Hypothesis: temperature stress and blood viscosity affects the leukocyte flexibility, coagulation, intracranial hypertension, and hemodynamics

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Abstract—The aim of the study was to investigating of the relationships between temperature, flexibility of leukocytes, and viscosity, flow rate, pressure, and coagulation of blood. Method: Healthy 37 cases were chosen with Simple Random Sampling Method. Heparinized bloods were collected and then leukocyte suspensions were separated with the clinical centrifuge. The viscosity and flexibility of the samples were measured at 25°C, 37°C, and 39°C with capillary tube viscometer. Hemodynamical parameters were calculated using Poiseuille's equation. The Pillai's Trace test was used for the statistical evaluation. Results: When the temperature of blood decreased from 37°C to 25°C, the viscosity of blood increased from 11.70+/-0.4s to 15.10+/-0.6s as 29.05% (p<0.0001). With a temperature increase from 37°C to 39°C, the viscosity of blood decreased from 11.70+/-0.4s to 10.12+/-0.35s as 13.50% (p<0.0001). Discussion: The data and flow charts of the study show that increase of blood viscosity due to decreased temperature could be related with decreased intracranial pressure, decreased blood flow rate, stasis, vasodilatation, headache, increased local concentration of coagulation factors that facilitate amplification of coagulation and formation of thrombus. Results of the study could provide capacities for distinct diagnosis, selective therapies, and regulation of cerebral blood flow; prevention from stasis, thrombus formation and bleeding; explanations of anemia related intracranial hypertension and headache; and it constitute a new expanded scalar base within mathematical accuracy for future investigations.

Key words: Temperature, blood viscosity, headache, coagulation, leukocyte flexibility, blood flow rate, hemodynamics.

Abbreviations: CBF: cerebral blood flow, CPP: cerebral perfusion pressure, CSF: cerebrospinal fluid, ICP: intracranial pressure MAP: mean arterial pressure.

I. INTRODUCTION

The aim of the study is to investigate the effect of temperature stress on flexibility of leukocytes and viscosity of blood, and then to calculate possible effects of them on regulation of cerebral blood flow and amplification of coagulation process.

Viscosity can be defined as internal friction coefficient or fluid's resistance to flow. A common method for determining the viscosity is "the capillary tube viscometer", and it depends on the measurement of the fluid's free flow time due to gravitational force through a vertical tube that has a constant radius, length, and volume. The relative viscosity value for serum is 1.4 to 1.8, for the plasma relative viscosity is 1.7 to 2.2, and the whole blood viscosity is between 2.5 and 4. Relationships between the blood viscosity, hemodynamics, blood coagulation and headache were reported in two in-vitro study of hematocrit related blood viscosity [1-3].

A. Factors affecting viscosity of blood

The viscosity increasing factors are; hyperglycemia, water loss, decreasing temperature of blood, increased fibrinogen concentration, hypergammaglobulinemia, fat ingestion, and increased mass of leukocytes and erythrocytes. The viscosity decreasing factors are; the reduced hematocrit, hemodilution and hydration, and several drugs such as glycerol, nifedipine, nitroglycerine, isosorbite dinitrate, pentoxifylline, calcium dobesilate and dextran which can be used for viscosity decreasing therapies [4-7].

Flexibility of leukocyte is the shape changing capacity of leukocytes, and peripheral resistance affected by the number and flexibility of leukocytes [8]. Determining the flow time of leukocyte with a capillary viscometer using mass of leukocyte suspension is cheaper and easier, and this flow time represents the flexibility and fluidity of leukocyte [9].

B. Effect of blood viscosity on hemodynamics

The relationship between blood viscosity and blood pressure is clinically important, and a compensatory increase in the diameter of common carotid artery is seen only at the young control groups but not at the elderly hypertensive [10,11]. When it is accepted that L (length of the vessel), (viscosity), v (flow velocity), a (radius of the vessel), r (distance from the center of the vessel for a flowing particle), F_1 (initial pressure) and F_2 (final pressure at the end of the distance) define the variables of Poiseuille's equation, $v = 1/4\eta L \ (F_1-F_2) \ (a^2-r^2)$, from which flow rate (Q) can be calculated as $Q = \pi a^4 \ (F_1-F_2) \ /8\eta L$. From the relationship between these parameters, the blood flow rate is directly proportional with the radius and the pressure difference between the two ends of the vessel ($F_1 - F_2$), and inversely proportional with the blood viscosity and length of the vessel. According to the equation and experiments, 1-fold increase in viscosity causes 4-fold decrease in the blood flow rate [12].

C. Temperature and hemodynamics

The major discussed effects of increased temperature on the circulatory system are decreased right atrial pressure, increased heart rate and cardiac output, and vasodilatation in skin that causes heat loss. In temperature stress of cold,

peripheral resistance increases due to the constriction of skin arteries and the increased viscosity of blood. A blood pressure control mechanism associated with blood viscosity is described, and it is stated that a hypertension attack could be a compensatory mechanism for ischemia due to the decreased blood flow rate of hyperviscosity [13,14].

D. Regulation of cerebral blood flow

Auto-regulation of blood circulation can be defined as the intrinsic tendency of an organ to keep its blood flow rate (Q) constant despite variations in the systemic blood flow and blood pressure. Stiff skull surrounds and protects brain from the environmental pressure, and a rise in intracranial pressure (ICP) may restrain blood flow and cause ischemia [15]. Monro-Kellie hypothesis states that the cranial compartment is incompressible, and the sum of volumes of brain, cerebrospinal fluid (CSF), and intracranial blood is constant. An increase in volume of the cranial constituents must be compensated by a decrease in volume of one or both of the two. For example, an increase in ICP will be compensated by the downward substitution of CSF and venous blood. Normally, cerebral perfusion pressure of blood (CPP) is constant fairly due to autoregulation, but it can be calculated over abnormal mean arterial pressure (MAP) or abnormal ICP, that CPP = MAP − ICP. One of the main dangers of increased ICP is that it can cause ischemia by decreasing CPP. Headache, nausea, vomiting, ocular palsies, altered level of consciousness, back pain and papilledema are symptoms and signs for rise in ICP [16,17].

E. Hyperviscosity and ischemia of brain

Hyperglycemia, leukemia, paraproteinemia, and polycythaemia increase viscosity of blood, and therefore they associated by increased risk of stroke and thrombosis of the brain. The symptoms of hyperviscosity syndromes are rich that include headache, somnolence, hemorrhagic diathesis, circulatory overload, thrombosis, and coma. The evidences suggest that hematocrit and viscosity are important factors in the control of cerebral blood flow (CBF). Conditions in which the hematocrit is raised such as polycythaemia are associated with a low CBF, and when the high hematocrit decreases, there is a significant rise in CBF [18,19].

F. Anemia, ischemia, and headache

When blood viscosity increases 20% due to hematocrit increase as 10.99%; blood flow rate decreases 16.67% (stasis and increased risk of thrombus formation), and an increase of blood pressure 20% or 4.66% vasodilatation is required to compensate this state. Inversely, low level of hematocrit may result in hypotension with decreasing blood viscosity [5-7,14]. Severe hemodilution with acute anemia may result in cerebral hypoxia, and increase in CBF observed after hypoxia and anemia by compensatory vasodilatation [20]. The headache associates with anemia, transient ischemic attacks, and idiopathic intracranial hypertension of anemia [21,22].

G. Hyperviscosity and coagulation

Stasis, hyperviscosity and Polycythaemia increase the prevalence of stroke, thrombus formation, disseminate intravascular coagulation and embolism. Blood coagulation involves an amplification phase of the coagulation cascade that requires an increased local concentration of circulating coagulation factors at the region of injury. There are strong relationships between hyperviscosity and hematocrit, and between coagulation and hematocrit. Platelet adhesion increases fivefold as hematocrit increase from 10 to 40%, and thrombus formation increase continuously as hematocrit increases from 10 to 70%, which are evidences for facilitated coagulation by increased blood viscosity [23-25].

II. MATERIALS AND METHODS

A total of 37 healthy subjects with no complaints who do not use any drugs for the last week were included into the study with the simple random sampling method from the visitors of Internal Medicine Department (H. Numune Hospital, Istanbul, Turkey) after their written informed consents were taken. The investigation confirms the principles outlined in the Declaration of Helsinki, and the local ethical committee. The study group was made up of 23 males and 14 females with a mean age of 30.3±6.1.

A. Preparation of the blood samples

After 12 hours fasting, from the brachial vein 50mL of blood with 50 IU/mL of heparin sodium was taken in the morning. Blood samples were centrifuged at 3000 rpm for 5 minutes by clinical centrifuge, which has a radius of 9.5cm, and the plasma was obtained as supernatant, buff-coat (layer of leukocytes on erythrocyte column) was collected as mass of leukocyte. Then, the mass of leukocyte separated from the sediment of erythrocyte by the way of suspending in pure plasma, centrifugations at 3000 rpm for 5 minutes and then suctions of Buffy-coat by a Pasteur pipette, twice. After that, heparinized blood, and the mass of leukocytes $(0.5 \times 10^5/\text{microliter}$, adjusted by pure plasma) were used as the samples for experiments, and the differences of flow times between three temperatures were evaluated as the data.

B. Measurement of viscosity of blood and flexibility of leukocytes

The flow times of samples were measured by a capillary tube viscometer that has a reservoir with a volume of 2mL at the upper part. It was filled with sample in the vertical position until the upper mark of the reservoir and the free flow time of the liquid to the lower mark of the reservoir was measured in seconds (s) and used as the data.[14] During the measurement of viscosity, each measurement was repeated and controlled three times, and the physical conditions (temperature and humidity) of the laboratory were kept constant and the flow time of the distilled water (calibration data) was the same. The viscometer was used at the selected constant three temperatures, at the same vertical position, without exposure to the direct sunlight and airflow. To represent the medical hibernation state, normal conditions, and state of high fever; 25°C, 37°C, and 39°C of the sample

temperatures were selected respectively that 25°C is also normal skin temperature of lower extremity without trousers.

The sum of the preparation and the measurement periods of the samples were standard, those 20 minutes for blood, and 45 minutes for leukocyte. When the orifice of sample tubes were closed with polymer membrane of paraffin (Parafilm), there were not any changes in flow times (viscosity) of samples at least for 4 hours at the laboratory temperature of 20 °C and 8 hours at 4°C. However, when samples were left in open tubes at least 2 hours, there were decreases in volumes and increase in the flow times of samples due to evaporation. The viscometer was washed to keep clean for each measurement with 0.9% sodium chloride solution, rinsed with distilled water and dried with acetone. In order to study at different temperatures, the viscometer was placed into a liquid coat leaving two ends of the device out vertically and heat-controlled water was circulated continuously in the closed and transparent coat system with a peristaltic pump. In order to make more accurate presentation in the graphic and statistics, instead of the "relative viscosity" value, which is calculated by dividing the flow time of the sample to the flow time of the distilled water, flow time (s) was used as data [14].

C. Hemodynamical calculations and statistical evaluation

The changing amount of hemodynamical parameters due to the changing temperature related viscosity was calculated with Poiseuille's Hydrodynamics equation (3-6). The Student t test, Pillai's Trace test, and Spearman's correlation test were used for statistical evaluation.

III. RESULTS

When the temperature of blood decreased from 37°C to 25°C, the viscosity of blood increased from 11.70+/-0.4s to 15.10+/-0.6s as 29.05% (p<0.0001). With a temperature increase from 37°C to 39°C, the viscosity of blood decreased from 11.70+/-0.4s to 10.12+/-0.35s as 13.50% (p<0.0001). When all the differences at three temperatures were evaluated together, the correlation between temperature and blood viscosity was r=-0.6 and P <0.001.

When temperature decreased from 37°C to 25°C, leukocyte flow time increased from 6.63+/-0.3s to 8.17+/-0.32s as 23.22% (p<0.0001).With a temperature increase from 37°C to 39°C, the leukocyte flow time decreased from 6.63+/-0.3s to 6.29+/-0.3s as 5.12% (p<0.001). There is a negative correlation between temperature and the flexibility of leukocyte (r= -0.62 and P <0.001). Flow times (viscosity) of leukocyte suspension at 25°C, 37°C, and 39°C were lower than heparinized blood viscosities of the same three temperatures (p<0.001).

IV. DISCUSSION

Results of the study and information given above suggest that temperature variations between 25°C and 39°C change the viscosity of blood in clinically and statistically important amounts. The stoichiometric relationships among viscosity, velocity, flow rate, and pressure are represented in Poiseuille's equation, and when a parameter of equation (e.g. viscosity) changes (e.g. due to temperature variations); to

keep the blood flow rate (Q) constant that is the main aim for physiological autoregulation (compensation) system of cerebral circulation, another parameter must be changed in equivalent amount. To calculate this amount of compensatory and equivalent change in a parameter, the Q and the other parameters must be constant in that calculation and equation except the changing one (e.g. viscosity) and the compensatory parameter. In addition, when a parameter of Poiseuille's equation changes in a given (measured) amount, an equivalent amount of a compensatory change can be shared by two or three other parameters with known percentages that are calculable by that equation. Here, the term of equivalent amount does not represent the equivalence of numbers, and it describes the mathematical relationship between parameters according to the stoichiometric ratios of them in that equation.

These interpretations, data, and relationships between the parameters of hemodynamics have mathematical accuracy. However, after that change in the blood viscosity, the physiological compensation is not done with the only one of the parameter, and most likely, blood circulation is compensated with more than one parameter changing at the same time. Therefore, it can be concluded and calculated that when viscosity of blood increases within physiological range in a healthy body; probable first compensation should be increasing blood flow rate via increasing heart rate and stroke volume, which may beneficial for some circulatory conditions, however it produces some cardiac burden. Although, when viscosity of blood increases up to level of hyperviscosity syndrome, ischemia and cardiac failure start according to level of myocardial and coronary reserve, and then the fate of patient may change to stupor, coma, and finally death with increasing insufficiency of blood circulation.

As a result, the preferred order and the changing percentages of those parameters in combine compensations of physiological and pathological conditions are not known sufficiently yet. To explain this order and percentages of parameters in combine and physiological compensations; measurements of intra-arterial pressure, velocity and flow rate of blood, and MRI angiography and Doppler ultrasound searches with in-vivo simultaneous new experiments are required. Results, physiological interpretations, and two flow charts of this study are covering all of the parameters of hemodynamics and they could provide realistic and mathematically accurate bases for future investigations and clinical evaluations of these complex conditions.

A. The Calculations of Temperature Effects on hemodynamics

When the blood viscosity increases 29.05% due to the temperature decrease from 37°C to 25°C, the blood flow rate decreases as 22.52%, and for the physiological compensation of this state, a 29.05% of blood pressure increase or 6.59% vasodilatation is needed. According to Poiseuilles' equation, if the viscosity (denominator of Poiseuilles' equation) changes from 100 to 129.05 (29.05%), the flow rate would decrease 100/129.05=22.52%. If viscosity η increases 29.05% in the denominator, to keep the equation constant, multiplier,

the pressure (F_1 - F_2) value must be increased with the same amount. When the viscosity increases 29.05%, in order to keep the constant flow rate (Q), the a^4 value must increase 29.05%; therefore, a^4_{final} =1.2905 x $a^4_{initial}$; a^4_{final} =$^4\sqrt{1.2905}$ x $a_{initial}$=1.0658 x $a_{initial}$; a_{final} =1.0658 x $a_{initial}$; if $a_{initial}$=100; a_{final} - $a_{initial}$=6.58. From this, 6.58% vasodilatation requirement can be found.

When the blood viscosity decreases as 13.50% due to temperature increase from 36°C to 39°C, according to the same equation, a 15.6% blood flow rate increase or 13.50% decrease in blood pressure or 3.57% vasoconstriction is needed for a physiological compensation. At 39°C, if the body prefers to keep the pressure constant, compensation would be seen by the increased heart rate. When stroke volume is constant, the increasing amount of compensatory heart rate is 13.5% that increases the blood flow rate as 13.5%. The result of increasing temperature represents the decreased blood viscosity that may compatible to high fever state of patients, acute anemia of bleeding and hemodilution, and a changing amount of hemodynamical parameters and the amplification of coagulation due to variations of temperature can be calculated and evaluated with our flow charts and sample calculations.

B. Calculation of the relationship between viscosity and coagulation

According to Fig 1, when blood flow rate decrease as 22.52% (due to decreased temperature and increased viscosity), the concentration of local coagulation factors (that could continuously be produced from surface of vascular lesion and aggregated thrombocytes) increase as 22.52% (per volume/ per time) in stasis region of vessel. Therefore, the amplification of coagulation cascade (that could be evaluated as number of collide and chemical interaction between coagulation factors) increases that it could increase the formation of thrombus. Inversely, when blood flow rate increase15.6%, (due to increased temperature; Fig 2), it results in decreased concentration of coagulation factors as per blood volume/per time at the region of vascular lesion that amplification phase of coagulation cascade and the probability of thrombus formation decrease, and the risk of bleeding increase.

However, when there is a sufficient reserve capacity of myocardium and circulatory system; possibly, a compensatory increase of blood pressure occurs, and it prevents the body from decrease in blood flow rate (stasis) and formation of thrombus in state of hyperviscosity. An important point of this state should be avoiding the strong therapy of compensatory hypertension of hyperviscosity syndrome. Because, the higher blood viscosity is required more compensation with more increased blood pressure, and a decreasing blood pressure in hyperviscosity syndrome could results in stasis, ischemia, hypercoagulation, and thrombosis due to decreased blood flow rate. These evaluations support the opinions; avoiding vasoconstriction at the region of vascular lesion or thrombus could be beneficial, and increasing blood flow rate with increased blood pressure and decreased blood viscosity (hemodilution)

should be useful after vascular trauma (surgery) and during formation of thrombus.

C. Mechanisms of headache and intracranial hypertension of anemia

The factors causing headache include increasing or decreasing arterial blood pressure, increasing or decreasing ICP, anemia and dilatation of carotid artery that is the cause of migraine. However, mechanism of benign intracranial hypertension and headache of iron deficiency anemia is not clear yet. Although, according to the results, calculations and flow charts of this study; anemia results in decreased hematocrit and blood viscosity, and therefore it produces increased blood flow rate and then compensatory vasoconstriction, which result in increased ICP. As a result, the mechanism of anemia related headache could be explained by changing parameters of hemodynamics in relation with blood viscosity and hematocrit levels. Interestingly, previous studies suggest that patients with increased blood viscosity have headaches at night hours frequently; occasionally, superimposed paroxysmal attacks of hypertension develop in that patients [26,27].

D. Mechanism of facilitated infections by cold environment

Flexibility of leukocyte constitutes a part of blood viscosity, and affects the microcirculation at the brain, skin, nasopharyngeal mucosa, pulmonary alveolar area, and possibly, it is a factor for functional capacity (phagocytosis, motility, metabolism, bacteria killing) of leukocyte. Therefore, the decreasing flexibility of leukocyte in cold environment could have negative effects on the microcirculation and the functions of leukocytes and hemodynamics. This suggestion should be a subject to new investigations.

V. CONCLUSION

Our method based on Poiseuille's equation and system analysis of blood circulation as a flow chart within mathematical and stoichiometric relationships suggests that a decrease of blood viscosity (e.g. due to increased blood temperature) could be related with decreased ICP, increased blood flow rate, decreased local concentration of coagulation factors (per volume / per time for a region of the vessel), inhibition of amplification phase of coagulation cascade, compensatory vasoconstriction, and headache. Inversely, an increase of blood viscosity (e.g. due to decreased blood temperature) could be related with change in ICP, decreased blood flow rate (stasis), increased local concentration of coagulation factors, facilitated amplification phase of coagulation cascade, formation of thrombus, compensatory vasodilatation, and headache. In addition, this study provides an explanatory mechanism for anemia related headache and intracranial hypertension.

Patients elderly that have not sufficient capacity of compensation by dilatation or vasoconstriction of brain vessels or patients having stroke due to hyperviscosity and thrombus formation or patients who have hyperviscosity syndrome and possibly hypotensive while surgical operation must be kept within more suitable (high) temperature and

must be kept away from temperature stress and cooling carefully. According to relationship between temperature and blood viscosity; keeping the temperature of brain constant is mandatory for keeping the blood flow rate of brain constant. Therefore, we can conclude that this information and evaluation increases the importance of insulator effects of hairs and sinuses (maxillary and frontal sinuses filled by air like an insulator on the face) of head, and that insulations prevent the brain from variations of temperature, viscosity and pressure of blood.

The result of this research and our flow charts of the system analysis in this manuscript are original and using them could provide expanded capacities for distinct diagnosis, selective therapies, regulation of the cerebral blood flow; prevention from stasis, thrombus formation, bleeding, headache; explanations for anemia related intracranial hypertension and headache; and it constitute a new expanded scalar base within mathematical accuracy for future investigations.

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EFFECT OF COOLING ON HEMODYNAMICS AND HOMEOSTASIS
Blood temperature decrease (from 37°C to 25°C)

Decreased flexibility of   **Increased blood viscosity (29.05%) and peripheral resistance**

leukocytes (23.22%)

Part of decreased peripheric resistance

<u>Hemodynamic changes:</u> **Decrease in blood flow rate 22.52% (Stasis)**

Compensatory mechanisms
(Circulatory Load)

Stasis (22.52%) and increased risk of thrombus

formation. Increased concentration of

coagulation factors per volume/ per time

for a region of the body:

Heart rate Increase

(22.52%, if stroke Volume constant)

Blood pressure   **Vasodilatation**   **Cardiac output**

Increase 29.05%;   **6.59% in radius**   **increase (22.52%)**

(NONE in

Angina Pectoris   Atherosclerosis)

(Cold weather angina)

Headache

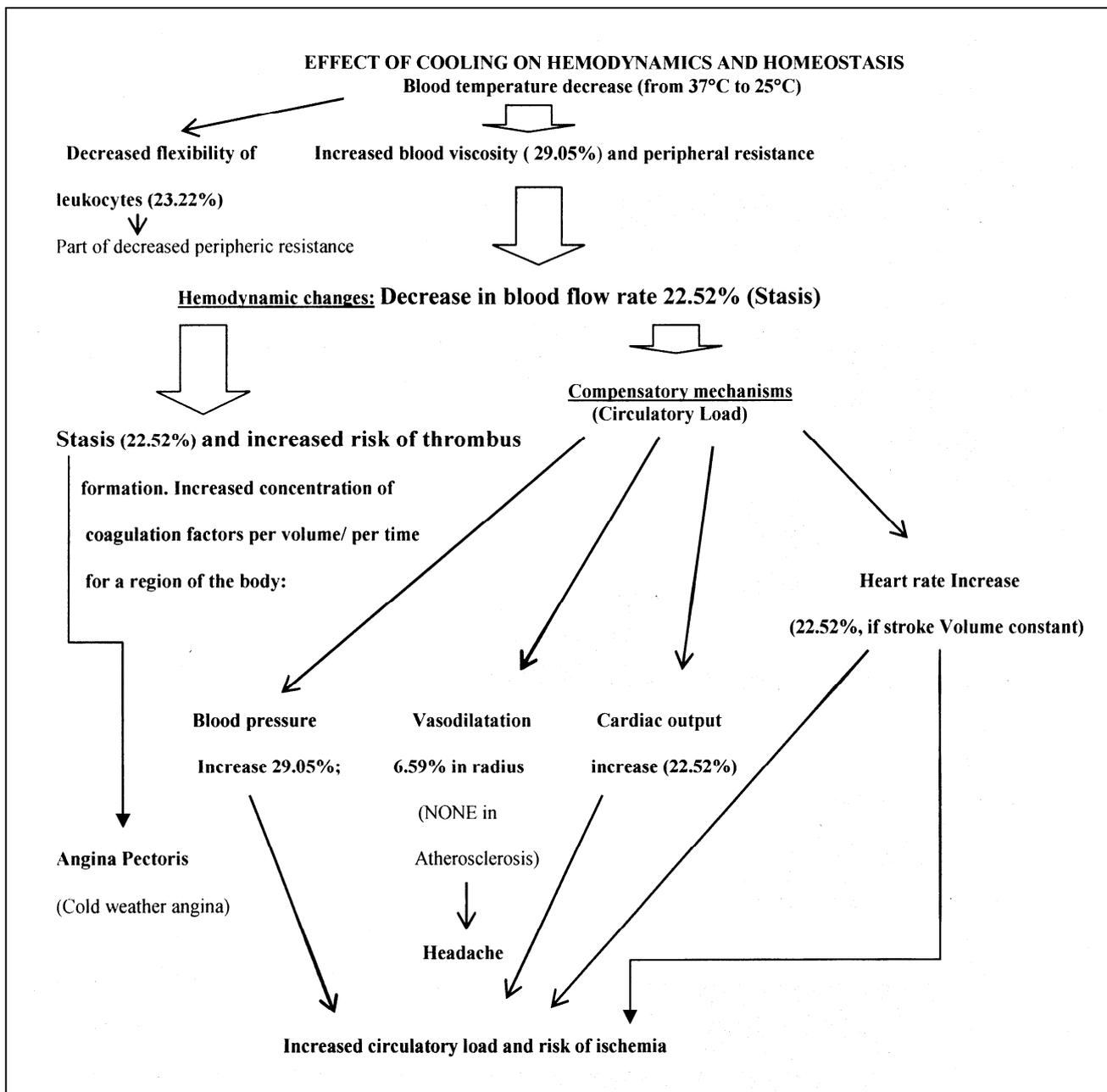**Increased circulatory load and risk of ischemia**

Figure 1. Relationships between decreased temperature, increased blood viscosity, changing hemodynamics, increased risk of ischemia and formation of thrombus. The stoichiometric relationships between the decreased blood temperature (from 37°C to 25°C), the increased viscosity and the compensatory changes of the blood pressure, the flow rate, the heart rate and the vessel diameter can be represented according to the Poiseuille's' equation as a system analysis in this flow chart. Increasing risk of thrombus formation is shown according to the decreased blood flow rate (due to the decreased temperature and the increased blood viscosity) results in stasis, and it increases the concentration (and amplification) of coagulation factors per volume/ per time for a region of the body.

EFFECT OF WARMING ON HEMODYNAMICS AND HOMEOSTASIS

Blood temperature increase (from 37°C to 39°C)

Increased flexibility of

leukocytes (5.12%)

Decreased blood viscosity (13.5%)

(Decreased peripheric resistance, 13.5%)

Part of decreased

peripheric resistance

Hemodynamic changes   **Compensatory mechanisms**

Blood pressure   **Heart rate increase**

decrease (13.5%),   **(15.6%, If stroke volume is constant)**

Vasoconstrictions (3.57 % in radius)   **Cardiac output increase (15.6%)**

(Mechanism of headache)   **Increased blood flow rate (15.6%)**

Blood Pressure increase (13.5%)   **Dilution of coagulation factors**

(Per volume/ per time for a region of the body)

Increased risk of ischemia

Decreased hemostasis, risk of bleeding

(If other factors are constant)

Increased circulatory load and increased risk of ischemia
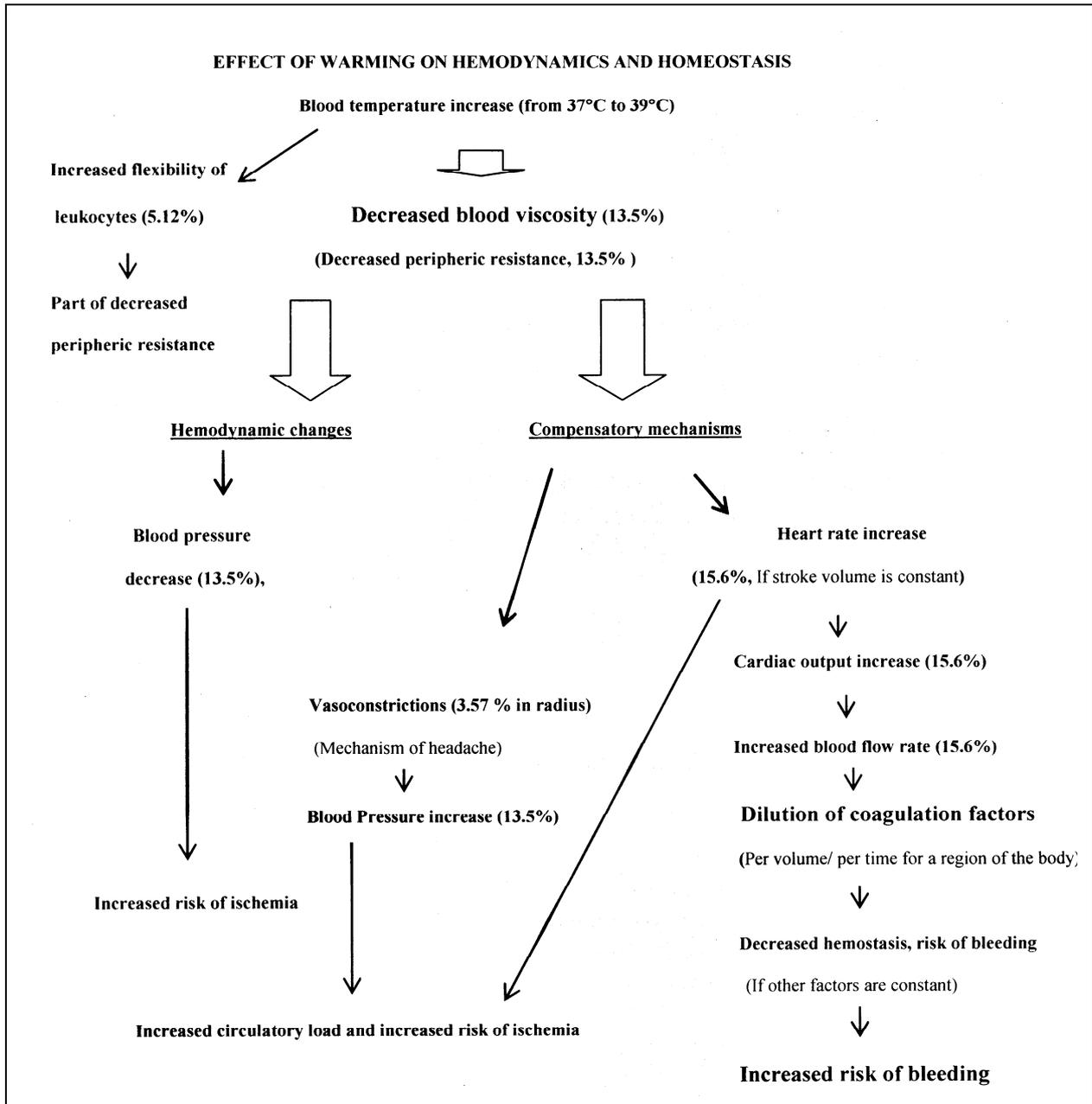
Increased risk of bleeding

Figure 2. Relationships between increased temperature, decreased blood viscosity, changing hemodynamics, increased risk of ischemia and bleeding. The stoichiometric relationships between the increased blood temperature, the decreased viscosity and the compensatory changes of blood pressure, the blood flow rate, the heart rate and the vessel diameter can be represented according to the Poiseuille's equation as a system analysis in this flow chart. Increasing risk of bleeding is shown according to the increased blood flow rate (due to the increased temperature and the decreased blood viscosity) that decreases the concentration (and amplification) of coagulation factors per volume/ per time for a region of the body.