Changes in coagulation and platelet functions in patients with coronary atherosclerosis receiving oral administration of aspirin monitored by the in vitro coagulation dynamic detection sensor

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Abstract

To solve the problem of monitoring the platelet functions in different stages during the arterial thrombosis process in a real-time and dynamic manner, this study aimed to propose a dual-channel in vitro coagulation dynamic whole-process detection sensing system to continuously monitor the changes in coagulation and platelet functions in patients with coronary atherosclerosis receiving oral administration of aspirin. Altogether 20 healthy subjects were randomly selected from the physical examination center. In addition, 20 patients with the initial diagnosis of coronary atherosclerosis who were naive to any antiplatelet drug therapy were also enrolled. After admission, the patients were administered with aspirin at 100 mg/day. For the healthy group, one single venous blood sample was collected from each of them. For the inpatients, they were given corresponding antiplatelet drug therapy, and venous blood samples were collected before administration (0 h), and at 6 h (6 h), 12 h (12 h), 18 h (18 h) and 24 h (24 h) after administration, respectively. Each blood sample was collected into the sodium citrate-containing anticoagulant blood collection tube. After each collection, the in vitro coagulation dynamic detection sensing system was used to detect each indicator. In the dual-channel in vitro coagulation dynamic whole-process detection sensing system developed in this study, one channel served as the experimental channel for patients with coronary atherosclerosis, which adopted the dry coagulation glass bead kit developed in this paper, where the thrombin was directly activated by the glass bead, and it was denoted as the nor channel. The other channel served as the blank control channel for the experimental channel, which adopted the dry coagulation glass bead kit developed in this study and was denoted as the non-channel. The normally distributed measurement data were expressed as means ± SD ($\bar{x} \pm s$) and compared by student's t-test between two groups. Analysis of variance (ANOVA) was applied in comparisons before and after treatment (in the case of homogeneity of variance, the LSD method was applied in analysis; otherwise, the Dunnett's C method was used for analysis). A difference of $P<0.05$ indicated statistical significance. □ Changes in the values of diverse parameters of nor-channel and non-channel in patients with coronary atherosclerosis before administration were different from the normal levels. On the whole, before administration, the activated clotting time (ACT) decreased, clot rate (CR) increased, and platelet factor (PF) increased, suggesting the abnormal platelet function in the blood of patients with coronary atherosclerosis. Meanwhile, after oral administration of aspirin, the changes in nor-channel showed not significant difference, indirectly indicating that the glass bead dry coagulation reagent developed in our previous study was the best coagulation activator. □ Patients with coronary atherosclerosis took aspirin for a long time (100 mg/day), and the maximum dose after admission was 300 mg/day. In these patients, the ACT increased, CR decreased, and PF declined. These changes were not significantly different compared with normal levels, suggesting that the increased dose was acceptable to patients, which might be used to guide clinical treatment. □ For patients with the initial diagnosis of coronary atherosclerosis, the nor-channel and non-channel data were significantly different after oral administration of aspirin (100 mg/day). To be specific, ACT increased, CR decreased, and PF declined. The PF changes were not consistent with our expectation, but they might be ascribed to the small sample size, thus indirectly reflecting that thrombin activation by glass beads was the rapidest and best approach among the platelet activation pathways, which more sensitively and accurately evaluated

the indicators for aspirin efficacy. This paper develops a new method to evaluate the in vitro antiplatelet drug efficacy based on the blood viscoelastic test. This method can evaluate platelet function in a rapider and easier manner; besides, it allows for the use of diverse bedside techniques, thereby displaying great application prospect in medicine and biomedical engineering.

1 Background

In recent years, the incidence rates of cardiovascular diseases (CVDs) such as myocardial infarction (MI), coronary heart disease (CHD) and cerebral thrombosis continuously increase. Therefore, it is necessary to monitor the pharmaceutical effect and adjust the dose of anticoagulant drugs for long-term anti-thrombosis treatment, and to persistently monitor the coagulation status in the patients. Currently, during the development of coagulant drugs and anticoagulant drugs by numerous pharmaceutical enterprises, it is essential to carry out continuous clinical trials and evaluations on the pharmaceutical effect and the dose. The coagulation detector and liquid detection method in clinical medicine have been frequently utilized for these purposes. However, these machines are associated with the drawbacks of large dimension, great manpower and material resource consumption in detection, and production of massive effluents that greatly affect the environment and are expensive in treatment. As a result, these machines are not applicable for the middle and small-sized enterprises due to their high costs. A large number of studies suggest that, there is no test equipment available to closely and timely monitor the platelet function during the different stages of the arterial thrombosis process. The new in vitro coagulation dynamic detection sensing technique proposed in this study has exhibited its important role in clinical coagulation functional tests. In this chapter, by virtue of the high precision and high stability of the above detection technique, we aimed to continuously monitor the changes in coagulation and platelet function in patients with coronary atherosclerosis receiving oral administration of aspirin. Besides, specific kits were utilized to evaluate the efficacy of oral antiplatelet drugs based on the antiplatelet mechanism of anticoagulant drug aspirin, and to guide clinical treatment [1].

At present, cardiovascular and cerebrovascular diseases, including MI, stroke and hematological diseases, are the major causes leading to human death. In China, over 900,000 deaths are induced by cardiovascular and cerebrovascular diseases every year. Research has indicated that, since the appearance in 1899, aspirin has been extensively used to prevent thromboembolism in some patients with cardiovascular and cerebrovascular diseases and coronary atherosclerosis as a kind of antiplatelet drug. Aspirin acts on suppressing cyclooxygenase (COX) that produces prostaglandin (PG). COX can transform arachidonic acid (AA) into the intra-annular peroxide, which exhibits multiple important physiological activities, including inflammation, fever, gastric mucosa protection, renal function regulation and platelet aggregation. Thromboxane (TX), the platelet intra-annular peroxide, can increase the expression of fibrinogen (FG) receptor on the platelet membrane, promote the cross-linking of fibrins between platelets, and form the platelet embolism. In addition, TX also shows synergistic effect with other activated platelet-released products (such as adenosine diphosphate (ADP), FG and coagulation

factor V), to further enhance platelet aggregation. Consequently, the production of these substances decreases after suppressing COX, which is suppressed by activating the platelet pathway.

Generally, for patients with coronary atherosclerosis, antiplatelet drugs should be withdrawn at 7–10 days before surgery to reduce the risk of increased blood loss. However, drug withdrawal will bring a great risk of perioperative thrombosis, especially for patients receiving drug eluting coronary stent. Research discovers that, oral administration of aspirin at different doses can substantially reduce the probability of perioperative thrombus events in patients with coronary atherosclerosis. But there is no available detection technique to evaluate the changes in coagulation and platelet function after oral administration of aspirin, which has become a challenge that troubles numerous cardiologists and drug developers. Therefore, it is urgently needed to develop a detection device to detect the heart and cerebral vessels (especially during the course of administration before and after thrombosis) in a real-time and whole-process manner, and to monitor the real-time changes in platelet function and coagulation condition [2–3].

For major surgical patients receiving antiplatelet drug treatment, platelet function analysis is of crucial importance, so as to maintain the optimal individual balance between perioperative platelet function and suppression (namely, bleeding and thrombosis). The traditional laboratory-based detection is labor-consuming, time-consuming and expensive, which can only be operated and interpreted in those with rich experience and abundant professional knowledge. The different automation technologies based on platelet aggregation can more rapidly and easily evaluate platelet function and allow for the use of multiple bedside techniques. However, they do not provide information on the whole coagulation process or the means to evaluate the efficacy of oral antiplatelet drug therapy. In comparison, the viscoelastic measurement-based new in vitro coagulation detection sensing technique proposed in this paper can monitor and evaluate the therapeutic efficacy of specific antiplatelet drugs like aspirin.

This paper proposed the dual-channel in vitro coagulation dynamic whole-process detection sensing system to continuously monitor the changes in coagulation and platelet function in patients with coronary atherosclerosis receiving oral administration of anticoagulant drug aspirin. In addition, the coagulation dry kits developed in our previous study were utilized to evaluate the therapeutic efficacy of oral antiplatelet drug targeting the antiplatelet mechanism in patients with coronary atherosclerosis, and to guide clinical treatment.

2 Working Principle Of The In Vitro Coagulation Dynamic Detection Sensor And Efficacy Evaluation Mechanism Of The Anticoagulant Drug

2.1 Working principle of the in vitro coagulation dynamic detection sensor

With the progressive development of electromagnetics, sensor technology, micro and nano-fabrication and computer technology, the in vitro coagulation detection technology is under rapid development. This paper investigated the phase change process of the tested blood samples. To this end, the electric coils

were placed into the uniform magnetic field through flexible support to produce the oscillation movement needed for test, so as to examine axial vibration of the connected mechanical probe element on the tested sample surface to determine the viscoelastic characteristics of the tested samples. Moreover, the dynamic changes in blood viscosity and density before and after blood coagulation were explored to construct the correlation curve regarding electric signal changes as a function of clotting time (CT), for evaluating the coagulation. The detailed working principle is presented in Fig. 1.

Under the action of the external excitation signal, the coils in the flexible support-based in vitro coagulation detection sensor designed in this paper vibrated in the uniform magnetic field produced between the magnetic magnet and the permanent magnet, which drove the axial vibration movement of the mechanical probe element. As a result, the connected disposal probe also conducted vibration movement at the same frequency in the tested sample. The monitoring of probe displacement and velocity by the sensor was non-linear relative to the coil driving frequency. Generally, obvious peak appeared at the position with natural resonance frequency, and such resonant frequency represented the changes induced by the changes in viscoelastic characteristics of the tested sample. By adopting this method, the viscosity change rule of the tested sample was indirectly detected, then this rule was then received by the coils and the uniform magnetic field, and finally converted into the viscosity data of the tested sample needed in the experiment [4–5].

2.2 Efficacy evaluation mechanism of anticoagulant agent

Aspirin is a classical anticoagulant drug, which has been used as a therapeutic agent for several hundred years. Research suggests that aspirin at different doses can be applied in multiple medical diseases, its clinical efficacy and suppression on platelet aggregation are related to the ability of subsequent mediator release. Platelets will aggregate after contacting multiple stimulants (such as arachidonic acid (AA), epinephrine (E), collagen and platelet activation factor (PAF). Therefore, it is generally suggested that aspirin suppresses aggregate and mediator release through the suppressive effect. Figure 2 exhibits the schematic diagram of the antiplatelet mechanisms of aspirin.

It is suggested in research that, aspirin can suppress AA, induce collagen and PAF. However, in many such methods, only narrow ranges of aspirin dose and stimulant concentration are used, and aspirin may also partially suppress platelet aggregation and mediator release induced by other products released by the ex vivo platelets. Due to the lack of such detection means, the role of aspirin in platelet aggregation induced by the products released by the activated platelets remains unclear. At present, plenty of clinical practice discovers that, aspirin achieves favorable outcome in the prevention and treatment of arterial thrombosis, and large-scale clinical experiments verify that aspirin significantly reduces the morbidity and morality rates in patients with coronary atherosclerosis. As shown in Fig. 2, aspirin acted on COX, under the action of platelet phopholipaseA2 (PLA2), the platelet membrane phospholipid released AA. Then, the presence of COX resulted in the production of TX by the intra-annular peroxide, and TX played an important role in the platelet aggregation and activation process. Therefore, this paper monitored the changes in coagulation and platelet function after oral administration of aspirin to judge the effect of drug-induced suppression on COX, thus evaluating the therapeutic efficacy of aspirin [6].

3 Materials And Methods For Anticoagulant Drug Efficacy Evaluation Experiment

3.1 Objects of study

Altogether 20 healthy subjects were randomly selected from the physical examination center of the project cooperation hospital from January 2018 to December 2019; meanwhile, 40 patients with coronary atherosclerosis were also randomly selected from the Cardiology Department, including 20 with initial diagnosis of coronary atherosclerosis and 20 confirmed patients admitted in the hospital. The detailed information is presented in Table 1.

Table 1
Detailed information of the objects of study

Name	Parameter	Note	Exclusion criteria
Number of the enrolled healthy subjects	n = 20	All the selected participants had no past history of smoking, drinking within the past one year, and no history of antiplatelet drug administration.	1. Those who even took non-steroid anti-inflammatory drugs (NSAIDs)
Sex ratio of healthy subjects	Male:female ratio = 2:1		2. Those with abnormal platelet function;
Average age of healthy subjects	40–50 years		3. Those with abnormal hypertension;
Number of enrolled patients	n = 40	All the admitted patients had clinical symptoms such as chest pain, chest distress that aggravated in activities, and grade II and above cardiac function.	4. Those with complicated arrhythmia;
Sex ratio of patients	Male:female ratio = 1:1		5. Those with congenital heart disease myocarditis;
Average age of patients	45–60 years		6. Those with abnormal heart-liver-kidney functions.

3.2 Experimental materials

The materials and machines needed in this experiment are displayed in Fig. 3. The detailed specifications and sources are shown in Table 2.

Table 2
Materials and device parameters and specifications needed in the experiment

Number	Material and device names	Sources
1	In vitro coagulation dynamic detection sensing system	Developed in this study
2	Dry coagulation glass bead kit	Previous research results of our group
3	Dry coagulation kit	Previous research results of our group
4	2 ml EDTAK2 anticoagulant blood collection tube	Nanjing Baden Medical Co., Ltd
5	1.5 ml centrifuge tube	Beijing Saibaoao Technology Co., Ltd
6	2 ml EP tube	Bensheng (Tianjin) Health Science and Technology Co., Ltd
7	50 μL and 1000 μL pipettes	Ebend (Germany)
8	Hettich ROTOFIX32A centrifugal machine	Dexiang Technology (Agency) Co., Ltd (Germany)
9	SZ-93A pure water distiller	Shanghai Chenlian Biotechnology Development Co., Ltd

3.3 Experimental methods

1)Experimental design

In the in vitro coagulation dynamic whole-process detector developed in this study, the dual-channel design was adopted, which realized the simultaneous detection by two channels and allowed for both inter-group and intra-group comparisons, showing certain innovativeness. In this experiment, one channel was selected as the experimental channel for patients with coronary atherosclerosis, and the dry coagulation glass bead kit developed in our previous study was adopted, where the thrombin was directly activated by glass bead, and the channel was denoted as the nor-channel. The other channel was selected as the blank control channel for the experimental channel, where the dry coagulation kit developed in our previous study was adopted, and the channel was denoted as the non-channel. The participant grouping was as follows [7].

Healthy group: 20 healthy subjects randomly selected from the physical examination center;

Patient group 1: 20 confirmed inpatients with coronary atherosclerosis who took antiplatelet drug aspirin (100 mg/day) for a long time, and the mode of administration after admission was aspirin at 300 mg/day.

Patient group 2: 20 newly diagnosed patients with coronary atherosclerosis who never received antiplatelet drug treatment, and the mode of administration after admission was aspirin at 100 mg/day.

2)Experimental methods

For the healthy group, one single venous blood sample was collected from each of subject. For the inpatients, they were given corresponding antiplatelet drug therapy, and venous blood samples were collected before administration (0 h), and at 6 h (6 h), 12 h (12 h), 18 h (18 h) and 24 h (24 h) after administration, respectively. Each blood sample was collected into the sodium citrate-containing anticoagulant blood collection tube. After each collection, the in vitro coagulation dynamic detection sensing system was used to detect each indicator.

The normally distributed measurement data were expressed as means

$$\text{means} \pm \text{SD}\ (\bar{x} \pm s)$$

and compared by student's t-test between two groups. Analysis of variance (ANOVA) was applied in comparisons before and after treatment (in the case of homogeneity of variance, the LSD method was applied in analysis; otherwise, the Dunntt's C method was used for analysis). A difference of $P<0.05$ indicated statistical significance

4 Results And Analysis Of Anticoagulant Drug Efficacy Evaluation Experiment

4.1 Experimental results

The normal reference value ranges of the in vitro coagulation dynamic detection sensing system prepared in this paper for different kits are shown in Fig. 4.

Test results of healthy group are presented in Fig. 5

For patients in patient group 1, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the ACT values. Then, the values at corresponding time points were compared with those in healthy group. As a result, there were not significant differences in the results ($P > 0.05$).

For patients in patient group 1, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the CR values. Then, the values at corresponding time points were compared with those in healthy group. The results revealed no significant differences in the results ($P > 0.05$).

For patients in patient group 1, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the PF values.

Later, the values at corresponding time points were compared with those in healthy group. The results suggested no significant differences in the results ($P > 0.05$).

Non-channel test results of patient group 1 at different time points are exhibited in Fig. 9–11.

The blood samples collected from patient group 1 at 0, 6, 12, 18 and 24 h were analyzed by the non-channel of the in vitro coagulation dynamic detection sensing system to obtain ACT value. Then, the values at corresponding time points were compared with those in healthy group. As a result, there was significant difference in ACT value at 0 h compared with control group ($P < 0.05$), while no significant differences were observed in ACT value at other time points ($P > 0.05$).

The blood samples collected from patient group 1 at 0, 6, 12, 18 and 24 h were analyzed by the non-channel of the in vitro coagulation dynamic detection sensing system to obtain CR value. Thereafter, the values at corresponding time points were compared with those in healthy group. As a result, there were significant differences in CR value at 0 and 24 h compared with control group ($P < 0.05$), while no significant differences were observed in CR value at other time points ($P > 0.05$).

The blood samples collected from patient group 1 at 0, 6, 12, 18 and 24 h were analyzed by the non-channel of the in vitro coagulation dynamic detection sensing system to obtain PF value. Thereafter, the values at corresponding time points were compared with those in healthy group. As a result, there was no significant difference in PF value at 0 h compared with control group ($P > 0.05$), whereas significant differences were observed in PF value at the remaining time points ($P < 0.05$).

2)Nor-channel test results of patient group 2 at different time points are exhibited in Fig. 12–14.

For patients in patient group 2, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the ACT values. Later, the values at corresponding time points were compared with those in healthy group. As a result, there were not significant differences in the results ($P > 0.05$).

For patients in patient group 2, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the CR values. Then, the values at corresponding time points were compared with those in healthy group. The results revealed no significant differences in the results ($P > 0.05$).

For patients in patient group 2, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the nor-channel of the in vitro coagulation dynamic detection sensing system to obtain the PF values. Later, the values at corresponding time points were compared with those in healthy group. The results suggested no significant differences in the results ($P > 0.05$).

Non-channel test results of patient group 2 at different time points are exhibited in Fig. 15–17.

For patients in patient group 2, their blood samples collected at 0, 6, 12, 18 and 24 h were analyzed using the non-channel of the in vitro coagulation dynamic detection sensing system to obtain the ACT values. Later, the values at corresponding time points were compared with those in healthy group. As a result, there was significant difference in ACT value at 24 h compared with control group ($P < 0.05$), while no significant differences were observed in ACT value at other time points ($P > 0.05$).

The blood samples collected from patient group 2 at 0, 6, 12, 18 and 24 h were analyzed by the non-channel of the in vitro coagulation dynamic detection sensing system to obtain CR value. Thereafter, the values at corresponding time points were compared with those in healthy group. As a result, there were significant differences in CR value at 0 and 24 h compared with control group ($P < 0.05$), while no significant differences were observed in CR value at other time points ($P > 0.05$).

The blood samples collected from patient group 2 at 0, 6, 12, 18 and 24 h were analyzed by the non-channel of the in vitro coagulation dynamic detection sensing system to obtain PF value. Later, the values at corresponding time points were compared with those in healthy group. The results revealed significant differences in PF value at all time points ($P < 0.05$).

Changes in the values of diverse parameters of patient groups 1 and 2 before and after administration are presented in Fig. 18–21.

4.2 Evaluation and analysis

For patient group 1, the values of diverse nor-channel parameters at corresponding time points were compared with the normal values. For ACT, it was observed from the test results that, the ACT values obtained by the non-channel of the in vitro coagulation dynamic detection sensing system before and after administration at diverse time points showed a shortening trend, but there was no significant difference when comparing them with normal values ($P > 0.05$). These results suggested that, long-term oral administration of aspirin (100 mg/day) was necessary for patients with coronary atherosclerosis, which greatly suppressed the platelet activation pathway, further demonstrating that ACT values were maintained within the normal range even in the presence of exogenous coagulation pathway. With regard to CR, the reduction at 0 h revealed no significant difference ($P = 0.089$), while the values at other time points significantly decreased, indicating that the exogenous coagulation pathway was involved during the coagulation activation process after oral administration of aspirin, which promoted the increased contents of fibrin in blood. Such result suggested that oral administration of aspirin reduced the fibrin content produced by the endogenous coagulation pathway, but more healthy subjects should be enrolled into the control group to compare whether excessive antiplatelet activity existed in such result. In terms of PF, the PF values obtained by the non-channel of the in vitro coagulation dynamic detection sensing system displayed a decreasing trend at each time point. The PF values at corresponding time points were compared with the normal values, and there was no significant difference in the results ($P > 0.05$), indicating that long-term oral administration of aspirin (100 mg/day) led to certain changes in platelet function of patients with coronary atherosclerosis activated by the exogenous coagulation pathway at

each time point. But such as variation range was within the normal level, further demonstrating that the current dose for patients was suitable, with no need for adjustment [8].

The values of diverse non-channel parameters in patient group 1 at corresponding time points were compared with the normal values. The kit used in the non-channel was the ordinary coagulation dry kit with no addition of glass beads; as a result, there was only blood coagulation shear force. For ACT, in patients taking aspirin for a long time, aspirin partially suppressed the activation of the platelet pathway, but the postoperative coagulation function was active, and ACT values were significantly shortened ($P = 0.027$). Such result sufficiently demonstrated that the daily dose of aspirin no longer satisfied the postoperative needs of patients, and it was necessary to appropriately increase the drug dose. At 6 h after oral administration of aspirin, the ACT values were slightly higher than those before administration and showed a shortening trend compared with the normal value. With regard to CR: the changes in CR value at 0 and 24 h were significantly different ($Ps < 0.05$), while those at the other time points showed no significant difference ($P > 0.05$). As revealed by such result, oral administration of aspirin at daily dose suppressed platelet activation for a short time in patients with coronary atherosclerosis, which indicated the insufficient routine dose and further suggested the importance of drug dose. As for PF, the PF value at 0 h was at normal level, but with the increase in drug dose, the PF values at the remaining time points significantly decreased. However, it was no enough to analyze the risk of postoperative bleeding from this indicator alone, and the conclusions should be drawn based on clinical results [9].

The values of diverse nor-channel parameters in patient group 1 at corresponding time points were compared with values in healthy group. The results suggested that, the ACT and CR values obtained by the nor-channel of the in vitro coagulation dynamic detection sensing system showed a decreasing trend at each time point. Compared with before administration, the values after administration were extended. However, there were no significant differences in the values at corresponding time points when compared with those from healthy group ($P > 0.05$). As suggested by these results, for patients with coronary atherosclerosis, oral administration of aspirin (100 mg/day) slightly extended ACT at each time point after administration, and the levels of fibrin produced by this pathway decreased accordingly. After oral administration, the PF values obtained by the nor-channel of the in vitro coagulation dynamic detection sensing system showed a decreasing trend at each time point. Values at corresponding time points were compared with those from healthy group, and all results were significantly different ($P < 0.05$). Based on this result, for patients with coronary atherosclerosis, oral administration of aspirin (100 mg/day) reduced platelet activation via the exogenous coagulation pathway at each time point, but such variation range was normal, and no significant decrease was observed [10].

The values of diverse nor-channel parameters in patient group 1 at corresponding time points were compared with values in healthy group. In patient group 1, the ACT values of blood samples collected at 0, 6, 12, 18 and 24 h were analyzed by the analyzer and compared with values in the healthy group. The results suggested that the ACT value at 0 h displayed significant difference ($P < 0.05$), while those at the other time points did not show significant differences ($P > 0.05$). Thereafter, CR values were compared with those in healthy group. The results indicated that changes in CR value at 0 and 24 h exhibited

significant differences ($P < 0.05$), while those at other time points revealed no significant difference ($P > 0.05$). Further, PF values were compared with those in healthy group, and it was found that changes in PF values were significantly different except for that at 0 h ($P < 0.05$). According to the above results, in the absence of exogenous coagulation mechanism, the comparisons of diverse non-channel parameters in patients with those in healthy group after increasing the oral administration dose demonstrated the presence or absence of excessive antiplatelet activity, and the parameter range might be determined if there was excessive antiplatelet activity [11].

The values of diverse nor-channel parameters in patient group 2 at corresponding time points were compared with values in healthy group. As for ACT, for patients with the initial diagnosis of coronary atherosclerosis who never received antiplatelet drug therapy, a certain amount of platelets were activated in their blood. The ACT value at 0 h obtained by the nor-channel of the in vitro coagulation dynamic detection sensing system was apparently shortened compared with normal value. But after administration of antiplatelet drug aspirin, the ACT values within 6 h were extended, and the efficacy of aspirin was preliminarily manifested at this moment. But the ACT values were still lower than the normal values, and there were no significant differences ($P > 0.05$). Subsequently, with the metabolism in the patient body, the ACT value at 12 h was shortened, suggesting the efficacy of aspirin was gradually weakened. The ACT values were higher than those before administration, but they were still shortened compared with the normal values. This phenomenon indicated that the dose of oral aspirin might be enhanced in the patients, but more healthy subjects should be enrolled for comparison to examine whether excessive antiplatelet activity existed in such result. For CR, its value at 0 h obtained by the nor-channel of the in vitro coagulation dynamic detection sensing system was apparently higher than that of the normal value ($P = 0.687$). This result demonstrated that oral administration of aspirin notably reduced the fibrin content produced by the endogenous coagulation pathway; therefore, the fibrin content produced by that pathway was higher than the normal value. The CR value detected at 6 h was still higher than the normal value, but it showed an apparently decreasing trend, with no significant difference ($P = 0.126$). Based on the above result, after oral administration of aspirin, the fibrin content in blood produced by the exogenous coagulation pathway was higher than the normal value; afterwards, with the metabolism in patient body, the CR value detected at 12 h was higher than the normal value ($P = 0.256$). This indicated that oral administration of aspirin alone no longer thoroughly suppressed the platelet activation function, and there was a risk of ischemia. Consequently, the anticoagulant drug should be increased or replaced to assist in treatment. With regard to PF, the changes in PF values at all time points were not significantly different. This might be mainly explained by the following three reasons based on clinical analysis. First of all, the sample size set to evaluate the anticoagulant drug efficacy by the new in vitro coagulation dynamic detection sensing technique was small, which was insufficient to reflect the overall variation trend of each parameter. Secondly, although the ACT and CR values showed corresponding variation trends after oral administration of aspirin, they were limited to reflect the activated platelet time parameter, but not attained the ideal requirement of suppressing platelet activation. According to the coagulation mechanism, thrombin was the most potent activation pathway to activate platelet function during the entire coagulation process. Nonetheless, it was analyzed that

platelets began to be activated by thrombin before the measurement of PF values, and PF values showed an increasing trend, yet this was not the truth. Therefore, the aspirin efficacy should be further analyzed when such condition occurs during interventional treatment.

In patient group 2, the values of diverse non-channel parameters at corresponding time points were compared with the normal values. The kit used in the non-channel was the ordinary coagulation dry kit with no addition of glass beads; as a result, there was only blood coagulation shear force. For ACT, in patients who never took antiplatelet drug, there was a certain amount of activated platelets in the blood. From the perspective of data, the ACT value at 0 h was apparently shortened compared with normal value ($P = 0.000$). At 6–18 h, the ACT values showed an increasing trend because of drug action after admission, but they were significantly different from the normal values. At 24 h, with drug metabolism, the platelet function gradually decreased, and the ACT value showed a decreasing trend ($P = 0.011$). Based on the above results, it was speculated that for patients with initial diagnosis of coronary atherosclerosis who received oral administration of aspirin at 100 mg/day after admission, the ACT was slightly extended, but was not at the normal level. With regard to CR, CR showed a similar variation trend to ACT. In the absence of any inducer, the CR values in patients with initial diagnosis of coronary atherosclerosis at 0 h were apparently higher than the normal value ($P = 0.000$), exhibiting certain endogenous coagulation function. After oral administration of antiplatelet drug aspirin at a certain dose, the CR values at 6–18 h slightly decreased but were higher than the normal level. With the drug metabolism, the platelet activation at 24 h showed a decreasing trend. Thus, it was further speculated that, the drug dose should be increased to maximally reduce platelet aggregation and prevent sudden disorders like thrombosis. In terms of PF, the PF values in patients before and after oral administration of aspirin were higher than the normal value, which were opposite to the expected results. Combined with clinical analysis, such results might be explained by two aspects. First of all, the sample size in this experiment was small, which did not objectively reflect the overall variation trend. Secondly, for patients with coronary atherosclerosis, the platelet function in blood decreased, and the PF value increased before and after administration because platelets were activated, suggesting that it might be necessary to increase the drug dose or replace the drug.

In patient group 2, the values of diverse nor-channel parameters at corresponding time points were compared with the values in healthy group. Compared with values at 0 h, the ACT values at 6, 12, 18 and 24 h (namely, after oral administration of aspirin in patients with coronary atherosclerosis) elevated, while the CR values decreased, and the differences were all statistically significant ($P < 0.05$). The above findings suggested that the exogenous coagulation pathway was involved in the coagulation mechanism. As analyzed previously, this pathway extended the ACT and reduced fibrin content, but the PF value showed an increasing trend. After analysis, platelets begun to be activated by thrombin before the measurement of PF values, so the measured PF values showed an increasing trend, but this was not the truth. Therefore, the aspirin efficacy should be further analyzed when such condition occurs during the interventional treatment. In addition, the changes in PF value might be related to the platelet activation by thrombin.

The values of diverse non-channel parameters in patient group 2 at corresponding time points were compared with those in healthy group. The blood samples collected from patients in patient group 2 at 0, 6, 12, 18 and 24 h were analyzed by the analyzer. According to our results, the ACT value at 24 h showed significant difference, while those at other time points did not show any significant difference ($P > 0.05$). With regard to CR, there were significant differences at 0 and 24 h ($P < 0.05$), while those at other time points did not show any significant difference ($P > 0.05$). Moreover, changes in PF values at all time points were significantly different ($P < 0.05$). The dry coagulation kit without any inducer was used in this experiment; therefore, our results truly reflected the change process after the drug acted on the blood, thus reflecting the antiplatelet drug efficacy, which might provide reference for platelet functional evaluation and guide clinical treatment.

5 Conclusions

This paper proposes a dual-channel in vitro coagulation dynamic whole-process detection sensing system to continuously monitor the changes in coagulation and platelet function in patients with coronary atherosclerosis receiving oral administration of aspirin. In addition, we adopt the coagulation glass bead dry kits developed in our previous study and the ordinary coagulation dry kit as the in vitro coagulation inducers to evaluate the efficacy of oral antiplatelet drug therapy targeting the antiplatelet mechanism in patients with coronary atherosclerosis and to guide clinical treatment. The experimental conclusions are shown below.

1)The changes in values of nor-channel and non-channel parameters in patients with coronary atherosclerosis before administration are different from the normal levels. To be specific, the ACT values decrease, CR values increase and PF value increase before administration, suggesting the abnormal platelet function in the blood of patients with coronary atherosclerosis. In addition, after oral administration of aspirin, the nor-channel parameters show no significant differences, which indirectly reflect that the glass bead dry coagulation reagent developed in our previous study is the optimal coagulation activator.

2)For patients with coronary atherosclerosis who take aspirin (100 mg/day) for a long time, their doses increase to 300 mg/day after admission. After administration, ACT values increase, CR values decrease, and PF value decrease, but these changes are not significantly different from the normal levels, suggesting that the dose increases can be accepted by the patients, which can guide clinical treatment.

3)For patients with the initial diagnosis of coronary atherosclerosis, the nor-channel and non-channel data are significantly different after the oral administration of aspirin (100 mg/day). To be specific, ACT values increase, CR values decrease, and PF values decrease. The PF values are inconsistent with expected experimental results, which may be related to the small experimental sample size. The above results indirectly reflect that activation of thrombin by glass beads is the rapidest and best approach among the platelet activation pathways, which can more sensitively and accurately evaluate diverse indicators for aspirin efficacy.

4)The experimental data suggest that, the in vitro coagulation whole-process dynamic detector developed in this paper has opened a new path for antiplatelet drug efficacy evaluation. With the technological revolution, the online detection of solidification phenomenon in more physiological and biological reactions can be tried in the future. Moreover, our developed detection system can also be used in the emerging fields such as fungal concentration detection and viral pneumonia detection.

Declarations

Acknowledgement

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Compliance with Ethical Standards:

Funding: This study was funded by Jilin Scientific and Technological Development Program (grant number 20200404180YY), Jilin Scientific and Technological Development Program (grant number 20200602050ZP).

Conflict of Interest: Author Qimeng Chen declares that he has no conflict of interest, Author Zibo Li declares that she has no conflict of interest, Author Ziqi Liu declares that he has no conflict of interest. Author Qiong Wu declares that she has no conflict of interest. Author Zhe Wang declares that she has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figures

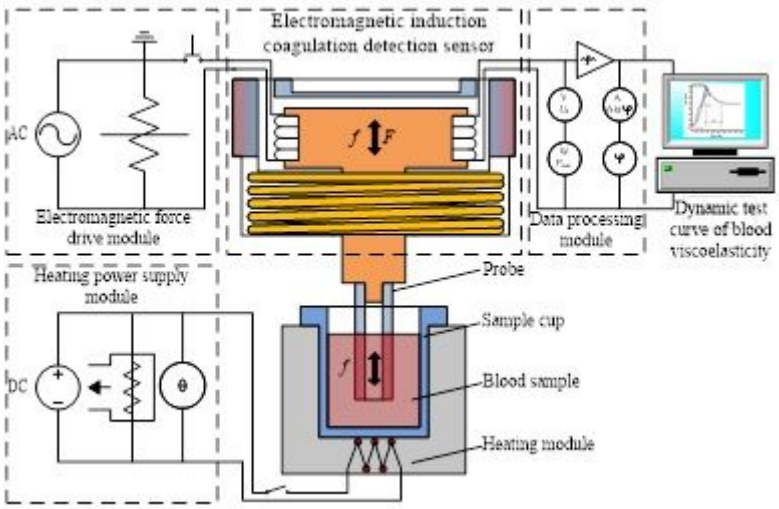


Figure 1

Schematic diagram of the sensor

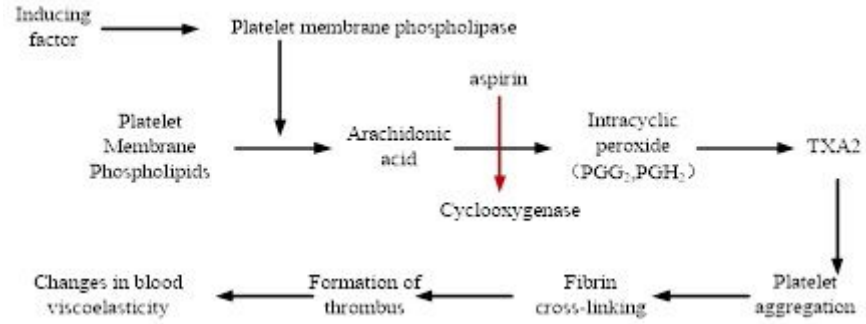


Figure 2

Schematic diagram of the antiplatelet mechanism of aspirin

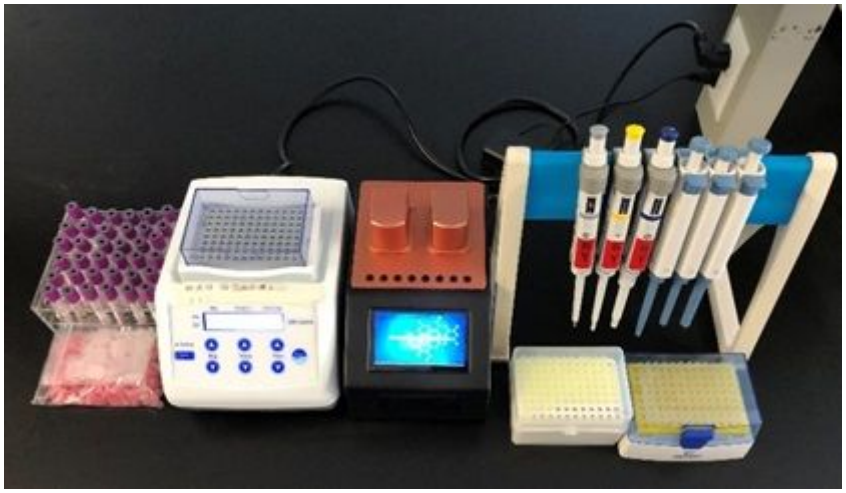


Figure 3

Main materials and devices used in the experiment

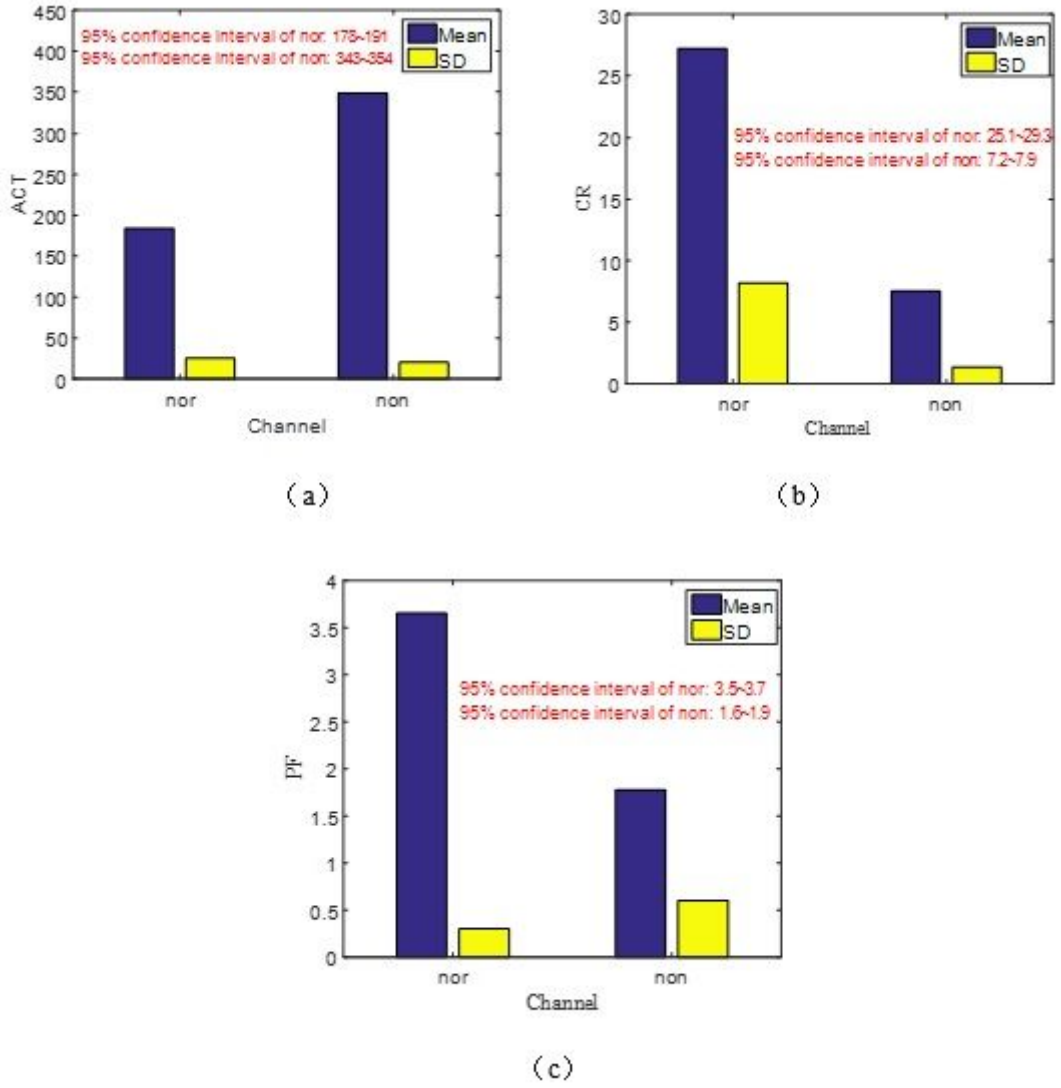


Figure 4

Major parameter reference ranges of the dual-channel in vitro coagulation dynamic detection sensing system (a) ACT reference range; (b) CR reference range; (c) PF reference range

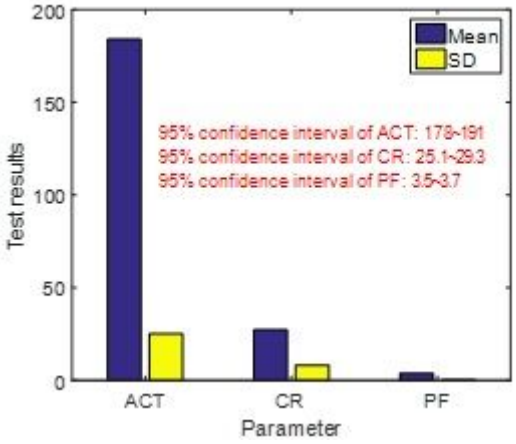
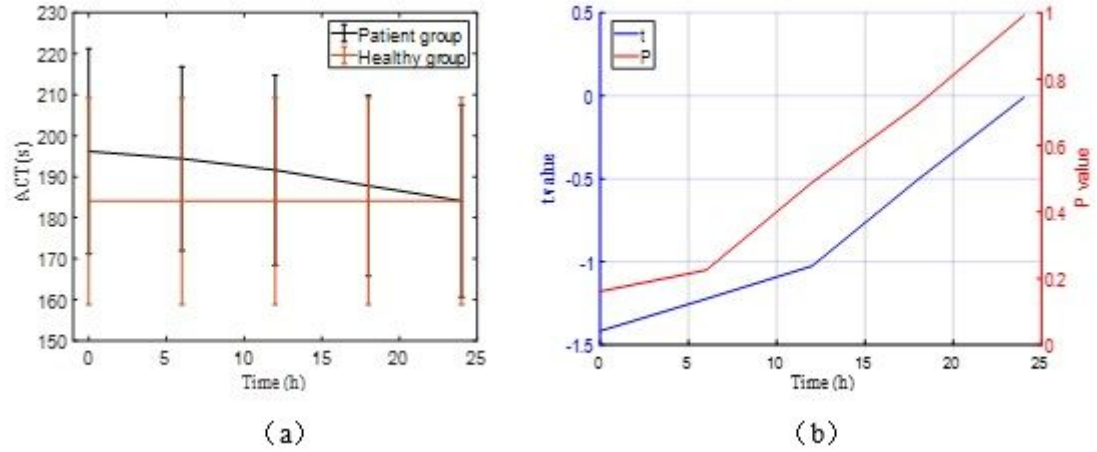


Figure 5

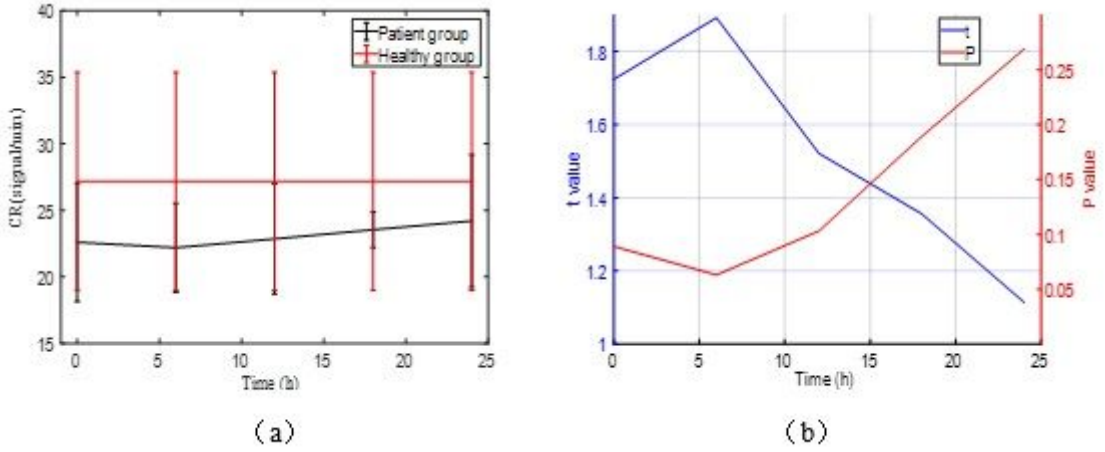
Test results of healthy group



（a） （b）

Figure 6

nor-channel ACT experimental results of patient group 1 at different time points (a) ACT experimental results at different time points; (b) t-values and P-values



（a） （b）

Figure 7

nor-channel CR experimental results of patient group 1 at different time points (a) CR experimental results at different time points; (b) t-values and P-values

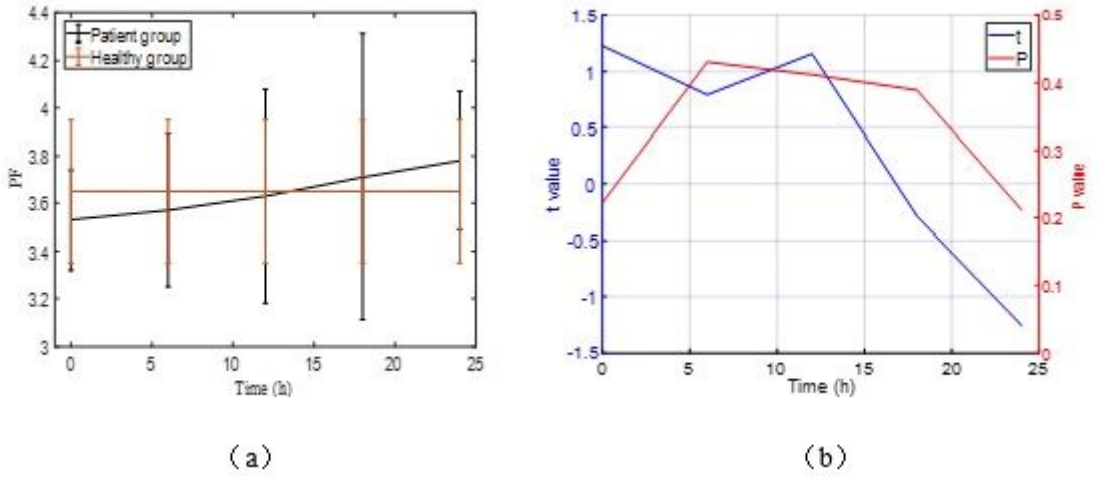


Figure 8

nor-channel PF experimental results of patient group 1 at different time points (a) PF experimental results at different time points; (b) t-values and P-values

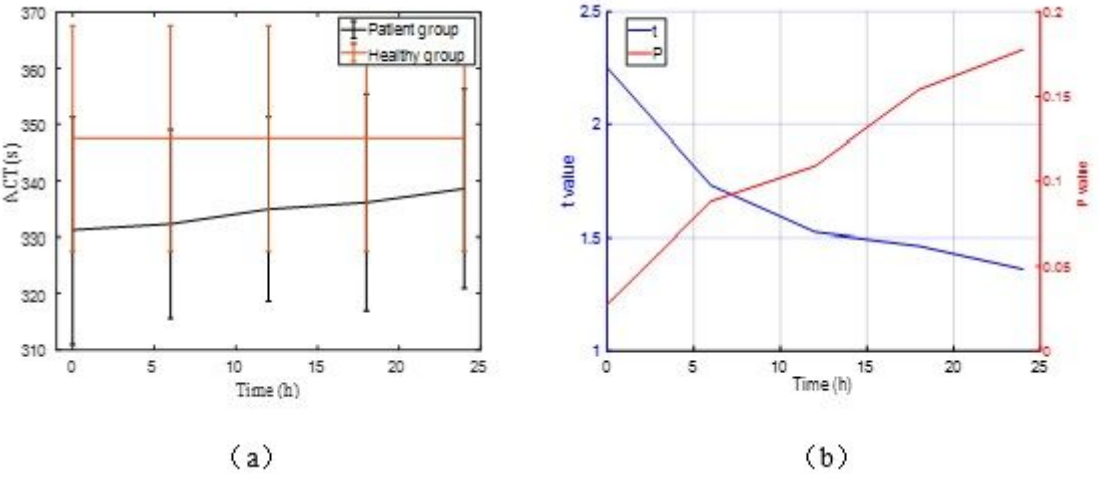


Figure 9

non-channel ACT experimental results of patient group 1 at different time points (a ACT experimental results at different time points; (b) t-values and P-values

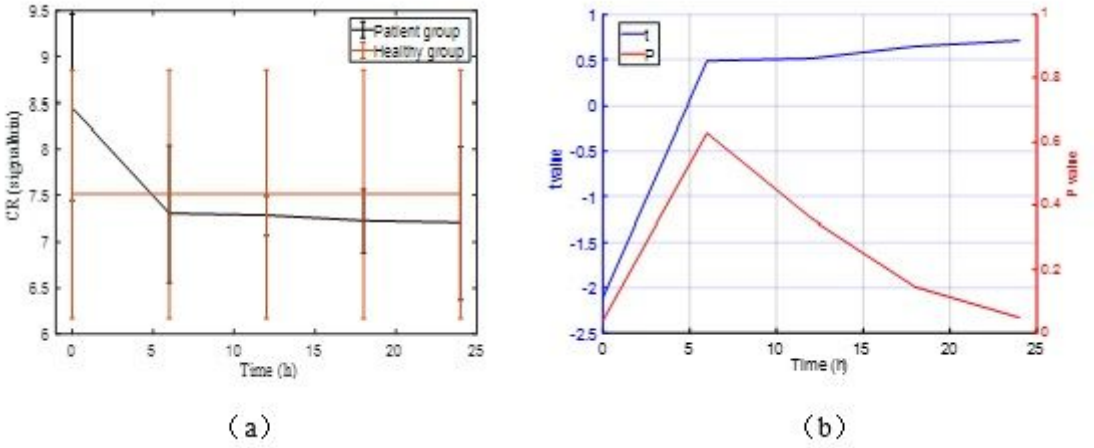


Figure 10

non-channel CR experimental results of patient group 1 at different time points (a) ACT experimental results at different time points; (b) t-values and P-values

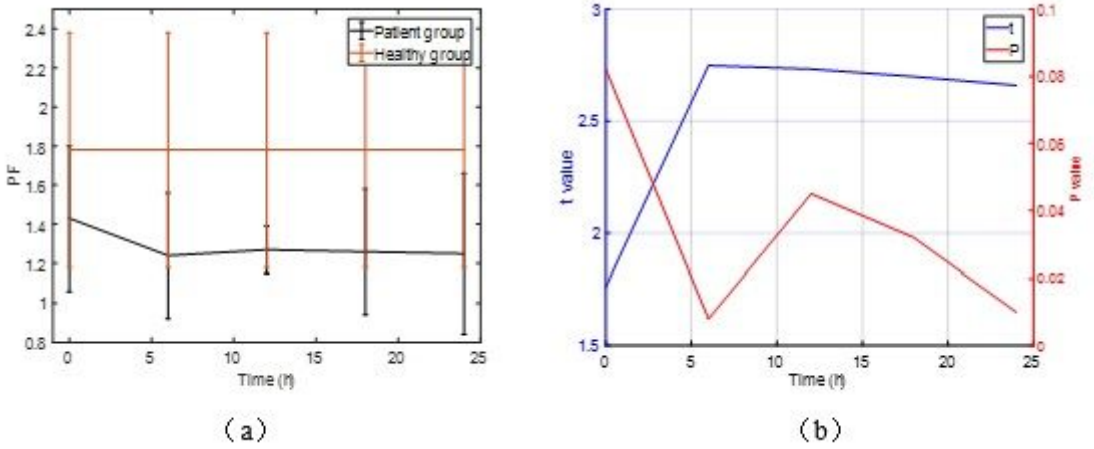


Figure 11

non-channel PF experimental results of patient group 1 at different time points (a) PF experimental results at different time points; (b) t-values and P-values

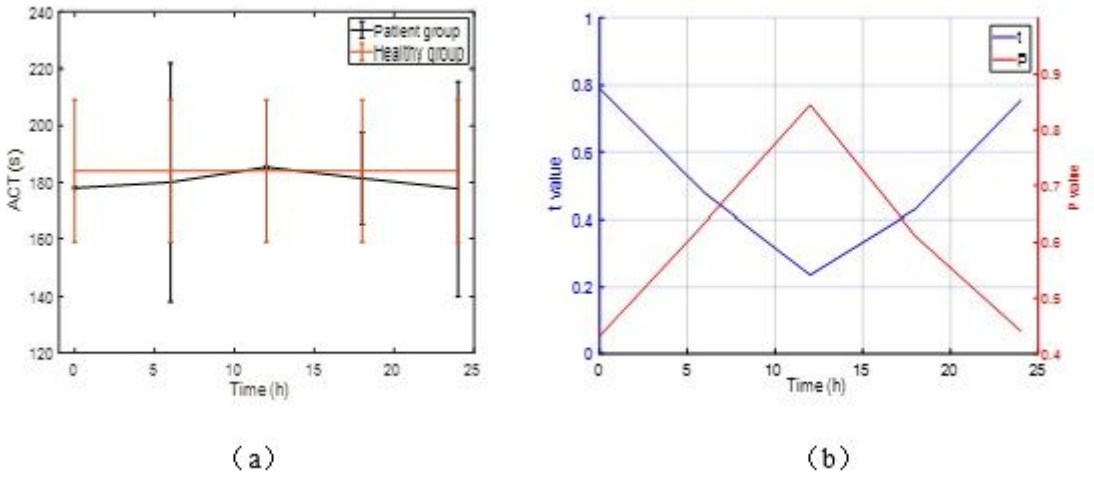


Figure 12

nor-channel ACT experimental results of patient group 2 at different time points (b) ACT experimental results at different time points; (b) t-values and P-values

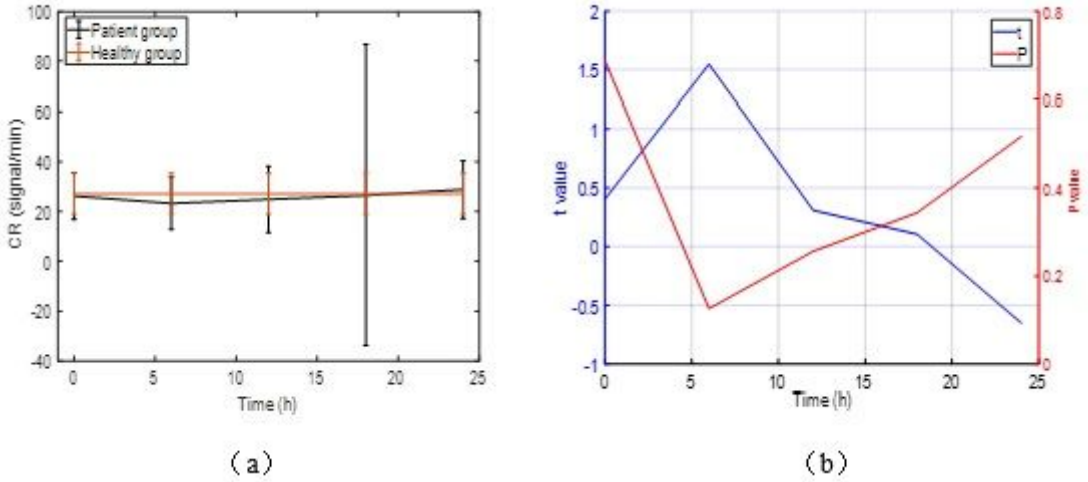


Figure 13

nor-channel CR experimental results of patient group 2 at different time points (a) CR experimental results at different time points; (b) t-values and P-values

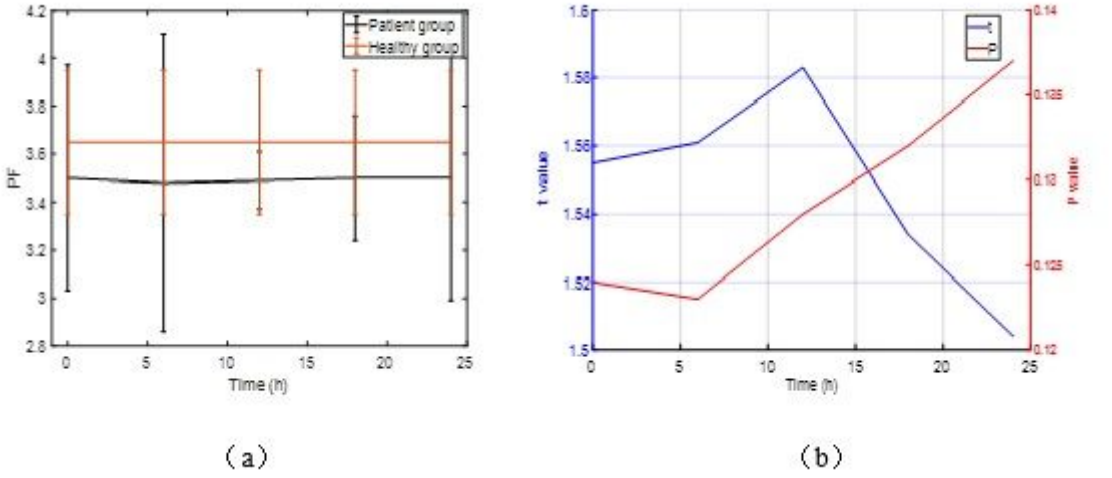


Figure 14

nor-channel PF experimental results of patient group 2 at different time points (a) PF experimental results at different time points; (b) t-values and P-values

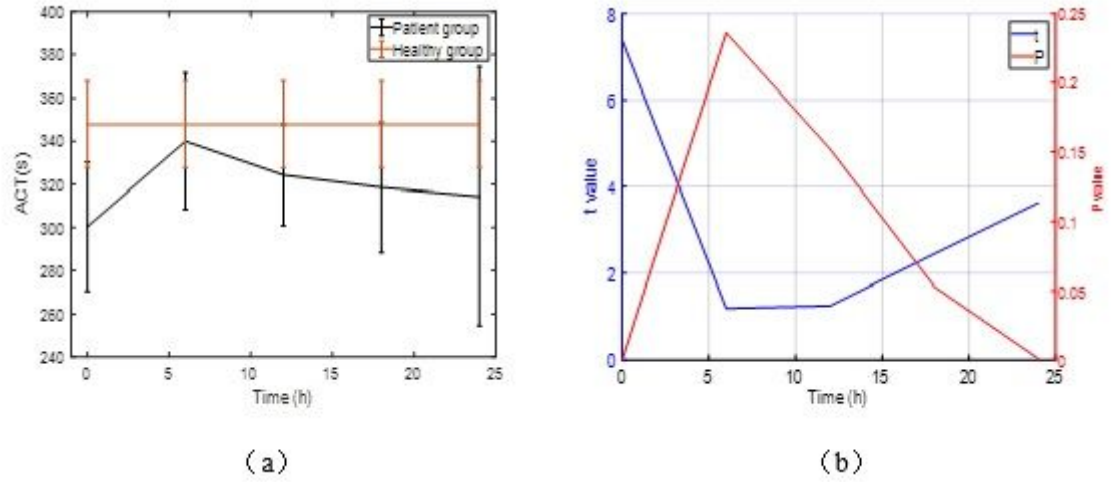


Figure 15

non-channel ACT experimental results of patient group 2 at different time points (a) ACT experimental results at different time points; (b) t-values and P-values

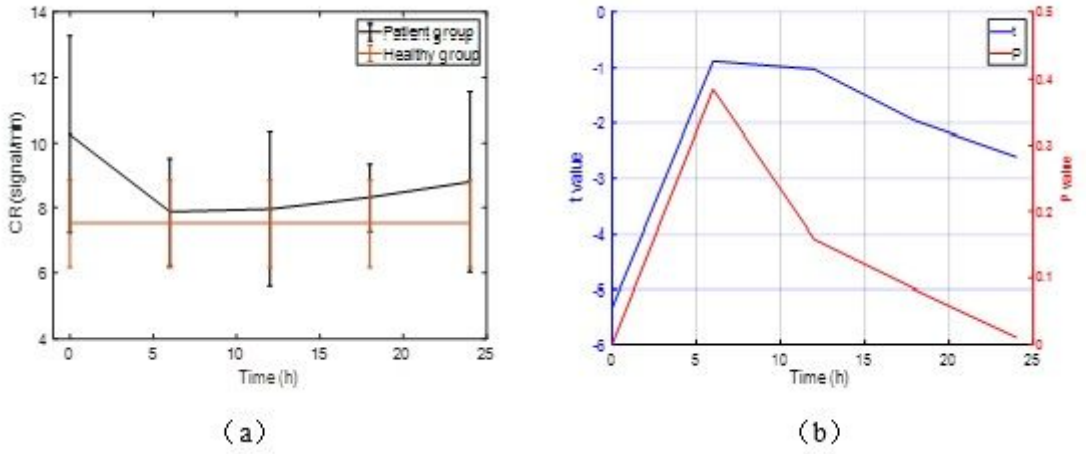


Figure 16

non-channel CR experimental results of patient group 2 at different time points (a) CR experimental results at different time points; (b) t-values and P-values

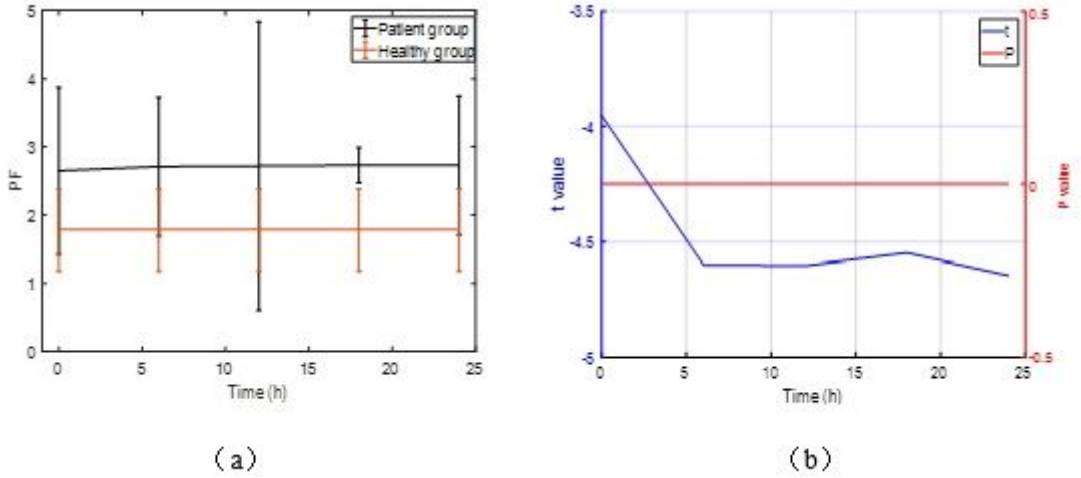


Figure 17

non-channel PF experimental results of patient group 2 at different time points (a) PF experimental results at different time points; (b) t-values and P-values

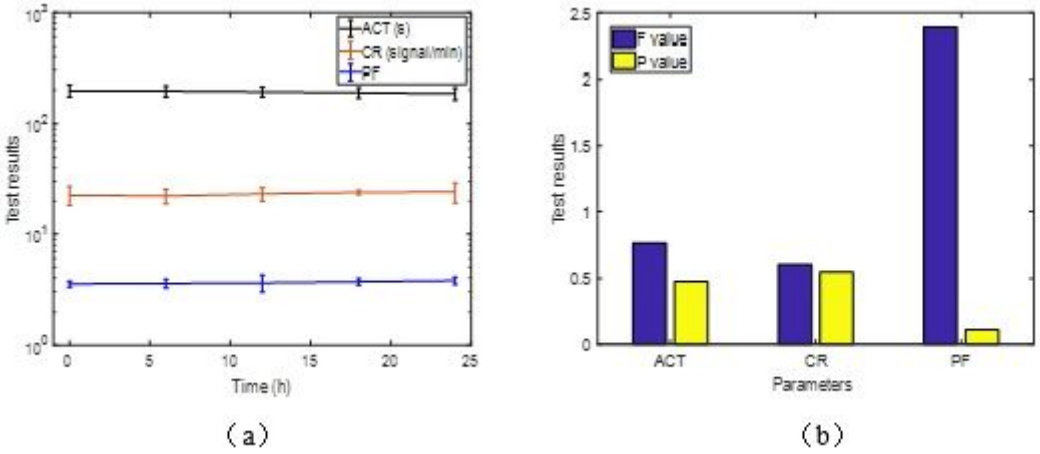


Figure 18

nor-channel experimental results of patient group 1 before and after administration (a) Nor-channel experimental results at different time points; (b) F-values and P-values

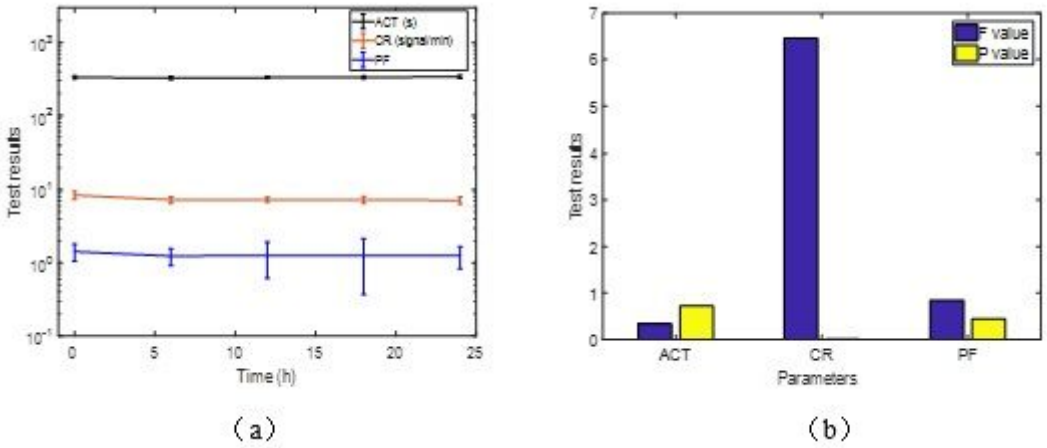


Figure 19

non-channel experimental results of patient group 1 before and after administration (a) Non-channel experimental results at different time points; (b) F-values and P-values

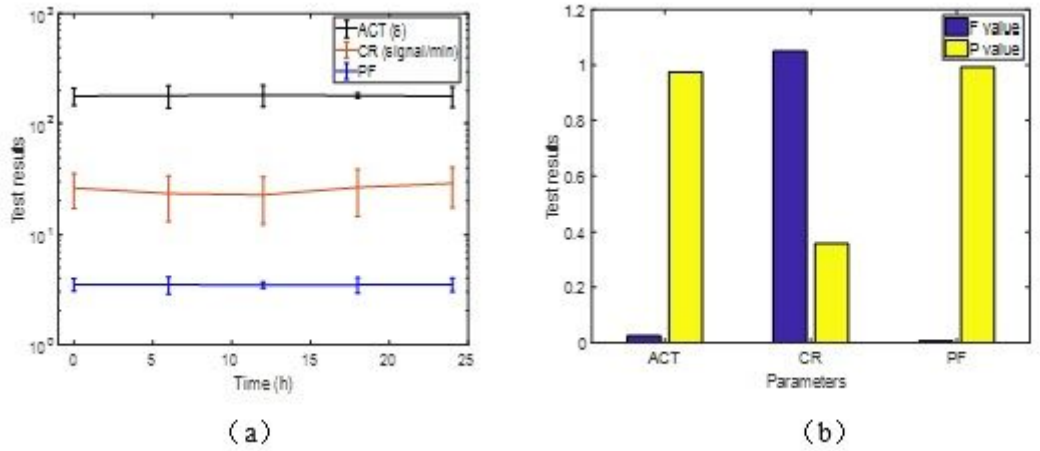
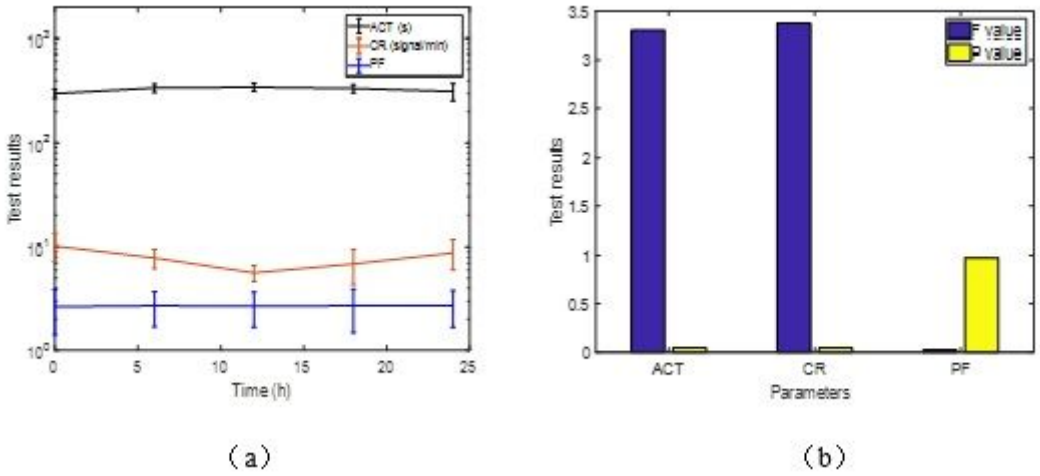


Figure 20

nor-channel experimental results of patient group 2 before and after administration (a) Nor-channel experimental results at different time points; (b) F-values and P-values



(a) (b)

Figure 21

non-channel experimental results of patient group 2 before and after administration (a) Non-channel experimental results at different time points; (b) F-values and P-values