = e^{-k_1 t} \quad (63)$$

$$\ln e^{-k_1 t} = \ln(1 - \frac{k_2 P_D t}{C_0}) \quad (64)$$

$$-k_1 t = \ln(1 - \frac{k_2 P_D t}{C_0}) \quad (65)$$

$$-k_1 = \frac{\ln(1 - \frac{k_2 P_D t}{C_0})}{t} \quad (66)$$

$$k_1 = -\frac{\ln(1 - \frac{k_2 P_D t}{C_0})}{t} = -\frac{\ln(\frac{C_0 - k_2 P_D t}{C_0})}{t} \quad (67)$$

$$k_1 = -\frac{\ln(C_0 - k_2 P_D t) - \ln C_0}{t} \quad (68)$$

$$k_1 = \frac{\ln C_0 - \ln(C_0 - k_2 P_D t)}{t} \quad (69)$$

P_D expressed in $\frac{J}{m^3}$ $for\ exemple\ and\ C_0\ in\ \frac{J}{m^3}\ (by\ using\ mC^2)$

The equation (34) can be studied beneath the following expression:
With $K = 2P_D^0$ and $L = \frac{k_1 C_0}{k_2 - k_1}$, the equation (34) becomes:

$$P_D = K\, e^{-k_2 t} + L e^{-k_1 t} - L\, e^{-k_2 t} \quad (70)$$

$$P_D = (K - L)\, e^{-k_2 t} + L e^{-k_1 t} \quad (71)$$

Mac Laurin (Taylor) can be used

$$e^x = 1 + x + \frac{x^2 t}{2} + \cdots \quad (72)$$

$$e^{-k_2 t} = 1 - k_2 t + \frac{{k_2}^2 t^2}{2} + \cdots \quad with\ -k_2 t = x \quad (73)$$

$$P_D = (K - L)\left(1 - k_2 t + \frac{{k_2}^2 t^2}{2}\right) \ldots + L\left(1 - k_1 t + \frac{{k_1}^2 t^2}{2} + \cdots\right) \ldots \quad (74)$$

$$P_D = K - k_2 t\, K + \frac{{k_2}^2 t^2}{2} K - L + k_2 t\, L - \frac{{k_2}^2 t^2}{2} L + L - k_1 t L + \frac{{k_1}^2 t^2}{2} L + \cdots \quad (75)$$

$$P_D = K + (k_2 L - k_2 K - k_1 L) t + \left(\frac{{k_2}^2}{2} K + \frac{{k_1}^2}{2} L - \frac{{k_2}^2}{2} L\right) t^2 + \cdots \quad (76)$$

3. RESULT AND DISCUSSION

Our theoretical discussion will focus on equations (34), (46) and (69). In these equations it appears the kinetic constants k_1 and k_2. We have shown in previous work [7] that k_2, called Kunyima constant, is nothing other than heart frequency which indicates the number of heartbeats usually measured per minute (bpm). In order for these above-mentioned equations to be meaningful, k_1 must also be measured per minute. The time t which appears in these equations must be at most one minute. Note that k_2 was calculated by

considering that P_D is a constant. In this alternative we compared equations (56) and (57) which lead us to calculate k_1 as shown by equation (69). The value of k_1 being known, we can successfully follow the kinetics of the evolution of the drug in the blood by means of the equation $C=C_0\ e^{-k_1 t}$ and know at each time the current concentration C of the drug in the compartment considered knowing the initial concentration injected.

In the case where P_D changes we have developed equations (34) and (46) where k_2 is a measurable heart frequency as usual and thus expresses the number of heart beats per minute.

As for the value of k_1, it will be taken either from equation (34) when it comes to differential pressure or from equation (46) when it comes to energy. In equation (46) it appears $F_0 = E_0 + 2P_D^0 + C_0$ which can be set equal to zero as the reference state to simplify the reasoning. As you can see, the beauty of these equations is that, unusually, energy, differential pressure, and concentration can add up, which at first sight seems silly. It is not because E_0 is a reference energy per unit of volume while P_D^0 which is a differential pressure can be expressed in the same unit. It is the same for the initial concentration C_0 (mol.L-1) which can be converted in the same unit by the equation E = mC^2. Fortunately, physics has foreseen everything.

Ultimately let us recall that biological system which is not in transient state acts with constant yield.

So the healthy heart should have a weak and constant exergetic yield, therefore a constant differential pressure.

All unwitting variation of differential pressure should be considered at first sight as a pathological case.

4. CONCLUSION

The value of k_1 can be calculated during one minute like k_2 if volumic cardiac power and initial concentration of drug are known in the case where P_D is constant (see eq.69). In the case where P_D is not constant the value of k_1 can be deduced from equation (34), k_2 remains always cardiac frequency. So kinetic study of the evolution of drug in blood (or in alimentary canal) can be successfully performed. Physical Cardiochemistry, this new discipline, is enriched of a new theory.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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