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Miniature Mass Spectrometry for Point-of-Care Testing the GPIIb/IIIa Inhibitor Tirofiban during Perioperative Period of Percutaneous Coronary Intervention

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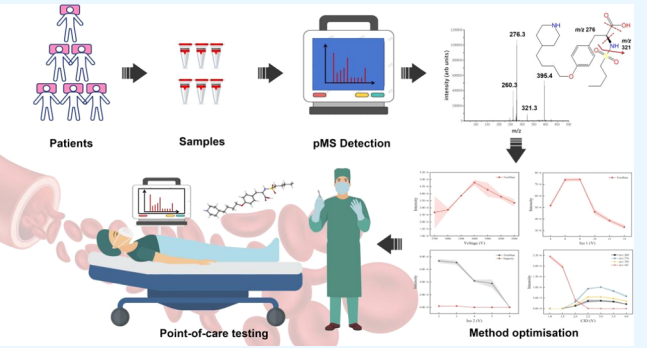
ABSTRACT: Precise administration of tirofiban must be carefully considered to achieve the best treatment efficacy and maximize safety for patients. Herein, a paper spray ionization (PSI) linear ion trap (LIT) portable mass spectrometer (pMS) based point-of-care testing (POCT) technique was developed for on-site sampling, clinical testing, and immediate analysis of tirofiban blood drug concentrations. The results showed that tirofiban formed a significant and stable parent ion peak at m/z 441.3 by MS1 full scan in positive ion mode, which fragmented into product ions at m/z 395.4, m/z 321.3, m/z 276.3, and m/z 260.3 through collision-induced dissociation (CID) in MS/MS. To improve ion response, the parameters were optimized to the voltages of ionization 3600 V, ion isolation 1 (ISO1) 8 V, ion isolation 2 (ISO2) 2 V, and collision-induced dissociation (CID) 3 V. This method was validated, and the limit of detection (LOD) and limit of quantification (LOQ) were found to be 10.1 and 33.7 $\mu g \cdot L^{-1}$, respectively. For precision, it had the relative standard deviation (RSD) of interday precision of 4.8 to 6.7% and the RSD of intraday precision of 7.8 to 8.3%. The recovery of the method ranged from 87.5 to 93.4%. Although matrix effects in blood samples had some inhibitory effects on the target signal formation, the method compensated for part of the matrix effects by establishing a matrix-matched calibration curve, which exhibited good linearity with a $R2$ of 0.9987. Finally, the method was applied to the detection of tirofiban in clinically collected blood samples. Out of 12 samples, ten had tirofiban concentrations between 35.4 and 72.1 $\mu g \cdot L^{-1}$ while the remaining two were below the LOQ. The method needs further optimization and validation in the future to improve its sensitivity and stability.



1. INTRODUCTION

Acute myocardial infarction (AMI) is the most severe type of coronary heart disease, characterized by sudden onset, high risk, rapid progression, and high incidence of in-hospital and out-of-hospital mortality.[1] The pathogenesis of AMI involves plaque rupture in the coronary arteries, leading to platelet activation and aggregation, resulting in thrombus formation and subsequent occlusion of blood vessels.[2] This leads to myocardial ischemia and the development of acute myocardial ischemic syndrome. Therefore, antiplatelet therapy plays a crucial role in the treatment of AMI. Percutaneous coronary intervention (PCI) is the preferred method for treating AMI, and preoperative use of antiplatelet drugs is necessary to inhibit platelet aggregation.[3] This not only improves myocardial reperfusion capability but also has important implications in preventing recurrent myocardial infarction.[4]

Antiplatelet therapy is a key measure in interventional treatment that has been confirmed and widely applied in clinical practice. Tirofiban, a nonpeptide platelet receptor GPIIb/IIIa highly selective antagonist, exhibits an antiplatelet aggregation effect in patients with acute coronary syndrome (unstable angina, non-ST-segment elevated myocardial infarction, ST-segment elevated myocardial infarction) and those undergoing coronary intervention.[5,6] Continuous intravenous infusion makes thrombus formation less likely, with an inhibition rate of platelet aggregation reaching 90% after 30 min, and the inhibitory effect is dose-dependent.[7] However, this is accompanied by an increased occurrence of bleeding complications or severe bleeding tendencies, with an 8-fold increase in the incidence of thrombocytopenia compared to

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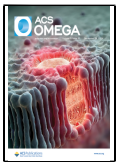

patients receiving dual antiplatelet therapy.[8] Due to variations in the severity of acute myocardial infarction and individual physiological differences among patients, the dosage and infusion rate of tirofiban are crucial. Excessive administration may lead to intracranial hemorrhage, intraperitoneal bleeding, pericardial bleeding, increased occurrence of nausea, fever, headache, rash, and occult blood in urine and feces.[9,10] For the assessment of the good efficacy and safety of high-dose tirofiban, it is urgently required to establish accurate and efficient real-time monitoring technologies for determining blood drug concentrations of tirofiban in acute myocardial infarction patients before and after interventional treatment.

Point-of-care testing (POCT) refers to clinical testing conducted at the patient's bedside, where samples are immediately analyzed, eliminating the complex processing procedures required in laboratory testing and providing rapid results.[11] The concept of POCT was introduced to enable testing of blood, gases, electrolytes, and coagulation near the patient's care site or nearby, transforming diagnostic testing from the traditional centralized laboratory environment to a paradigm closer to the patient's environment.[12] POCT diagnostic systems adhere to the standards defined by the World Health Organization (WHO), providing rapid results for the testing targets, enabling users to make timely adjustments, and improving quality of life.[13] POCT offers several advantages including short processing time, ease of use, portability, minimal sample consumption, and the ability to achieve real-time monitoring. Currently, leading biotechnology companies are engaged in the development of novel POCT diagnostic systems, continually advancing and expanding their capabilities. The commercial market is becoming increasingly mature. However, there remains a gap in the monitoring of drug concentrations, such as tirofiban, in the blood.

Mass spectrometry (MS) is an important analytical technique in the laboratory, which separates sample components by ionization and provides accurate identification based on their mass-to-charge ratios. Wiseman et al. reported a desorption electrospray ionization (DESI) coupled with linear ion trap MS capable of directly recording the spatial intensity distribution of drugs from tissue sections of the brain, lungs, kidneys, and testes without prior chemical processing.[14] Manicke et al. developed a high-throughput quantitative analysis technique for drugs in biological samples based on a 96-sample array and DESI-MS.[15] However, traditional MS is limited by its large size, high energy consumption, and stringent operational environment requirements, making it suitable only for laboratory use.[16] In contrast, pMS, with their mobility and capability for rapid on-site detection, offer a promising solution for clinical POCT applications.[17−20] Furthermore, by integration of ambient mass spectrometry (AMS) with pMS, barriers to in situ MS applications can be overcome. For example, by combining the simplicity of paper spray ionization (PSI) with the pMS, MS analysis can transition from the laboratory to real clinical environments, enabling MS-based POCT.[21] As the demand for pMS continues to increase, it is of great significance to conduct research on related technologies in this field.

This study aims to address the monitoring needs of tirofiban medication during the interventional treatment of AMI patients. It proposes the development of a POCT technique for tirofiban blood concentration analysis, which can be performed on-site, near the patient, using a pMS.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents. The chemical standard tirofiban was bought from Aladdin Biochemical Technology Co., LTD (Shanghai, China). Methanol and acetonitrile were chromatographically pure and were supplied by Merck (Darmstadt, Germany). All of the experimental water was purified by a Millipore-Q (Millipore, Billerica, MA) purification system. All other chemicals and solvents, unless otherwise specified, were guaranteed reagent grade and purchased from Sigma-Aldrich Chemical Co. LLC. (St. Louis, MO).

2.2. Paper Spray Ionization pMS Instrument and Condition. The Mini π mass spectrometer was purchased from PURSPEC Technologies Inc. and was used for the development of a POCT method for tirofiban. The core components of this instrument include a cartridge inlet, a discontinuous atmospheric pressure interface, paper spray ionization (PSI), and a linear ion trap (LIT) mass analyzer. The dimensions of the instrument are 57 cm (length) × 24 cm (width) × 32 cm (height), with a total weight of less than 22 kg. It operates at a power of 40 W, with a peak power consumption of less than 80 W. The Mini π mass spectrometer is capable of analyzing and detecting various compounds in both positive and negative ion modes. It offers scanning modes such as full scan, product ion scan, etc., with a scanning range of m/z 50 to 1000. During the sample analysis process, compounds are ionized by PSI and instantaneously introduced as ions by a pulse voltage, after which ion manipulation and mass analysis occur during the remaining scan cycle. The pMS parameters were voltage 3600 V, ISO1 8 V, ISO2 2 V, and CID 3 V. The instrument is controlled, and data acquisition is performed using the SpecMS software developed by PURSPEC Technologies Inc., Beijing, China.

2.3. Human Blood Samples. AMI patients admitted to the Department of Cardiovascular of Sanmen People's Hospital from June 2023 to September 2023 were included in the study. The inclusion criteria are as follows: patients must be between 18 and 75 years of age, regardless of gender. They should meet the diagnostic criteria for STEMI (Guidelines for the Diagnosis and Treatment of Acute ST-segment Elevation Myocardial Infarction, 2019), with symptoms starting within 12 h. Patients must agree to undergo PCI, have heart function classified as Killip class ≤ III, and have no contraindications for PCI. The exclusion criteria are as follows: patients with allergies to tirofiban, aspirin, or other medications; those with a history of intracranial hemorrhage; individuals who have had a stroke or transient ischemic attack within the past six months; patients who have been on oral anticoagulants in the past 30 days and cannot discontinue them; those who have received clopidogrel or ticagrelor from other manufacturers or formulations due to specific indications; patients who have undergone or are planned to undergo thrombolytic therapy within 24 h before or after enrollment; individuals with a history of major surgery within 30 days before the intervention or those planned for major surgery during the study; patients with a history of gastrointestinal bleeding within the past six months or severe bleeding disorders or bleeding tendencies; individuals with severe liver or kidney dysfunction; and those who refuse to participate in the study. The study included a total of 12 cases, with 6 males and 6 females, and a mean age of 60.4 ± 9.2 years. Tirofiban exhibits platelet aggregation inhibitory effects within 5 min of intravenous injection, with

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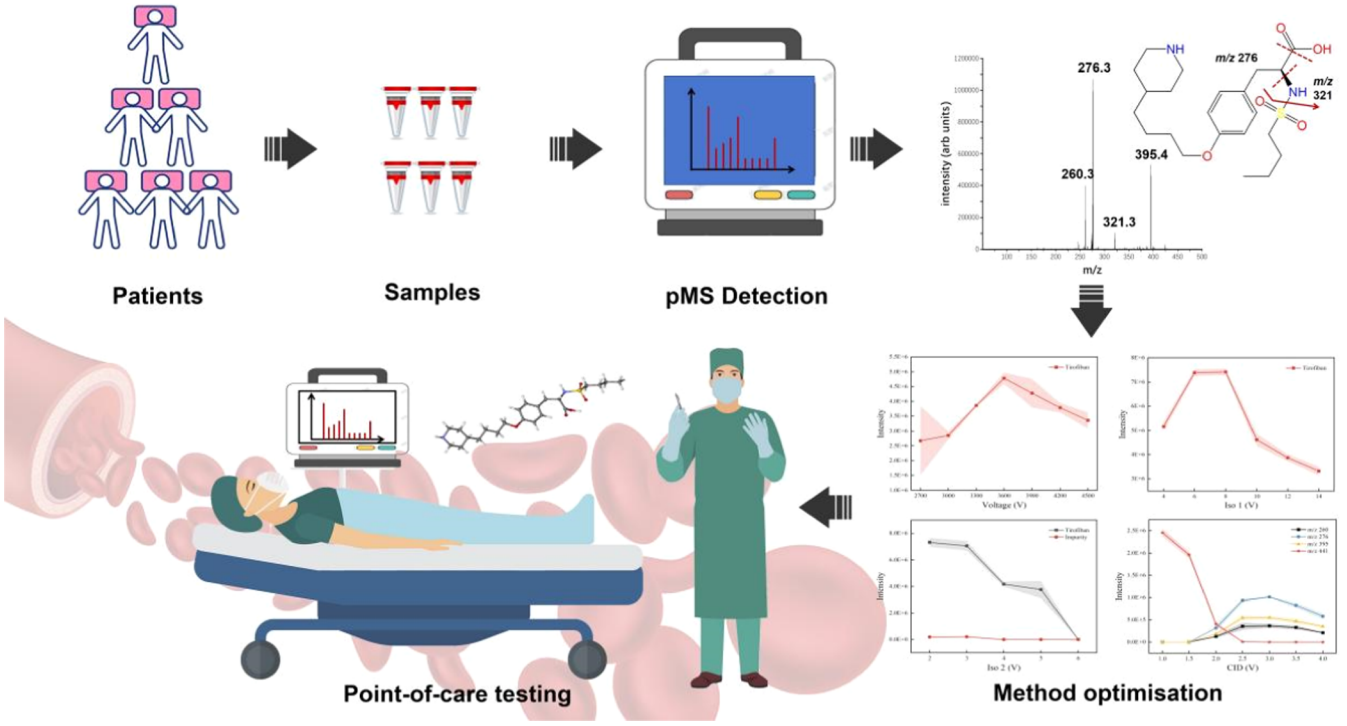

Figure 1. A scheme of the technical process of this study.

a peak time of less than 30 min and steady-state blood concentration achieved within 1 h. Therefore, 10 min after intracoronary or intravenous injection of tirofiban, 1 mL of peripheral venous blood was collected. Performance tests were conducted on 6 healthy volunteers, with 3 males and 3 females, and a mean age of 58.6 ± 10.4 years. All of the blood samples were collected and stored at −80 °C.

This study was approved by the Ethics Committee of Sanmen People's Hospital (No. 2023-015), and informed consent was obtained from all participants, explaining the purpose and procedures of blood sample collection for measuring tirofiban and the use of the data. All studies were conducted in accordance with the principles outlined in the Declaration of Helsinki.

2.4. Sample Preparation. A stock solution of tirofiban was prepared with methanol at a concentration of mg·mL^{-1}. For method validation, a series of working solutions of tirofiban were prepared by diluting the stock solution with methanol. Matrix-matched samples were also prepared by spiking the blank blood samples with different volumes of stock solution. Each sample of 10 μL was deposited onto the paper substrate in the cartridge, which was subsequently placed in the cartridge dryer for 40 s to for a dried sample spot. For analysis, 50 μL methanol was used as a solvent to elute the analyte from the matrix followed by the application of a high voltage to the paper substrate for ionization.

2.5. Data Analysis and Statistics. The mean value, SD, and level of significance were calculated and analyzed using Microsoft Excel 2007. The identities of tirofiban were confirmed by the comparison of the MS1 and MS2 spectra with the corresponding reference substances. The technical process of this study is shown in Figure 1.

3. RESULTS AND DISCUSSION

3.1. Ionization and Fragmentation of Tirofiban. First, the ionization capabilities of tirofiban were compared in positive and negative ion modes. A concentration of 50 μg·L^{-1} was used for injection, and the intensity and stability of the parent ion of tirofiban were observed. The results (Figure 2A) showed that tirofiban formed a significant and stable parent ion peak at m/z 441.3, with an intensity of 6.4e4 in positive ion mode. However, the parent ion of tirofiban was not observed in the negative ion mode. Therefore, subsequent research on tirofiban was conducted in the positive ion mode. In the spectrum of the full scan, there were several impurity peaks competing with the parent ion of tirofiban, and the target peak at m/z 441.3 could not be confirmed as pure tirofiban, as it could be overlapping with impurities instead of tirofiban. Thus, the spectrum of full scan was not suitable for qualitative and quantitative analysis of tirofiban.

Further analysis was performed using product ion scans to study tirofiban. Following the fragmentation of the parent ion at m/z = 441.3, a number of abundant product ions were produced. As illustrated in Figure 2B, the principal product ion peaks included m/z 395.4, m/z 321.3, m/z 276.3, and m/z 260.3, among others. Due to ion interference, quantification could not be achieved using the parent ion m/z 441 in MS1. Therefore, the construction of multiple reaction monitoring (MRM) transitions based on the product ions observed in MS2 can enhance the selectivity and accuracy of the quantification. The probable fragmentation pathway of tirofiban is shown in Figure 3. The product ion at m/z 395.4 may correspond to the loss of one formic acid molecule from the parent ion, while the product ion at m/z 321.3 is likely generated by the breakage of the S−N bond in the parent ion, resulting in the loss of residue C4H8O2S. The product ion at m/z 276.3 is the strongest signal in the MS2 mass spectrum of tirofiban, but its structure is not well-defined. It is possible that

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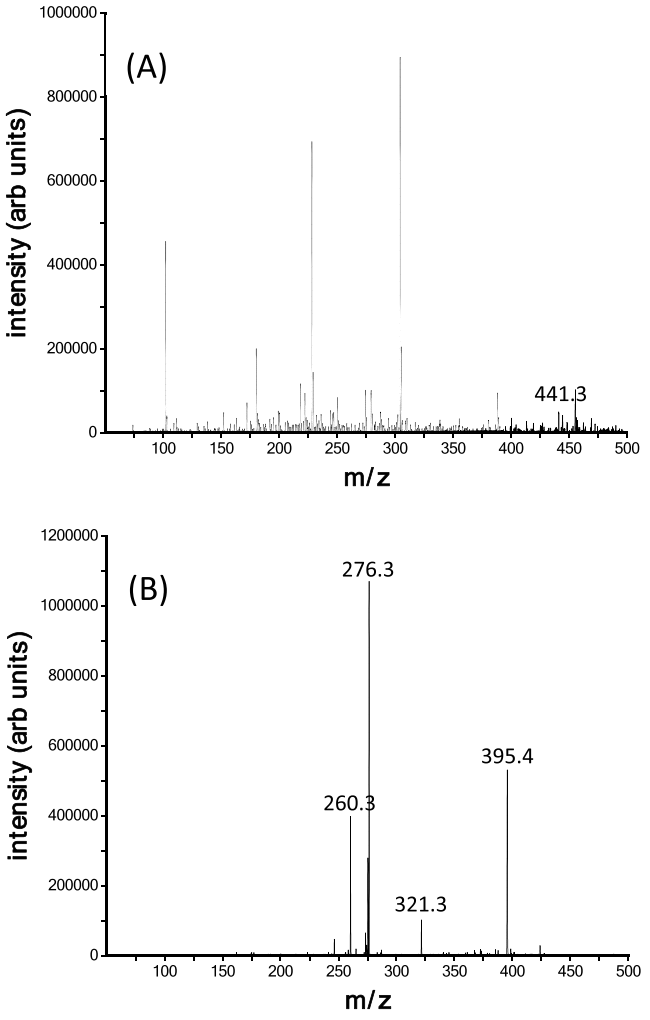

Figure 2. (A) pMS1 of the tirofiban standard and (B) pMS2 of the tirofiban standard (m/z 441) in positive ion mode.

it is obtained by a further loss of NO2 from the product ion at m/z 321. Next to the product ion at m/z 276, a product ion at m/z 275 was observed, which is postulated to be derived from the loss of one formic acid molecule from the product ion at m/z 321. Further loss of an amino group from this product ion would yield the product ion at m/z = 260. The fragmentation mechanisms and chemical structures of product ions mentioned above are theoretical speculations. Since the focus of this study is on the quantitative analysis of tirofiban, further verification of these fragmentation mechanisms was not pursued. The results are summarized in Table 1.

Table 1. Ion Information and pMS Parameters for Tirofiban

compound	parent ion, m/z	product ion, m/z	voltage (V)	ISO1 (V)	ISO2 (V)	CID (V)
tirofiban	441.3	395.4; 321.3; 276.3; 260.3	3600	8	2	3

3.2. Optimization of pMS Parameters. The ionization of tirofiban is influenced by multiple parameters, including voltage, ISO1, ISO2, and CID. This study aimed to optimize these parameters to improve the signal response of the parent ion and the product ions, and the results are shown in Figure 4. First, the voltage conditions were optimized within the range of 2700−4500 V. As the voltage increased, the signal of tirofiban parent ion (m/z 441) gradually enhanced and reached a maximum value of 4.8e6, with a coefficient of variation (CV) of 4.1% at 3600 V. Further increase in voltage led to a gradual decrease in the signal of the parent ion. Subsequently, the parameter ISO1 was optimized. The signal of the tirofiban parent ion exhibited a similar trend of increasing and then decreasing within the range of 4−14 V for ISO1. When ISO1 increased from 4 to 8 V, the signal intensity of the tirofiban parent ion peaked at 7.4e6, with a CV of 1.9%. Subsequently, the signal gradually decreased with the increase in ISO1. ISO2 is another important parameter affecting the signal of the tirofiban parent ion, showing a negative correlation with its intensity. As the ISO2 value increased,

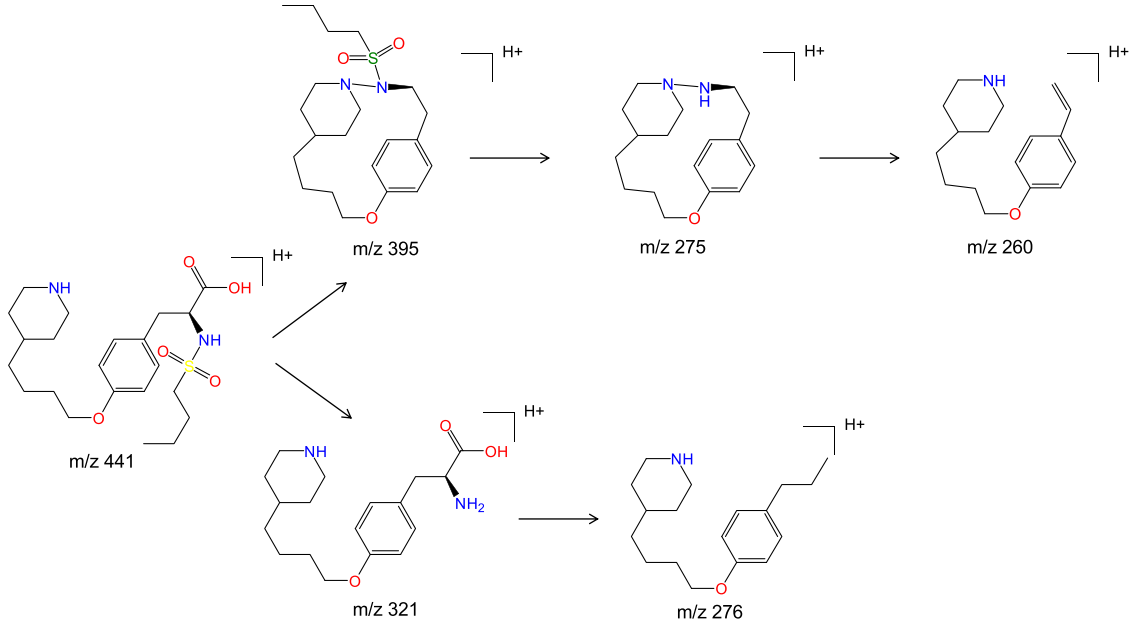

Figure 3. Fragmentation pathway of tirofiban.

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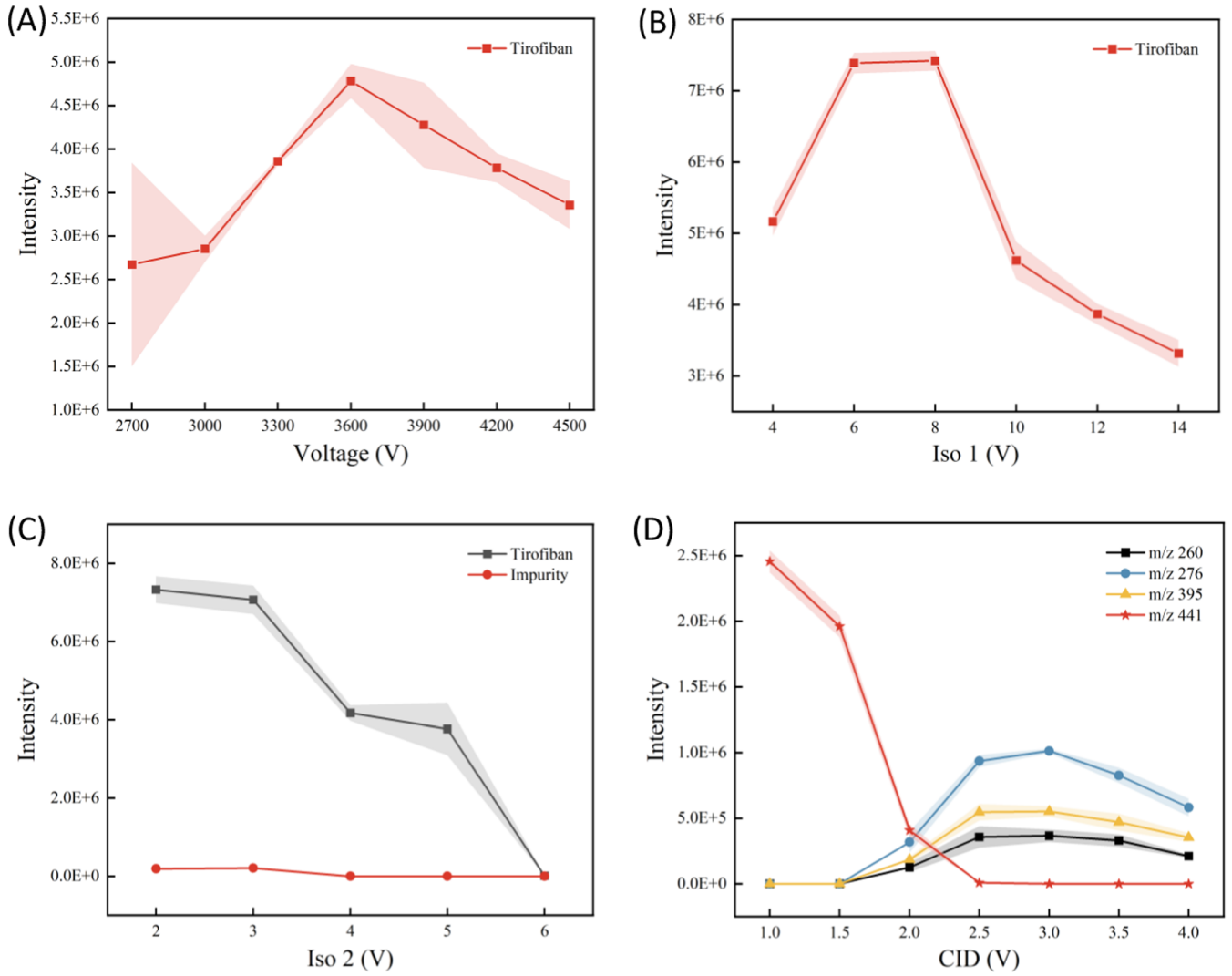

Figure 4. Optimization of the most important parameters for fast analyzing tirofiban by pMS-POCT, including the (A) voltage of ionization, (B) ISO1, (C) ISO2, and (D) CID.

Table 2. Method Validation in Terms of Linearity, Sensitivity, Precision, and Recovery for pMS-Based POCT Detection of Tirofiban

	linearity	sensitivity $\mu g \cdot L^{-1}$		precision RSD		
spiked level ($\mu g \cdot L^{-1}$)	*R*2	LOD	LOQ	intraday	interday	recovery, %
50	$y = 309.19x + 5733.5$	10.1	33.7	4.3	8.1	87.5
250	$R2 = 0.9987$			5.6	7.8	92.1
1000				4.8	8.3	93.4

the signal intensity of the parent ion gradually weakened. When initially set at 2 V, the signal already reached its strongest value of 7.3e6, with a CV of 4.7%. CID, an important energy parameter affecting the fragmentation of the parent ion, needed to be further optimized to enhance the signal intensity of the product ions. The CID optimization range was 1−4 V. When CID was set at 1 or 1.5 V, only the parent ion was observed without any product ions, indicating insufficient collision energy. At CID of 2 V, three tirofiban product ions appeared in the spectrum: *m*/*z* 260 (1.3e5), *m*/*z* 276 (3.2e5), and *m*/*z* 395 (1.8e5). As CID further increased, the signal of the parent ion gradually decreased. When CID was set at 2.5 V, the signal of the parent ion became very weak, while the signals of the product ions were enhanced. At CID of 3 V, the parent ion was no longer observed, and all three product ions reached their peak intensities: *m*/*z* 260 (3.7e5), *m*/*z* 276 (1.0e6), and *m*/*z* 395 (5e5). With further increases in CID, the intensities of the product ions gradually decreased. In conclusion, the optimized ionization parameters for tirofiban in this experiment were voltage 3600 V, ISO1 8 V, ISO2 2 V, and CID 3 V, which will be used in subsequent experiments.

3.3. Method Performance. *3.3.1. Linearity.* The linear range of the method was examined by constructing a calibration curve for the target analyte. The calibration curve should adequately cover the concentration range required for detection and take into account the influence of the method recovery. Standard solutions were prepared for tirofiban with concentrations of 5, 25, 50, 100, 250, 500, and 1000 $\mu g \cdot L^{-1}$.

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Determination was carried out under optimum MS conditions using multiple reaction monitoring for quantitative analysis, which involved selecting the parent ion of interest and selecting the major product ions of the analyte after collision dissociation. A standard working curve for tirofiban was constructed with the peak area of tirofiban as the vertical axis and concentration as the horizontal axis. The regression equation and correlation coefficient of the calibration curve are presented in Table 2.

3.3.2. Sensitivity. The limit of detection (LOD) and limit of quantitation (LOQ) are two important indicators used to assess the sensitivity. The LOD, also known as the detection limit, refers to the concentration corresponding to three times the baseline noise of the peak position of the target analyte in the spectrum of a representative blank sample matrix (blood samples from health volunteers), which is commonly known as a 3-fold signal-to-noise ratio (S/N). The LOQ, on the other hand, is the concentration corresponding to a signal-to-noise ratio (S/N) of ≥10 for the method that exhibits observable baselines. Experimental results demonstrate that the LOD and LOQ of the POCT detection method for tirofiban developed using the Mini π miniature mass spectrometer were 10.1 and 33.7 $\mu g \cdot L^{-1}$, respectively, which exhibit high sensitivity and are capable of meeting the clinical requirements for tirofiban POCT detection in blood samples.

3.3.3. Precision. Precision is primarily assessed through repeatability and reproducibility experiments. For representative blank matrix samples, three sets of experiments were prepared, conducted over 3 days with one set of experiments per day. For each blank matrix, 18 parallel samples were weighed and added according to the "three-level six-replicate" principle for precision evaluation, with concentrations of 50, 250, and 1000 $\mu g \cdot L^{-1}$ added at each level. Six replicates were prepared for each level, and the average recovery rate and coefficient of variation were calculated for each level to simultaneously assess the method's repeatability and within-laboratory reproducibility. The obtained results are listed in Table 2. The experimental results demonstrate that the relative standard deviation (RSD) for tirofiban repeatability experiments ranged from 5.6 to 6.7%, while the RSD for intraday experiments ranged from 7.8 to 8.3%. This suggests that the method exhibits good repeatability, within-laboratory reproducibility, and high precision.

3.3.4. Recovery. This method involves adding tirofiban to the blank matrix at concentrations of 50, 250, and 1000 $\mu g \cdot L^{-1}$, with six replicates at each level, and calculating the mean recovery rate for each level. Healthy human blood samples were selected as blank matrix representatives for spiked recovery experiments, and the results are shown in Table 2. The table shows that the average spiked recovery rate of terrofenib was in the range of 87.5 and 93.4%. The mean recovery rates at all three spiked levels were able to meet the requirements for the rapid detection of tirofiban in clinical practice, indicating high accuracy and method reliability.

3.4. Matrix Effect. Sufficient consideration should be given to the influence of the sample matrix on the response of the target analyte. Typical matrix effects include ion suppression and ion enhancement, and the formation of matrix effects can be attributed to competitive inhibition or enhancement by strongly ionizing substances in the matrix, changes in the surface tension of the ion source caused by endogenous substances, making it difficult for ions to be released from droplets, etc. Due to the complexity of clinical blood samples, interferences from the matrix can occur during analysis, affecting the accuracy of quantitative analysis.

Matrix effect evaluation can be carried out by comparing the standards in solvents and those in blank matrices. In this experiment, a standard solution with a theoretically prepared concentration of 100 $\mu g \cdot L^{-1}$ was prepared in methanol and directly analyzed to obtain the corresponding peak area response. Simultaneously, a representative blank sample was selected, spiked with standard solution, and analyzed to obtain the peak area. Experimental results revealed a significant decrease in the response of tirofiban, indicating a matrix suppression effect. Measures to compensate for matrix effects include matrix-matched calibration curves to minimize matrix interference, and the use of a low injection volume of 5 μL.

3.5. Method Application in Real Cases. Blood is a commonly used sample matrix for tirofiban monitoring. Developing a POCT technique based on a pMS system can enable rapid tirofiban detection during the perioperative period of catheterization in the catheterization laboratory, which can guide clinicians in precise drug administration, preventing inadequate thrombolysis due to insufficient medication and the occurrence of bleeding and other adverse reactions due to excessive medication. In this study, 12 blood samples were selected, and tirofiban was directly analyzed using the pMS system in a cardiac catheterization room. Out of 12 samples, ten had tirofiban concentrations between 35.4 and 72.1 $\mu g \cdot L^{-1}$, while the remaining two were below the LOQ. This indicates that the developed POCT tirofiban method based on the pMS system can be reliably used for semiquantitative analysis of tirofiban in clinical samples.

4. CONCLUSIONS

This study developed a pMS method based on POCT technology for real-time sampling, clinical testing, and analysis of the blood drug concentrations of intravenously injected tirofiban. However, despite certain progress, there are still aspects that can be improved. First, further research is needed to reduce the matrix interference caused by matrix effects in the blood samples and improve the sensitivity of the instrument. Second, in future studies, exploration and optimization of fast purification pretreatment methods for the target compound should be conducted to enhance the ion response of Tirofiban and further improve the sensitivity of the method. Future development should involve the application of this POCT-pMS method in more clinical scenarios for the rapid analysis and monitoring of other drugs. In conclusion, this study provides a novel method for real-time monitoring and analysis of the blood drug concentration of intravenously injected drugs. Despite some room for improvement, this research provides valuable references and guidance for future work with the potential to play an important role in clinical practice.

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D.Z. contributed to conceptualization, writing—original draft preparation. J.W. contributed to methodology and investigation. Q.W. contributed to formal analysis. Y.L. contributed to methodology. S.W. contributed to validation and data curation. W.Z. contributed to resources. Y.Z. contributed to resources. H.D. contributed to writing—review and editing. Y.S. contributed to investigation. H.W. contributed to supervision and project administration. Q.S. contributed to conceptualization, supervision, and funding acquisition.

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Notes

Declarations: Ethics approval This study has obtained human research ethics approval from the Ethics Committee of the Sanmen People's Hospital (2023-015).

The authors declare no competing financial interest.

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