AUTOMATED THERAPEUTIC ANTICOAGULATION: A CLOSED-LOOP APPROACH USING A MODIFIED MEASUREMENT DEVICE

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ABSTRACT
Measurement of the activated clotting time (ACT) is an important and regularly performed task in hospitals for thrombosis prevention. Required adjustments of anticoagulation therapy are most often done manually by using a therapeutic look-up table adapted to patient weight. This process is prone to human errors and an automated solution for calculating the required change and readjusting the individual infusion rate of an anticoagulant therefore would provide benefits. Currently no automated blood anticoagulation system is available and we thus decided to expand an existing ACT measurement device with real-time reporting capabilities. We intercepted the electrical signals to the device’s seven segment displays and converted the electrical signals of the numbers using a Raspberry Pi. Then an automated closed-loop heparinization following a look-up table approach as used in clinical practice was implemented. To prove the feasibility of the system, a successful test for 96 hours in an anaesthetized animal was performed. While this study has shown that automatic closed-loop adaptation in a medical environment is feasible, we discuss possible implications of this approach, outline open problems and address issues that need to be solved towards a more automated and better medical care in general.

KEY WORDS
Intensive care, automation, activated clotting time, closed-loop, pattern matching, anticoagulation

1 Introduction
Management of blood coagulation is a routine task in medical facilities to make blood less likely to clot or thicken, drastically reducing the risk of thrombosis. This therapeutic hemostasis management is achieved by application of anticoagulation drugs like heparin with a patient specific infusion rate that is often depending on the patient weight. To manage the adaption of the required infusion rate, the current state of the patient’s blood coagulation has to be established. The measurement of activated clotting time (ACT) is one of the most commonly used point-of-care (POC) tests for this task [1] and used to monitor anticoagulation effects. It measures the seconds needed for the whole blood to clot up. The ACT is usually used when the partial thromboplastin time (PTT) test takes too much time or is not useful. However, ACT measurement may be affected by anticoagulation drugs and illness.

Whereas such measurements are frequently performed, the gathered information for adaption of therapy is only handled manually. Processing steps for management of blood coagulation involve reading the measured result, deciding the correct therapeutic action e.g. by looking it up in a standardized table, calculating the required change for the individual patient and changing the rate of the anticoagulant infusion. All this steps require manual actions of nursing staff whereas increasing workload and job stress is a severe problem with the broad variety of tasks and procedures to be performed [2]. This stress combined with understaffing and other factors furthermore increases the chance of human errors and is especially critical when manual transmission of information is involved [3]. Once those errors cause medical consequences they become a major problem and may even lead to life threatening situations.

Automation for repeated procedures can aid solving those problems by reducing nursing workload and human error potential on one hand and increased stability and accuracy of controlled variables on the other [4]. With the help of such automated processes and electronic documentation caregivers may then finally be able to focus on more important tasks that require their attention [5]. Of course, besides technological possibilities, another entirely different matter are legal obstacles in terms of automation which need to be addressed. However those issues bearing on ethical and liability questions are not limited to the medical sector but must be solved in general for many more fields of research and thus shall not be further discussed at this point.

Unfortunately, while increased workload and understaffing constantly become more urgent matters, technical obstacles for creating aiding solutions are still present and may even be growing with a broader variety of electronic medical devices. Patient measurements are stored in many different formats in the individual devices and are most often not integrated into a central system. This leads to a heterogeneous landscape that requires great efforts to handle [6]. Exporting stored information from devices using floppy disks, serial communication or USB is often possible. However, currently most devices are not capable of exporting measured results directly as they are performed, triggering
the sending of a single result after the measurement is completed. Data export can only be performed for multiple measurements in bulk at a later point in time. Therefore, those solutions are not sufficient for automation and closed-loop controls that may help in daily clinical practice.

In this paper, we focused on the specific aspect of gaining access to ACT measurements to provide a novel solution for automating the task of hemostasis management. Our goal of research was the development of a system for fully automated processing of ACT measurements and adaption of therapeutic heparinization and limiting required human interaction to blood withdrawal and placing the blood sample in the ACT measurement device. Using an existing ACT measurement device without an interface provided by the device manufacturer we developed a solution to obtain those measurements. The results are then fed into an existing medical framework and used to automatically adapt the infusion rate of heparin without the need for manual interaction. This ruled out the potential of human errors during rate calculation and interaction with the infusion pump and reduced workload.

2 Materials and Methods

2.1 ACT measurement

The ACT measurements for this study were performed with an ACT-Plus (Medtronic plc, Ireland) measurement device. Unfortunately this device only allows retrospective data export via serial port or floppy disks. To obtain an ACT measurement, a blood sample is collected from an arterial catheter with a small syringe and inserted in the array of two pre-heated high-range activated clotting time (HR ACT, Medtronic) cuvettes up to a marked level. The ACT is then calculated in the device by stirring the blood sample cuvettes at body temperature until clotting is achieved. The individually measured clotting times for the two cuvettes are calculated in seconds and shown on the device’s segment displays as an increasing timer until the measurement is finished.

2.2 Data collection from ACT measurement device

The used Medtronic ACT-Plus device has no interface to directly access the measurement results, the displayed data output had somehow to be captured. As we wanted to avoid using a camera and image processing to obtain the data from the displays we decided to access the 7-Segment LEDs directly. This provided a promising and reversible solution for capturing data while minimizing the risk of breaking the device in the progress. For providing easy access to our framework over Ethernet, we decided to use a Raspberry Pi Model B. The measurement setup with our breakout board and the Raspberry Pi is shown in Figure 1.

We obtained the required information to interface with the ACT device by tracing the printed circuit board and measuring the potentials and control signals. The information to the displays is multiplexed and by using the correct timing and pattern of the segments we could reconstruct the displayed information. Each of the two numeric displays consists of three 7-segment displays. Both displays are multiplexed in parallel presenting the data for each digit with a rate of about 200 Hz in successive order. Using a standard 40-pin ribbon cable we were able to intercept the communication to the display and connect to a custom made electronic board. On this board analog comparators with open-collector outputs were used to compare the voltage of the display segments to a reference voltage set with a potentiometer and get the digital information of each lit segment. Pull-up resistors at the output pins of the open-collector outputs were used to adapt the segments’ states to the 3.3V logic levels of the Raspberry Pi for further processing of the digital information. The used data capturing circuit is shown in an exemplary manner for a single segment in Figure 2.

2.3 Pattern matching and processing

For processing the obtained information of the lit segments on the ACT device, a C++ program to be run on the Rasp-
Figure 2. Schematic example for processing one display segment of the ACT device by comparing the observed voltage to a preset reference voltage and shifting the voltage level for Raspberry Pi input using a pull-up resistor.

The Raspberry Pi was written. Given the information about the currently active digit and the parallel data for the lit segments at the Raspberry Pi’s GPIO-Pins, pattern matching was performed to map the electrical signals to a displayed number. Observing all 3 digits and repeating the process therefore allows for the recognition of both displayed 3-digit ACT measurements. Fortunately, both displays were synchronized and no additional action for processing both displays individually was required. The patterns were observed for a short time frame to reduce errors and gain an accurate result by collecting the recognized numbers and reporting the most frequently occurring observation. Recognition of a new measurement and detection of its completion were performed automatically by observing changes in the displayed pattern. A new measurement is started when an incrementing sequence of numbers is detected. If no change in the displayed number is detected for a predefined time frame of 3 seconds, the measurement is considered as finished and the results are automatically transmitted. The results were fed into the TICoMS [7] data processing system, which is already used for measuring a patient monitor, ventilation device, infusion pumps and a blood gas analysis (BGA) device. Therefore, to complete this setup, the automated collection of the ACT results was an important aspect for us. Although the setup would allow a fully automated control of heparinization, we implemented an additional step, in which the caregiver has to authorize each ACT result, because faulty ACT measurements can happen occasionally due to different causes in the process of blood sampling and should be dealt with before automated actions based on a faulty measurement are performed.

2.4 Automated adaption of heparin infusion

Given the results of the measurements, an automatic closed-loop adaption of the heparin infusion for maintaining the therapeutic heparinization can be established. In accordance to clinical standards, a weight-adapted look-up table approach was implemented for calculating the required heparin infusion rate and carry out infusion pause and bolus if required. For this study the therapeutic scheme proposed by Raschke et al. [8] was used. Table 1 shows the implemented look-up table for regulation of the heparin infusion rates in relation to the body weight and the initial rate and bolus at the beginning of the therapeutic procedure. The obtained ACT measurement is automatically send to this application and processed. The limits for the look-up table can be set in a configuration file and the required patient weight is set in the application with a graphical user interface as shown in Figure 3.

<table>
<thead>
<tr>
<th>Measured ACT [s]</th>
<th>Action</th>
<th>Rate adaption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>Bolus</td>
<td>↑ 4 U/kg/h</td>
</tr>
<tr>
<td>70 – 90</td>
<td>Bolus</td>
<td>↑ 2 U/kg/h</td>
</tr>
<tr>
<td>91 – 110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>111 – 130</td>
<td></td>
<td>↓ 2 U/kg/h</td>
</tr>
<tr>
<td>&gt; 130</td>
<td>Pause</td>
<td>↓ 4 U/kg/h</td>
</tr>
</tbody>
</table>

Table 1. Therapeutic chart used for the automated heparinization algorithm. Based on [8] with reduced bolus.

2.5 Infusion pump control

Control of heparin infusion was performed with an modified infusion pump (Perfusor Space, B.Braun Melsungen, 226
Germany). This pump was previously integrated in the used software framework and can be remotely accessed over Ethernet to obtain the current infusion rate or set a new one. We used this feature to allow the automated heparinization software to read the current rate of the heparin infusion pump and adapt it according to the used therapeutic plan.

2.6 Evaluation

After verifying the basic functionality of the system with a set of test cases, the system was tested in a study trial on a living animal for 96 hours. During that time the proposed system was used for the automated closed-loop heparinization of a pig. The local animal experimental committee approved these studies in accordance with the National Guidelines for Animal Care and Handling. The heparinization according to the therapeutic look-up table is part of the study protocol and was previously done manually. Human supervision is present at all times for safety reasons and validation of each measurement is performed by checking the detected ACT measurements, manually calculating the required adaption and comparing it with the proposed automated action. If no invalid measurement is observed and the proposed action is correct, manual confirmation of the ACT measurement is performed on a graphical user interface during this evaluation process.

3 Results

The initial verification of the proposed solution was performed successfully without any errors for all test cases with defined heparin levels. Our solution then was deployed to the actual research environment. The closed-loop system ran successfully for the whole 96 hours with no objections by the human observer. All ACT measurements were successfully detected and automatically processed at all times and automated adaption of the heparin infusion rate by the automated infusion pump was performed correctly in all cases as well. An example of the automatic therapeutic adaption with the results of the measured ACTs and the actual heparin infusion rate during the whole experiment are shown in Figure 4.

4 Discussion

Currently, therapeutic heparinization is performed manually. In this paper, we have presented a novel system for automatic closed-loop control of heparin infusion by intercepting the signals to the device’s display and feeding the results in an existing framework to calculate the required action and automatically adapt the infusion rate. To the best of our knowledge, this is the first time it was shown that such a fully closed-loop control of heparinization is feasible. After successful initial tests, we deployed our automated solution to a research environment involving animal studies where we have shown the system to work flawlessly for 96 hours.

In comparison to the traditional method, the human error potential is drastically reduced in our novel approach. The manual measurement and adaption process involves several additional steps: First, the measured mean ACT value has to be noted or remembered. Second, using the look-up table, the correct action has to be determined corresponding to the measured value. Third, the required action has to be adapted for the specific patient. This involves looking up the patient’s weight and calculating the bolus volume and infusion rate according to this value. Fourth, the required actions have to be noted or remembered and carried to the patient’s bed. Fifth, the infusion pump has to be manually adjusted for the required bolus and the new infusion rate.

Each of the noted steps provides a human error potential involving the numerical values required for the next step. If any disturbance in the adaption process may occur, whether it be an emergency with another patient or just a question on the hallway on the way to the patient, numbers may get mixed up, resulting in a wrongful adaption of the therapy. Of course this can be avoided by noting all required actions but at the cost of increased workload.

Our proof-of-concept approach was intended to show the feasibility of such an automated system and reduce workload in the specific setting. Previously performed manually, now automated adaption drastically reduces the required workload and minimizes human error even in stressful situations. This clearly shows benefit of automation for such a routine task. If verification is required for safety reasons, a simple sanity check of the obtained measurements can still be performed either by human supervision or an automated system with human verification if anomalies are detected. However, for general application with multiple patients, an additional step of patient selection for the current measurement has to be implemented. Such a step may introduce another human error potential and has to be care-
fully evaluated. To solve this problem, additional automated measures may be used. This could involve labeled samples or additional verification of the patient ID in the verification process of the measurement. Even more advantaged methods like automated detection of blood withdrawal to ensure that no patient of whom no blood was withdrawn can be selected, may be considered. Future studies may focus on the comparison of the established clinical approaches using look-up tables with fuzzy logic and other closed-loop systems as it might allow for a much more precise and fine-grained adaption of therapeutic measures. Furthermore, interactions with other parameters that may influence blood coagulation should be evaluated and may be considered for a more advanced adaption of therapeutic heparinization.

This presented task is only an example for many similar procedures that are performed in clinical settings on a daily basis while facing the same technological problem: limited data accessibility of medical devices. As of 2016 there is still a too high number of different protocols and a lack of interaction [9]. Overcoming the major obstruction of missing interfaces and standards for connecting to medical devices is essential to give automation a chance as a faster and safer way of adapting standardized therapies by reducing caregivers’ workload of repeated tasks and reducing the risk of human errors that may cause clinical complications.

5 Conclusion

We presented a novel system for closed-loop control of therapeutic heparinization. The system was successfully deployed and tested for 96 hours on an anesthetized animal. While this work is an example for the benefits that arise by automation, it also highlights other important issues. Improved data accessibility is a key to this achievement and needs to be addressed for many more routine tasks performed in clinical settings where manual interaction is required to follow a protocol on a daily basis. A broad variety of tasks could easily be automated or at least improved to reduce workload and susceptibility to errors in the processing of medical information if data accessibility and interaction of medical devices could be improved. For the future it would be important that manufacturers of medical devices provide interfaces for real-time data acquisition, thus supporting research towards integrated systems and closed-loop automation in hospitals.

Acknowledgment

We express our thanks to B.Braun Melsungen AG, Melsungen, Germany, for supporting this research by providing a remote-controllable infusion pump and support in terms of handling and accessing their device as part of this research.

References