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The Principles of Ultrasound Coagulation Monitoring

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Abstract

Many clinical conditions can lead to excessive bleeding. Clotting prevents excessive bleeding when the blood vessel is damaged. Coagulation tests measure blood's ability to clot, as well as how long it takes to clot and help doctor to identify specific coagulation factor deficiencies and to put on appropriate treatments. To provide coagulation tests you need to use special blood coagulation monitoring devices – coagulometers. This paper gives consideration to the new method of the coagulation tests and monitoring using ultrasound.

Keywords: *Ultrasound, Phase displacement, Coagulation monitoring device.*

1. Introduction

Coagulation is the process by which the body ensures prevention of blood loss after injuries. The coagulation cascade describes the components of blood and how they are involved in the process of clot formation. It consists of the extrinsic pathway (primary hemostasis) and the intrinsic pathway (secondary hemostasis). Primary hemostasis involves interaction between the vessel wall and the blood platelets, terminating in the formation of a primary hemostasis plug. Secondary hemostasis involves the formation of fibrin, in and around the primary hemostasis plug.

Hemostasis, the earliest and quickest mechanism of tissue repair, prevents excessive loss of blood, a liquid connective tissue [1].

When this delicate balance between clotting and bleeding is disturbed, hemorrhagic diathesis or hyper coagulable syndromes can appear and lead to potentially fatal complications such as a heart attack. Coagulation monitoring is used to predict the risk of bleeding, to diagnose potential causes of hemostatic disease and to guide appropriate therapies.

The first attempt in coagulation monitoring was visual observation of physical clotting process. Later manual timing of whole blood clotting in glass tube permitted to provide more accurate measurements. Further discoveries in coagulation monitoring led to more sophisticated laboratory equipment for hemostasis tests including the prothrombin time, activated partial thromboplastin time, and specific assays of platelet function and fibrinolysis.

The most common used coagulation-screening tests are the activated partial thromboplastin time (aPTT) and the prothrombin time (PT). The PT provides a functional determination of the integrity of the extrinsic (tissue factor) pathway of coagulation and is sensitive to the vitamin-K dependent clotting factors as well as to factors of the common pathway. It is a widely used laboratory assay for the detection of inherited or acquired coagulation defects related to the extrinsic pathway of coagulation, and is the standard test for monitoring oral anticoagulation therapy. The aPPT in contrast to the PT, measures the activity of the intrinsic and common pathways of coagulation. It is utilized to detect congenital and acquired abnormalities of the intrinsic coagulation pathway, monitor patients receiving heparin or coagulation factor replacement therapy, and to detect inhibitors of the intrinsic and common pathways [2].

The range of ultrasonic frequencies which are utilized for therapeutic ultrasound span the range from20 kHz to about 3 MHz and beyond this lie the frequencies used in diagnostic ultrasound [3]. High power ultrasound can disrupt cell membranes through acoustic cavitation. This is so effective that one of the standard pieces of equipment in a biochemistry or microbiology laboratory is an ultrasonic cell disruptor which rapidly breaks down cell walls to release the contents. This disruptive energy has been applied to the in vivo destruction of blood clots (thrombolysis) [4].

2. The principles of coagulation monitoring

Currently automated systems and devices that perform assays for the determination of the coagulation status of human blood have replaced many of the manual procedures of the past. In modern laboratories coagulometers are used to perform hemostasis tests. Coagulometer is an analyzer which allows converting the specific measure of coagulation into a quantifiable value. It measures time interval between the coagulation cascade initiation and its endpoint. The endpoint of clotting time has been defined as the time at which a fibrin clot is formed. By the method of the fibrin clot detection all coagulometers are divided:

a) electromechanical (a steel ball within the plasma sample is subjected to magnetic field, resulting in swinging movement of the ball, which is detected by the electromagnetic sensor);

b) optical (detection of clot formation measured by change in amount of light passed through test by photo detector);

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c) electrochemical (blood mixes with reagents that start the clotting reaction and as the blood clots device detects a change in the sample impedance).

All this devices have their limitations and disadvantages. In addition, some assays require additional preparative steps such as plasma separation. Therefore, it is obvious that a demand for devices which can test not only plasma, but the whole blood is still exist.

Earlier it was suggested to use ultrasound for detection of the clot formation [5]. This method of fibrin clot detection is based on the monitoring of variations in amplitude of the ultrasound signal passed through the blood sample. When the fibrin clot is formed the amplitude decrease on 20% and at this moment the coagulation time fixed. But the ultrasound signal amplitude differs a lot according to the state of acoustic contact between ultrasonic sensor and measuring cuvette surface. It is difficult to achieve good contact between the cuvette and the sensor because of the small size of contact surface. Bad contact reduces the signal amplitude and causes measuring uncertainty.

This paper presents a modification of the previous method. It is suggested to analyze the ultrasound signal phase variations instead of amplitude variations. Phase displacement is independent of the contact surface state and measuring value will be more precise.

Cuvette with the blood sample placed between ultrasonic probe and transducer (Fig. 1). When soluble fibrinogen begins to polymerize into a fibrin clot, fibrin strands formation increase ultrasonic waves' path length and the phase displacement between the signals before and after the blood sample appears. It is possible to determine the coagulation cascade endpoint by the value of the phase displacement.

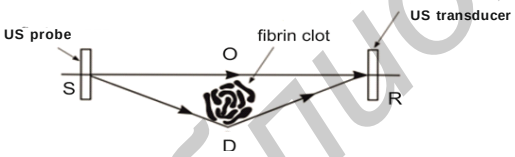

Fig. 1. Fibrin clot formation.

To verify the theory about detection of the fibrin clot in the blood sample by analyzing ultrasound phase displacement value the laboratory mock-up was constructed (Fig. 2).

This mock-up include the oscillation generator (1), ultrasonic probe (2) and transducer (4), cuvette with a blood sample (3), digital oscilloscope (5) and the heating unit (6).

The oscillator generates sine-wave AC signal at different frequencies. The ultrasonic probe converts electric signal into mechanical vibrations, which pass through the blood.

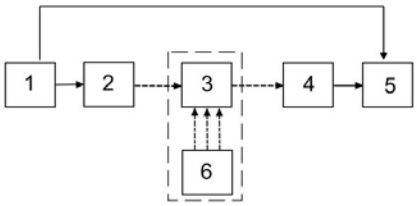

Fig. 2. Laboratory monitoring scheme.

When the mechanical vibrations achieve the transducer, it converts them back to electric signal. The heating unit maintains constant temperature of the sample. Both signals from probe and from transducer come to the vertical channels of the oscilloscope. Technique of measurement step-by-step:

1. Fill the cuvette with 0,1 ml calcium chloride, carefully stir and warm it up to the 37° C.
2. Add to another cuvette 0,1 ml of blood plasma and warm it up to the 37° C.
3. Add to the cuvette with blood plasma 0,1 ml of aPTT reagent, stir carefully and incubate solution of blood plasma and aPTT reagent during 5 minutes.
4. Turn on the oscilloscope and observe on the oscilloscope display two sine wave signals (Fig. 3.

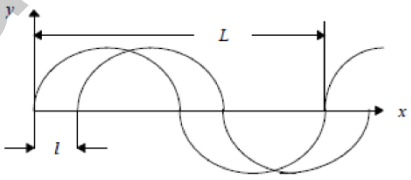

Fig. 3. Picture on the oscilloscope display.

5. Measure on the oscillogram linear dimensions *L* and *l*, which are correspond to the signal cycle *T* and time displacement *Δt*, then calculate phase displacement and put this value into the table:
6. Change frequency with step 100 kHz and repeat step 5 until the frequency will reach 1900 kHz.
7. Set up frequency 100 kHz and add to the cuvette with blood plasma calcium chloride to initiate coagulation cascade measure on the oscillogram linear dimensions *L* and *l*, calculate phase displacement according to the formula 1 and put this value into the table.
8. Change frequency with step 100 kHz and repeat step 7 until the frequency will reach 1900 kHz.

The scheme of the ultrasound coagulation monitoring device (Fig. 4) include the following blocks: oscillation generator unit; input/output stage; ultrasonic (US) probes; control unit; heating unit; power supply unit; input/output device. The sine-wave oscillation unit could be built upon the popular Hartley circuit scheme as it is commonly used in oscillator applications and the recommended frequency range is from 20 kHz to 30 MHz [6].

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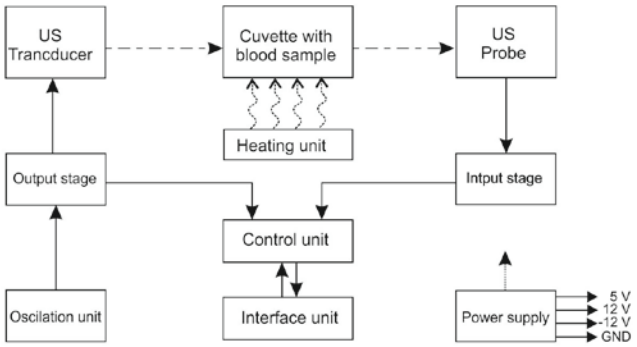

Fig. 4. Ultrasound coagulation monitoring device scheme.

As a control unit it is possible to use the microcontroller C8051F040 suitable for data acquisition applications. It combines a comprehensive set of analog and digital peripherals with High-Speed CPU and FLASH memory. With on-chip VDD monitor, Watchdog Timer, and clock oscillator, the C8051F04x family of devices are truly standalone System-on-a-Chip solutions.

The main purpose of the microcontroller in ultrasound coagulation monitoring device is to calculate phase displacement, fix the endpoint of coagulation cascade and count coagulation time. The architecture of C8051F040 allows to proceed all this tasks after it would be configured by user firmware. Also, microcontroller can provide the data transmission to the PC as it has RS-232 interface.

An interface unit provides communication between the monitoring device and the user. It includes the keyboard with control buttons and the LCD screen.

3. Experimental results and discussion

During the experiment, three blood samples was exposed to the ultrasound signal and phase displacement was calculated for three samples (ϕ_1, ϕ_2, ϕ_3) in frequency range from 200 kHz to 2000 kHz with 300 kHz step before coagulation and after it. Then an average value of phase displacement ($<\phi>$) was calculated. The results of measurements before coagulation represented in Table 1 and after it in Table 2.

Table 1. Phase displacement before coagulation

f, kHz	**200**	**500**	**800**	**1000**
ϕ_1, °	0±3	28±3	16±3	0±3
ϕ_2, °	0±3	30±3	18±3	0±3
ϕ_3, °	0±3	28±3	20±3	0±3
$<\phi>$, °	0±3	29±3	18±3	0±3
f, kHz	**1100**	**1400**	**1700**	**1900**
ϕ_1, °	0±3	23±3	32±3	0±3
ϕ_2, °	0±3	30±3	33±3	0±3
ϕ_3, °	0±3	30±3	34±3	0±3
$<\phi>$, °	0±3	28±3	33±3	0±3

Table 2. Phase displacement after coagulation

f, kHz	**200**	**500**	**800**	**1000**
ϕ_1, °	0±3	33±3	30±3	0±3
ϕ_2, °	0±3	36±3	36±3	0±3
ϕ_3, °	0±3	33±3	33±3	0±3
$<\phi>$, °	0±3	34±3	33±3	0±3
f, kHz	**1100**	**1400**	**1700**	**2000**
ϕ_1, °	0±3	23±3	36±3	0±3
ϕ_2, °	0±3	30±3	34±3	0±3
ϕ_3, °	0±3	33±3	36±3	0±3
$<\phi>$, °	0±3	29±3	35±3	0±3

According to the data from Table 1 and Table 2 a plot average phase displacement ($<\phi>$) versus frequencies was made (Fig. 5).

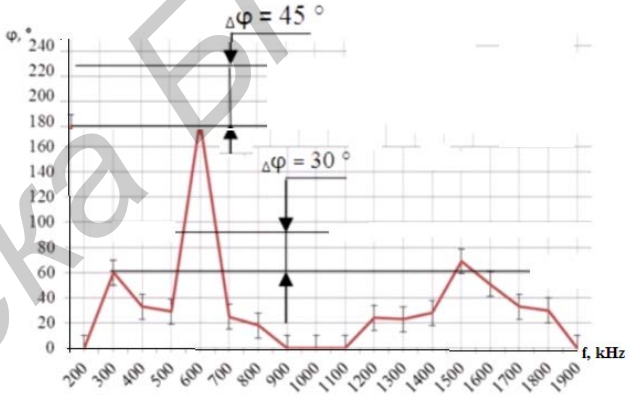

Fig. 5. Phase displacement versus frequency plot.

During the experiments on the laboratory mock-up it has been discovered that at the moment of the fibrin clot formation the most noticeable phase displacement of ultrasound signal in a range from 200 to 2000 kHz appeared at the frequency 600 kHz and is equal to 45°. This value is relevant to the particular measuring system because the resonance of the frequency depends on the cuvette dimensions. Change in phase displacement can be used to monitor the onset of clotting. So on the base of above-described method it is possible to develop an ultrasound coagulation monitoring for the determination of prothrombin time (PT) and activated partial thromboplastin time (APTT). On the basis of undertaken studies and in accordance with the existing laboratory requirements new device should comply with the following requirements: internal mechanism for detecting clot formation, automated time measurement of the clotting endpoint, internal device for maintaining constant 37°C temperature, tests results in a user-friendly display format, ability to transmit data to the PC.

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4. Conclusions

An ultrasound in coagulation monitoring could provide a more accurate measurement in whole blood, improve outcomes and reduce measuring time. It is possible to design ultrasound device for monitoring of coagulation process on the base of ordinary cheap and easily-accessible electronic components. So it could be mass producible and reproducible Combining integrated-circuit technologies with the special microcontroller firmware provides a powerful platform for ultrasound monitoring device development.

During the experiments it was find out that the most suitable frequency of ultrasound probing signal for coagulation monitoring is 600 kHz. So using an oscillator with this frequency it is possible to develop an ultrasound coagulation monitoring device. The possibility of transmission acquired data to the PC in this device would also be of benefit. It is provide an opportunity to create medical expert system on the base of ultrasound coagulation monitoring devices. Medical expert system can accumulate knowledge of the medical specialists and propose the provisional diagnosis immediately after the coagulation test. The medical expert system with ultrasound monitoring device put together in a hardware-software system for coagulation monitoring and therapy. Such systems can be successfully applied in central laboratory testing for coagulation measurements, for determining a potential causes of hemostatic disease and for guiding appropriate therapies.

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