IS IT EASY TO DEFINE DIC SYNDROME?

The possibility of intravascular blood coagulation existence in the microvascular vessels and capillaries without the presence of a large thrombus in the arteries and veins is known from the middle of 19th century. Selye [1] thinks that the first description of that phenomenon was made in a German journal written by the Russian doctor S. Botkin, who was working with R. Virhov at that time. This phenomenon became well-known after being entitled disseminated intravascular coagulation (DIC) or DIC syndrome. For the last 40 years there were a lot of published works about it. This problem is very interesting, because it presents danger for human life.

It is impossible to know exactly about the prevalence of this pathology, because there is a jumble in terminology that does not help statistics to be exact. One of the reasons of so high mortality from disseminated intravascular coagulation (DIC) is due to the impossibility to always make exact diagnosis, and as M. Levi thinks it is provoked in the absence of generally accepted idea of DIC syndrome. We investigated these markers and the intensity of intravascular blood coagulation in a number of patients. Our understanding of the problems of DIC was formulated on the grounds of a thirty-year study of the problem involving over 1,500 patients. Thereby, the conception of constant intravascular microcoagulation (CIMC) was developed with the following aims: to report the existing material and bring to researchers and doctors in practice information about the presence of the phenomenon of CIMC and to resolve debatable questions of definitions and practical usage of up-to-date information about DIC with the help of CIMC conception.

SUMMARY

The possibility of intravascular blood coagulation existence in the microvascular vessels and capillaries without the presence of a large thrombus in the arteries and veins has been known from the middle of 19th century. It is impossible to know exactly about the prevalence of this pathology, because there is a jumble in terminology that does not help statistics to be exact. One of the reasons of so high mortality from disseminated intravascular coagulation (DIC) is due to the impossibility to always make exact diagnosis, and as M. Levi thinks it is provoked in the absence of generally accepted idea of DIC syndrome. We investigated these markers and the intensity of intravascular blood coagulation in a number of patients. Our understanding of the problems of DIC was formulated on the grounds of a thirty-year study of the problem involving over 1,500 patients. Thereby, the conception of constant intravascular microcoagulation (CIMC) was developed with the following aims: to report the existing material and bring to researchers and doctors in practice information about the presence of the phenomenon of CIMC and to resolve debatable questions of definitions and practical usage of up-to-date information about DIC with the help of CIMC conception.

Keywords: disseminated intravascular coagulation; diagnosis; constant intravascular microcoagulation

Among them, compensated and decompensated DIC [5], chronic DIC [6], evident and latent DIC [7], and pre-DIC. One more reason of such a high mortality from DIC is the presence of misunderstanding regarding the early diagnosis of this life-threatening clinical phenomenon, and also in the choice of treatment of these patients after making this menacing diagnosis.

Why is it so difficult to make such a simple decision as the formulation of the determination of DIC? We can answer this question by observing the metamorphoses in the process of study of DIC syndrome. This term was proposed in the USA by a young American pathologist Donald McKay [8] in 1950, when he performed autopsy. McKay discovered numerous thrombi in the vessels of a female who had died in obstetric hospital, because of hemorrhagic diathesis. He proposed the term „disseminated intravascular coagulation”. His senior colleagues Seegers and Schneider [9] carried on and made this term public. The term DIC syndrome became widely used in medicine after 4th American Congress of Obstetricians in 1951, where Seegers and Schneider reported the case of McKay [9, 10]. The phenomena began to be actively studied by many scientists, and each of them tried to give it different names. So Lasch [11] named it consumption coagulopathy, Selye [1] and Machabeli [12] “thrombo-hemorrhagic syndrome”, and Owen and Bowie [13] proposed to name “intravascular blood coagulation and fibrinolysis”. However, the suggestion of McKay [8] was preserved and has continued to be most popular and recognized until the present time.

Biochemists, physiologists and clinicians paid great attention to DIC syndrome. This made it possible to study the facts of biochemical transformation of blood in the course of fibrin and platelet thrombus formation and to create new methods of identification of the
intravascular blood coagulation markers. Today, we consider them to be the products of fibrinogen and fibrin degradation, which are: fibrin-monomer, D-dimer, β-thromboglobulin, platelet factor 4 and etc. Many clinicians began to use the above-listed methods in their researches and discovered that sometimes patients had a higher level of these symptoms than healthy persons. In this situation they also began to use the term „disseminated intravascular coagulation”. Owen and Bowie [13] proposed to name such phenomena chronic DIC syndrome. However, this made problems to doctors in practice, because they often could not exactly differentiate acute from chronic DIC, and did not know how to manage such patients.

**IS IT EASY TO DETECT DIC SYNDROME?**

Indeed, it is very difficult, even theoretically, to draw a borderline between compensated undiscovered DIC and pre-DIC, and decompensated discovered DIC and its undiscovered variants. We devoted our attention to this question from the beginning of the 1970s. When we studied some features of hemocoagulation in patients, we revealed important rippling of separate performances of both different and identical patients when blood sampling was investigated separately. This enabled us to make some suppositions about the constant activity of intravascular blood coagulation in the human body and even suggest that we can interfere in pathologic process through purposeful pharmacological regulation of blood coagulation (1974) [14]. The work, which was done at the laboratory of Paul Didishaim (1977) [15], where we studied the adhesion of platelets to the artificial surface – cuprophen, gave us the reason to suggest a possibility of quantitative determination of the intensity of formation of the platelet clot in the bloodstream on the ground of measuring the level of the platelet factor 4 in plasma. The possibility of determination of procoagulant markers and platelet components of hemocoagulation made it possible to note differences in their intensity and suggested that they are relatively independent from each other. Investigations that we performed on a large group of patients with chronic heart disease and diabetes mellitus, had a higher activity of platelet part of hemocoagulation than fibrin formation [18, 19]. Patients who had rheumatoid arthritis revealed increased intensity of fibrin formation, which was termed as a part of procoagulation, and it was noted that the intensity of platelet clot formation was less intensive [20, 21]. In patients who had acute leukaemia the intensity of platelet section of hemocoagulation was almost identical to the increase of intensity of procoagulation. A section on the evidence of increased blood fibrinolytic activity compared with increased hemocoagulation also showed the absence of strict parallelism between them (1980) [22].

We also studied the more accurate state of intravascular clot formation with the help of TTP (thrombus protein precursor), which helped us to detect the fibrin–monomer without fibrin peptides A and B [23, 24]. The level of TTP was measured in patients with acute coronary syndrome and in haemophilic patients, when there was the presence of different clinical states, thrombosis and bleedings. In the course of this study we revealed the following interesting fact. In the blood of persons with haemophilia we expected to find low coagulation and accordingly a low level of TFP-fibrin–monomer. However, it was found that the level of TFP was higher than that in healthy persons (Table 1).

The disclosed information made us to look more carefully into the marker level of intravascular blood coagulation of healthy persons [23, 24]. The results of our research were compared with the information that we had received from researchers from all over the world. All this has made it possible to draw a conclusion that the process of intravascular blood microcoagulation exists permanently, considerably modifying in its intensity, and that is why some definite corrections in the interpretation of DIC were made.

**CONCEPT OF CIMC**

Our understanding of the problems of DIC was formulated on the grounds of a thirty-year study of this problem and on having studied more than 1,500 patients. It is possible to summarise the results of our work published in domestic and foreign journals as follows [25]:

- Constant presence of the markers of intravascular coagulation in plasma of healthy and sick persons gives us the basis to think that intravascular microclotting of blood is constantly present, and that there is the need to underline its existence by the term constant microvascular microcoagulation (CIMC).
- Intensity of CIMC may be different. The level of the markers of intravascular microcoagulation of blood, which is measured in the plasma of healthy persons, must be adopted as “normal”. The increasing of the intensity of intravascular microcoagulation may be seen in some transient disorders and following intensive physical stress (exercise). After such situations have passed, the intensity of intravascular microclotting can return back to the “normal” level. Investigated patients with some chronic diseases exhibit a constant increase of the intensity of intravascular microcoagulation. They usually do not show any special clinical traits except of the usual clinical picture of the main disease. Previously, these states were named “chronic intravascular micro-

| Disease                                      | Number of patients | Data       |
|----------------------------------------------|--------------------|------------|
| Coronary heart disease (myocardial infarction) | 19                 | 6.99±2.85  |
| Unstable angina                              | 8                  | 7.84±2.77  |
| Stable angina                                | 21                 | 11.1±2.4   |
| Haemophilia A                                | 8                  | 1.57±0.56  |
| Healthy persons                              | 23                 | 0.99±0.26  |

**Table 1. Level of fibrin monomers, deprived fibrinopeptide a and b in patients with coronary heart disease and haemophilia**
coagulation". It is possible that special regulation of this stage of the constant intravascular microcoagulation can improve the prognosis of the disease. When CIMC is sufficiently intensive it is possible to cause a change in the clinical picture and organ dysfunction. In such situations it must be considered as the highest stage of CIMC. This and only this stage of CIMC must be named DIC syndrome (Table 2).

- DIC syndrome is the only stage of CIMC, where the increase of its intensity is an independent cause of the damage of body organs and body tissues, such as bleeding, multiple organ damage, hypotony, micro- and macrothrombosis and their different combinations.

- Differences in the degree of the intensity of intravascular microcoagulation of blood can be changed, and only in the definite stage it leads to the progress of the apparent clinical picture of DIC. At that time the manifestation of clinical picture of the syndrome may come true very quickly. In connection with the above priorities in diagnostics requires a combination of laboratory analyses with the obtained findings subjected to characteristics and clinical picture of the disease.

Thus, after the suggestion of the conception of CIMC the idea of DIC and its place in the variety of intravascular blood coagulation can become more concrete and definite (Table 2).

### DIC AS A STAGE OF CIMC

We think that the identification of the idea of DIC should be guided by McKay’s [8] observations, with the addition of something new that can help to include it into the idea of greater accuracy and clarity. This should be defined more exactly and help to understand the nature of clinical manifestations which should be expected by the doctors who make the diagnosis of this phenomenon. It is needed to get information about the structure of intravascular microclots. But the term DIC should be mentioned only in the situation when the phenomenon is characterized by the intensive formation of intravascular microclots that are generated at the microvascular level, which can have different morphologic structure, different forms of clinical manifestation leading to acute dysfunction of organs and tissues, with life-threatening outcome.

Of course, such situations must produce the evidence of degradation of fibrin and fibrinogen and platelets activity. The level of fibrynopeptide A, D-dimer, soluble complexes of fibrin-monomer, fibrin-monomer without fibrynopeptides, β-tromboglobulin and platelet factor 4 that are circulating in the human blood, make it possible to have the information about the intensity of intravascular microcoagulation of blood. However, the wide level of fluctuation of these rates in both healthy and ill persons present a difficult task for the practitioner.

Many researchers have tried to identify the threat of DIC progress by taking stock of different clinical and laboratory parameters. Japanese researchers suggested estimating the danger of DIC progress by scoring systems (APACHE II and MOD). The International Subcommittee for DIC is also actively studying this question. It suggested the following: the diagnostic criteria of DIC are submitted in Table 3. In addition, the following algorithm of action is proposed: the algorithm of open DIC diagnostics, which includes the following stages of occupation (Scheme 1) [7]. In the first stage the risk evaluation of DIC onset is put into effect. It is necessary to detect the presence of such diseases happening to such patients which are associated with the possibility of phenomenon progress. It is accepted to consider such diseases as the following: infections, tumours, obstetric problems, injuries and burns, immune conflicts, etc. When they are present, the continuation of algorithm passage is recommended. In the second stage the performance of coagulation tests is proposed, which could make it possible to specify the condition of intravascular hemocoagulation. It is proposed to consider such tests as the following: quantification of platelets, the level of fibrinogen, indication of prothrombin time, and also the determination of soluble

### Table 2. Levels of constant intravascular microcoagulation (CIMC) of blood intensity

| Grade | CIMC | Features |
|-------|------|----------|
| 1st   | Normal CIMC | Levels of CIMC markers are "normal" |
| 2nd   | Transient increased CIMC | Levels of CIMC markers are increased, but they are unstable and do not produce special clinical changes in the main disease picture |
| 3rd   | Sustained increased CIMC | Levels of CIMC markers are increased. This state is stable, but does not have special clinical manifestations. Its regulation could be important and may increase the positive outcome of the disease |
| 4th   | CIMC-DIC-Syndrome | Increase of constant intravascular coagulation is rapid and produces impact on organ function, threatening the life of patients (DIC syndrome) |

### Table 3. Diagnostic criteria of DIC [7]

| Classification | Definition | Diagnostic criteria |
|----------------|------------|---------------------|
| Biological DIC | Haemostatic defect without clinical presentations | Increase of D-dimer level and 1 large criterion* of platelets consumption or coagulation factors or 2 small criteria* of platelets consumption or coagulation factors |
| Clinical DIC   | Haemostatic defect with hemorrhagic or ischemic manifestations | All is identical with biological and signs of microvascular bleeding and/or thrombosis |
| Complicated DIC| Haemostatic defect with hemorrhagic or ischemic manifestations which lead to organ dysfunction | All is identical with clinical and signs of organ involvement |

* Laboratory criteria for disseminated intravascular coagulation: D-dimer more than 500 mg/l; consumption of platelets – low (platelet count 50-100,000/mm³) and higher (platelet count is less than 50,000/mm³), consumption of coagulation factors is low (INR=1.2-1.5) and higher (INR>1.5).
fibrin monomer or D-dimer level. The level of increasing of each index is marked by appointed scoring scale. Then the calculation of organ function is performed, which is more frequently involved in the course of syndrome development. They are central nervous system (CNS), cardiovascular system, lungs, liver and kidneys. Their functioning is also estimated in the scoring scale. The analysis of hemorrhagic manifestations takes stock of their presence or absence, which is also fixed in the scoring scale, and total calculation of points, and this, to the author’s opinion, makes it possible to speak about DIC presence or absence to an even greater degree of probability. The quantity of points, which is higher then 7, must be adopted as a great probability of this phenomenon and determines the necessity of repeated analysis of these rates on the next day. Thereby, based on the total score diagnostics conclusion is made.

Considering these attempts positively we should look at them critically. Indeed, the number 1 value could not resolve the question about confirmation or negation of DIC diagnosis. We have received evidence that such a term of the biological DIC stage 1-3 of our CIMC only confuses the doctor’s mind. Indeed, when we reveal that the patient has a high level of D-dimer and other signs of fibrin formation and the reduction of the quantity of platelets and fibrinogen (non-metering their dynamics) will lead to the situation when the doctor will decide that the patient has DIC. In doctor’s practice the term DIC is usually associated with a condition which is life-threatening for the patient. That is why the diagnostics of this disease calls for active actions, which could be unjustified, because the increase of mark level of fibrin formation is not specific only in the extreme stage 4 of CIMC (acute DIC), while platelet count of the patient could be low for many other reasons. Besides, initially the patient may have a high platelet count and/or fibrinogen rate and having DIC, with reduced platelet and and/or fibrinogen, not to mentioned the level. So it turns out that there is no DIC. In such cases the doctor could start the necessary therapy too late.
At present the International Subcommittee of DIC continues to work out refinements of DIC with different types of diseases (injuries, obstetrical pathology, sepsis) and search or new subtle markers – the predictors of DIC.

It seems to us that the identification of subtle marks level of intravascular blood coagulation could not help us to predict the progress of extreme stage of CIMC (acute DIC according to ISTH), because they would only reproduce the intensity of CIMC, which could arise in different diseases, as well as in healthy persons and would not lead to DIC. Because we understand this problem well enough we dare say that the transition of the intensity of intravascular blood coagulation to the stage of DIC can be specified, not on the ground of point calculation, but in the following way: morbid events characterized by a high risk of DIC progress (sepsis and other infections, neoplasm, traumatic and surgical tissue involvement, obstetrical pathology, vascular lesions and vascular anomaly, auto-immune diseases, allergic reactions); for timely and early recognition of DIC progress it is recommend to do case monitoring of the rates of fibrinogen and platelet levels. Progressive reduction of these rates in combination with clinical picture should be the reason for the diagnosis and the beginning of therapy.

Thereby, the conception of CIMC was developed with the following aims:

a) To reproduce existing material and bring to researchers and practitioners information about the presence of the phenomenon of CIMC in humans;

b) To resolve debatable questions of definitions and practical usage of up-to-date information about DIC with help of CIMC conception.

CONCLUSION

We hope that further conception design of CIMC could give us a definite answer about the role and place of purposeful regulation of blood coagulation in therapy of many human diseases.

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Otкривање дисеминоване интраваскуларне коагулације помоћу концепције константне интраваскуларне микрокоагулације

Игор Бокарев, Лудмила Попова
И.М. Московска медицинска академија „Сеченов“, Москва, Русија

КРАТАК САДРЖАЈ
Могућност интраваскуларне коагулације крви у крвним судовима и капиларима, без великог тромба у артеријама и вена ма, позната је од средине деветнаестог века. Није могуће тач но сазнати преовлађивање ове патолошке с обзиром на мно штво различитих терминологија која ометода израђивање пречи зне статистичке анализе. Један од разлога високе стопе смртности од дисеминоване интраваскуларне коагулације (ДИК) лежи у немогућности да се увек постави тачна дијагноза. Пре ма мишљењу Марсела Левија (Marcel M. Levi), то је резултат не постојања општеприхваћене идеје о ДИК. Ми смо истражива ли ове показатеље и интензитет интраваскуларне коагулаци је у крви код великог броја болесника. Наше разумевање про блема дисеминоване микрокоагулације формулисано је на основу тридесетогодишњег истраживања овог проблема код више од 1.500 болесника. На тај начин развили смо концеп цију константне интраваскуларне микрокоагулације (КИМК), имајући у виду следеће циљеве: а) давање извес таој са ку пљеном материјалу; б) пружање истраживачима и лекарима информације о заступљености феномена КИМК; и в) решава ње дискутабилних питања дефинисања и примене у практици најновijих информација о ДИК помоћу концепције КИМК.

Кључне речи: дисеминована интраваскуларна коагулација; дијагноза; константна интраваскуларна коагулација