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Dynamics Cardiovascular Diseases Immune System; Mathematical Modeling

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Abstract: *In this work, investigations were carried out in relation to the cardiovascular system, the main diseases that affected it, the situation that exists worldwide, in the Americas, in Brazil and Cuba in relation to these diseases; in addition, existing statistics regarding mortality due to these diseases in the indicated countries and regions are researched. A model is developed, through a system of differential equations, where it is assumed that the patient has or does not have the presence of thrombi and/or atheromatous plaques; for the case in which there are no disturbances in the process, this system has two equilibrium positions, the trajectories of the system are studied in the vicinity of the equilibrium positions and conclusions are drawn for both cases in correspondence with the magnitudes treated in the process; Examples are given for each of the situations presented and it is verified that the system trajectory graphs correspond to the theoretically demonstrated results.*

Keywords: *Lymphocytes, Macrophages, Atheroma plaques, Thrombi*

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I. INTRODUCTION

Chronic non-communicable diseases are all those diseases that are not transmitted from person to person; These diseases may include: cancer, diabetes, kidney failure, liver cirrhosis, mental and psychological illnesses and cardiovascular diseases, among others.

“Chronic non-communicable diseases constitute the main group of causes of death worldwide, being responsible for premature deaths, loss of quality of life, in addition to adverse economic and social impacts. These diseases are responsible for close to 70% of deaths worldwide, which is equivalent to more than 38 million deaths per year, significantly exceeding deaths from external causes and infectious diseases. Around 45% of deaths due to non-communicable diseases in the world are caused by cardiovascular diseases, which is equivalent to more than 17 million” [6], [17] and [27].

Research into the behavior of cardiovascular diseases in the world, in the Americas, in Brazil and in Cuba, is undoubtedly a topic of transcendental importance; as this gives an idea of its behavior in the world, region and countries indicated; but this situation is no different in almost all pises. In the world, 30% of total mortality is caused by cardiovascular diseases, in the Americas it is 28%, in Brazil it is close to 30%, and in Cuba it also appears as one of the main causes of death, with a percentage close to 27% [22] and [24].

Due to the worrying situation that exists worldwide regarding these diseases, the World Health Organization is developing an emergency program to give special attention to chronic non-communicable diseases and, in particular, cardiovascular diseases, which represents the from a social point of view, for its effects in different directions, in particular a life-long treatment for these patients. There are currently free patient care programs in many countries; as well as a constant orientation of what these diseases represent for the entire society, [3], [4] and [14].

The cardiovascular system is made up of: the heart, which is the organ responsible for pumping blood, the blood vessels, which are made up of a system of closed ducts through which blood circulates throughout the body. The three main types of blood vessels that form the cardiovascular system are: arteries, veins and capillaries [12].

Blood transported around the body through blood vessels allows our body's cells to receive nutrients and oxygen. The process of blood entering and leaving the heart is achieved through the contraction and relaxation of this organ.[7], [13] and [23].

Cardiovascular diseases are all pathological changes that affect some parts of the cardiovascular system. This includes coronary, cerebrovascular and arterial diseases. The main risk factors associated with these illnesses are smoking, high cholesterol, a sedentary lifestyle, poor diet and unhealthy habits, such as excessive alcohol consumption, etc. Obesity favors the appearance of fatty deposits (atheromas) in blood vessels, which leads to high blood pressure and thrombus formation, [15] and [21].

Heart attack is among the most common and dangerous cardiovascular diseases, which consists of the interruption of blood flow; this event can cause death in many cases, this occurs due to the blockage of a coronary artery by a plaque or thrombus, which can be a direct consequence of arteriosclerosis, due to the factors indicated above. [10], [19] and [21].

Heart failure is also common and serious, consisting of poor pumping of blood by the heart due to the inability to deliver sufficient oxygenated blood to the body. Over time, symptoms such as difficulty breathing, tiredness, weakness, swelling, increased volume of the lower limbs and palpitations, among others, appear [8], [20].

There are many cells whose function is to defend the human organism from different types of agents that attack us, including macrophages and lymphocytes. Macrophages are irregular cells that form part of our immune system; these cells are essential in the dynamics between the immune system and cardiovascular diseases: type 1 macrophages are more active against inflammatory processes, type 2 have less inflammatory activity, but are essential for reducing atheroma plaques. There are several studies that illustrate this important immunological and defense activity of our body by macrophages, this activity is also present in the myocardium after a heart attack, [1], [28].

Lymphocytes are produced in the bone marrow. As part of the immune system, they are responsible for defending the body against different infections and other external attacks, it increases when there is a change of this type, and this is an indicator of the presence of a disease.

Lymphocytes have an anti-inflammatory function, helping to reduce the size and progression of plaques, attenuating lesions caused by inflammation, allowing a better prognosis of coronary artery disease; the immune system actively participates in cardiovascular homeostasis in physiological and pathological situations. [9] and [25].

There are three types of lymphocytes B, T and NK (natural keller), in [7] a model of virus-immune system interaction with activation of NK cells is presented; type B is responsible for producing antibodies to destroy antigens; the T recognizes and destroys abnormal cells, coordinating the immune system's response together with type B cells; NK cells act as a first line of defense against virus-infected cells.

When the immune system is not capable of eliminating the offending agent, the process will generally evolve into a critical or chronic phase characterized mainly by persistent acute inflammation and tissue destruction. In the face of cardiovascular diseases such as atherosclerosis, heart failure, and systemic arterial hypertension, inflammation actively participates. The formation of atherosclerotic plaques inside the arteries leads to a chronic reduction in blood flow; plaque instability with rupture, thrombus formation and blood vessel occlusion may occur, [2] and [26].

The reaction of the human organism through the immune system in the presence of some agent or foreign body that can alter the normal rhythm of life will be essential for the formulation of the model; which aims to simulate the action of the human body to combat cardiovascular diseases, [11] and [15].

The mathematical modeling of the functions of human organism systems has been a special focus of the research group, in particular the defense carried out by the immune system; as well as its strengthening, which is achieved not only through vaccines and other medicines, but also naturally through its own social activities [7].

As a result of the research, a model of interaction between macrophages and lymphocytes is presented, as part of the immune system, in the face of the formation of atheroma plaques and thrombi. To carry out a qualitative analysis of the model and draw conclusions [7] and [25] certain mathematical theories are used using differential equations. As lymphocytes and monocytes can be measured in a blood test, it is possible to create a database and identify the system coefficients that model the process to reach conclusions regarding the patient's diagnosis [9], [12].

II. MODEL FORMULATION

To formulate the model, it is considered that the person is leading a normal life; that may or may not present some type of symptom of cardiovascular disease and that certain aspects that cause cardiovascular diseases may or may not appear in the blood. This work simulates the confrontation of macrophages and lyphosites with atheroma plaques and thrombi that cause cardiovascular disease.

These immune system cells, due to their protective function, do not reproduce indiscriminately, but can increase depending on their concentration and stabilize below a certain constant value, or decrease depending on their concentration, and will increase depending on the concentration of atheroma plaques. and/or thrombi;

the concentrations of plaques and/or thrombi increase, in a controlled manner, depending on their own concentration and decrease depending on the concentration of the indicated immune system cells.

In the model, two functions that depend on time were considered $\tilde{x}_1$ which represents the total concentration of macrophages and/or lymphocytes at the time t and $\tilde{x}_2$ which represents the total concentration of atheroma plaques and/or thrombi in the circulatory system at time t. In addition, the magnitudes were taken into account $\bar{x}_1$ and $\bar{x}_2$ which represent the respective optimal concentration values. In correspondence with this; unknown functions are introduced $x_1 = \tilde{x}_1 - \bar{x}_1$ e $x_2 = \tilde{x}_2 - \bar{x}_2$. From here it can be deduced that when $x_1 \to 0$ and $x_2 \to 0$ then $\tilde{x}_1 \to \bar{x}_1$ and $\tilde{x}_2 \to \bar{x}_2$ which constitutes the objective of this work. Therefore, the model can be written as follows,

$$\begin{cases} x_1' = -a_1x_1 + a_2x_2 + X_1(x_1, x_2) \\ x_2' = -b_1x_1 + b_2x_2 - b_3x_2^2 + X_2(x_1, x_2) \end{cases} \quad (1)$$

Where the coefficients, $a_i > 0$, $b_j > 0$ for $(i = 1,2)$, and $(j = 1,2,3)$, the functions $X_i(x_1, x_2), i = 1,2$ are infinitesimals of higher order for sufficiently small values of the unknown functions x_1 and x_2; which, from the model's point of view, represent certain entropies or disturbances that can alter the normal course of the process from both a positive and negative point of view in relation to disease control. In their most general form, these functions can be represented by power series that converge in a neighborhood of the origin of the coordinates, which can be written as follows,

$X_i(x_1, x_2) = \sum_{|p|\geq 2} X_i^{(p)} x_1^{p_1} x_2^{p_2}, \quad i = 1,2, \quad |p| = p_1 + p_2$.

These entropies include great emotions, stress, highly adverse or favorable situations from both a personal and social point of view, unexpected information and even the treatment itself.

From the characteristics of the model it can be deduced that, when there are no entropies, for an imperceptible influence of macrophages and/or lymphocytes, the concentrations of atheroma plaques and/or thrombi satisfy the following equation,

$$x_2' = b_2x_2 - b_3x_2^2 \quad (2)$$

The solution to equation (2) is given by the following expression,

$$x_2(t) = \frac{cb_2e^{b_2t}}{1 + cb_3e^{b_2t}}$$

From here it can be deduced that $x_2(t) \to \frac{b_2}{b_3}$; This corresponds to what was indicated before, that the concentration of atheroma plaques and/or thrombi increases in a controlled manner and their values stabilize, with a constant value as the supreme, which is given by the quotient $\frac{b_2}{b_3}$.

Example1: Be the system,

$$\begin{cases} x_1' = -2x_1 + 2x_2 + x_1x_2^2 \\ x_2' = -x_1 + \frac{3}{2}x_2 - \frac{1}{2}x_2^2 + 5x_1^2 \end{cases} \quad \textbf{(3)}$$

Corresponding to the above, from the second equation of system (3) we arrive at the equation,

$$x_2' = \frac{3}{2}x_2 - \frac{1}{2}x_2^2$$

Which represents the variation in the concentration of atheroma plaques and/or thrombi with reduced action of macrophages and/or lymphocytes, whether their values are above or below y=3, the solutions converge to this straight line, as shown in the following graph.

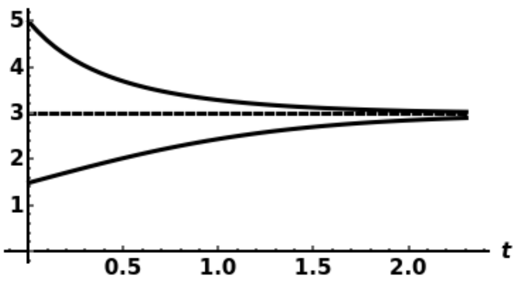

Fig.1: Graph of x_2 about t.

Likewise, in the insignificant presence of atheroma plaques and/or thrombi, the variation in the concentrations of macrophages and/or lymphocytes will decrease in correspondence with the characteristics indicated above.

Note1: From the graph in Figure1, the interaction in the human body between macrophages and lymphocytes with atheroma plaques and thrombi is in correspondence with the preliminary analysis carried out to formulate the model, therefore, in principle, the simulation of the process is in correspondence with reality .

Note2:: If the influence of macrophages and lymphocytes is imperceptible, then the concentrations of atheroma plaques and thrombi will grow up to a certain value and will never exceed this value; this can cause instability and a cytic state in the patient; however, when the presence of plaques and/or thrombi is not significant, then the concentrations of macrophages and lymphocytes will decrease over time depending on the needs of our body.

It makes sense to carry out a qualitative study of the system (1) to draw conclusions about the behavior of the trajectories; In this case, qualitative and analytical theories of differential equations can be applied giving conclusions for all possible cases, but initially only the first approximation method will be used.

Theotem1: If the conditions $a_1 > b_2$and$a_2 b_1 > a_1 b_2$are satisfied, then the solutions of system (1) are asymptotically stable.

The characteristic matrix equation of the linear part of the system (1) has the form,

$$\begin{vmatrix} -a_1 - \lambda & a_2 \\ -b_1 & b_2 - \lambda \end{vmatrix} = 0 \Rightarrow \lambda^2 + (a_1 - b_2)\lambda + (a_2 b_1 - a_1 b_2) = 0$$

The conditions indicated in the theorem guarantee that the conditions of the Hurwitz theorem on the negativity of the real part of the eigenvalues of the matrix of the linear part of the system (1) are satisfied; In this way, applying the first approximation method guarantees the asymptotic stability of the solutions of this system.

Note3: If the conditions

$a_1 > b_2$and$a_2 b_1 > a_1 b_2$are satisfied, then the total concentrations of macrophages and lymphocytes converge to ideal values, and the concentrations of plaques and/or thrombi converge to values acceptable by our body, which guarantees that the disease would be controlled. If once the coefficients have been identified, it is found that these conditions are not met, appropriate measures must be taken to avoid a crisis in the patient.

Note4: The fact that lymphocytes can be measured through blood analysis guarantees the existence of a data-base through which the matrix coefficients of the system (1) can be identified, which would allow, through theorem 1, to predict the behavior future of the process and guide healthcare personnel on the need to take measures to guarantee the patient's stability.

The situation may arise that when identifying the coefficients through the database, the coordinate origin is unstable, which would mean that the total concentrations do not converge to the ideal values; but still a hasty decision cannot be made, because in the absence of entropies, system (1) has the form,

$$\begin{cases} x_1' = -a_1 x_1 + a_2 x_2 \\ x_2' = -b_1 x_1 + b_2 x_2 - b_3 x_2^2 \end{cases} \qquad (4)$$

System (4) has, in addition to the origin, another equilibrium position (h, k) where,

$h = \frac{a_1 b_2 b_2 - a_2^2 b_1}{a_1^2 b_3}$, $k = \frac{a_1 b_2 - a_2 b_1}{a_1 b_3}$.

To perform an analysis of the trajectories in a neighborhood of the point(h, k), the following coordinate transformation will be performed,

$$\begin{cases} y_1 = x_1 - h \\ y_2 = x_2 - k \end{cases}$$

Thus system (4) adopts the form,

$$\begin{cases} y_1' = a_1 y_1 + a_2 y_2 \\ y_2' = -b_1 y_1 + (b_2 - 2 b_3 k) y_2 - b_3 y_2^2 \end{cases} \qquad (5)$$

To determine the behavior of the trajectories of the system (5), we must start from the eigenvalues of the matrix of the linear part of the system, for this we need to determine the solutions of the corresponding characteristic equation, which has the form,

$$\begin{vmatrix} -a_1 - \lambda & a_2 \\ -b_1 & b_2 + 2 b_3 k - \lambda \end{vmatrix} = 0,$$

This equation is equivalent to,

$$\lambda^2 + (a_1 - b_2 + 2b_3k)\lambda + (a_2b_1 - a_1b_2 + 2a_1b_3k) = 0 \qquad (6)$$

Using the conditions of Hurwitz's theorem for the negativity of the real part of the roots of the characteristic equation, the numbers $n_1$and n_2 need to be positive, where,

$$\lambda^2 + n_1\lambda + n_2 = 0$$

$$n_1 = a_1 - b_2 + 2b_3k = \frac{a_1^2 + a_1b_2 - 2a_2b_1}{a_1},$$

$$n_2 = a_2b_1 - a_1b_2 + 2a_1b_3k = a_1b_2 - a_2b_1$$

From here one can deduce the validity of the following theorem which provides a condition that guarantees the stability of the null solution of system (5).

Theorem2: If the condition$a_2b_1 < \min\left(a_1b_2, \frac{a_1^2 + a_1b_2}{2}\right)$ is satisfied, then the solutions of system (5) are asymptotically stable.

In this way, applying the first approximation method guarantees the asymptotic stability of the trivial solution of the system (5).

In example (1), if you have the system,

$$\begin{cases} x_1' = -2x_1 + 2x_2 + x_1x_2^2 \\ x_2' = -x_1 + \dfrac{3}{2}x_2 - \dfrac{1}{2}x_2^2 + 5x_1^2 \end{cases}$$

In the absence of entropies, the following example is deduced.

Example2: Let the following system of equations represent the dynamics between the immune system and cardiovascular diseases in the absence of entropies.

$$\begin{cases} x_1' = -2x_1 + 2x_2 \\ x_2' = -x_1 + \frac{3}{2}x_2 - \frac{1}{2}x_2^2 \end{cases} \qquad (7)$$

This system has two equilibrium positions $(0,0)$ and $(1,1)$; the origin is unstable, as its characteristic equation is,

$$\lambda^2 + 2\lambda - 1 = 0$$

The graph corresponding to system (7), of x_2 in relation to x_1, is shown below.

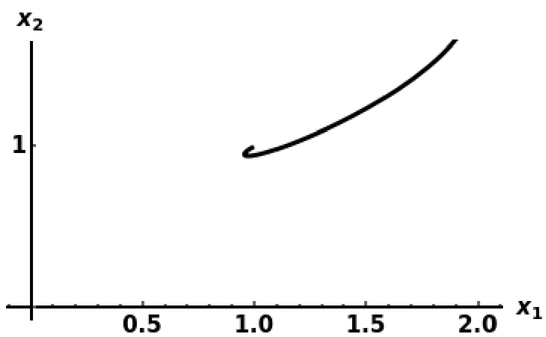

Fig.2: Graph of$x_2$aboutx_1.

Here it is possible to verify both the characteristic equation and the graph of the instability of the equilibrium position corresponding to the origin of coordinates; but the convergence of the solutions to the equilibrium position $(1,1)$ can be verified.

To analyze the behavior of trajectories close to the point $(1,1)$, the coordinate transformation is performed,

$$\begin{cases} y_1 = x_1 - 1 \\ y_2 = x_2 - 1 \end{cases}$$

The system is thus obtained,

$$\begin{cases} y_1' = -2y_1 + 2y_2 \\ y_2' = -y_1 + \frac{1}{2}y_2 - \frac{1}{2}y_2^2 \end{cases} \qquad (8)$$

The characteristic equation of system (8) has the form,

$$\lambda^2 + \frac{3}{2}\lambda + 1 = 0$$

Here Hurwitz's conditions on the negativity of the real part of the system's eigenvalues are satisfied and, consequently, the corresponding equilibrium position is asymptotically stable.

Next, the graph corresponding to the trajectories of system (8) of y_2 in relation to y_1 is made.

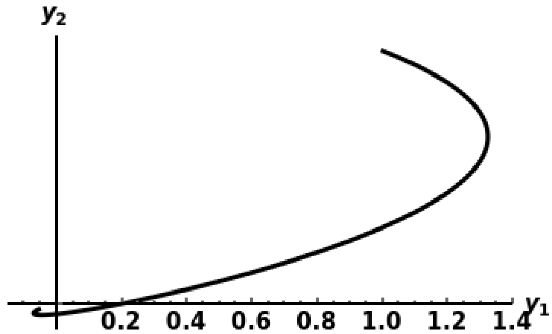

Fig.3: Graph of y_2 about y_1.

From the graph in Figure 3, the stability of the system (8) can be deduced, as with any initial condition it is possible to verify the convergence of the trajectories towards the origin of coordinates; this is in correspondence with the condition of theorem2 which is satisfied and can be easily verified

.

Note5: If the point (h, k) is sufficiently close to the coordinate origin, it can be ensured that the total concentrations of immune cells involved in the process converge to ideal values, and the total concentrations of atheroma plaques and thrombi converge to acceptable values; therefore, even with the presence of the disease, there would be a favorable process and in this case the possibilities of complications due to cardiovascular disease are minimal.

III. CONCLUSIONS

!.- The use of mathematical modeling to study the dynamics between cardiovascular diseases and the immune system is important for health professionals, as it allows illustrating the behavior of the patient's disease at a given moment, indicating the need to take timely measures to prevent according to the situation presented.
2.- To reach conclusions about the patient's condition, it is essential to investigate whether or not the following conditions are met $a_1 > b_2$ and $a_2 b_1 > a_1 b_2$, as these conditions are sufficient for the total concentrations of macrophages and lymphocytes to converge to ideal values, while the concentrations of atheroma plaques and/or thrombi converge to acceptable values, this guarantees control of the disease.
3.- Even in the case where the null solution of system (1) is not asymptotically stable, which indicates that there is no convergence of total concentrations to their ideal values, it does not mean that the patient is always in a critical state, as he may suffer of some type of disease but with concentrations of thrombi and/or plaques with values very close to acceptable values and the patient would be in a basal state as shown in theorem2 and the graph in the example indicated.
4.- When for some patient the process is such that the condition is satisfied
$a_2 b_1 < \min(a_1 b_2, \frac{a_1^2 + a_1 b_2}{2})$, the total concentrations converge to the values h and k and if the point (h, k) is sufficiently close to the origin, then the patient would have the disease under control, but in these cases one must have constant control of their situation. to avoid a relapse.
5.- To avoid or minimize the effects of cardiovascular diseases, it is recommended that the following measures be taken in our daily lives:
-control blood pressure,
-minimize the effects of diabetes,
-maintain a healthy diet,
-do not smoke,
-avoid excessive alcoholic beverages,
-perform physical activities,
-Try to reduce the stress load.

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