In Vivo Testing of the Semi-Closed Loop Infusion System: the Preliminary Observations

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Abstract—An In Silico testing of our novel automated clinical decision support system (ACDSS) in a prototype semi-closed loop (SCL) infusion system was previously reported. The decision making therein is based on the evaluation of hemodynamic and hemodilution parameters in compliance with an algorithm that implies interchangeable application of fluid infusion, vasopressor injection and red cell transfusion. Before starting the clinical validation trial, several amendments to the clinical algorithm were made on the basis of minor deficiencies revealed during an In Silico testing. For an intervention group in an on-going prospective randomized clinical trial, our prototype SCL infusion system is applied continuously for 12 perioperative hours in patients undergoing total hip replacement. This report describes our preliminary observations of the system’s performance in first 12 patients from an intervention group who completed the study.

Index Terms—Closed-loop, major orthopedic surgery, fluid infusion, decision support system, noninvasive hemoglobin, continuous noninvasive arterial pressure.

I. INTRODUCTION

Concerns regarding clinical applicability and reliability of closed-loop systems were recently addressed by the reports of successful preliminary validation of automated systems for hemodynamic management. An automated injection of vasopressors in response to the feedback from a continuous noninvasive arterial pressure (CNAPTM) measuring device was applied in a closed-loop system for the management of arterial blood pressure (ABP) during surgery [1]. A closed-loop fluid infusion system was applied for perioperative management of the volume status in response to the continuous feedback from a device for noninvasive measurement of cardiac stroke volume variation [2], [3]. Automated intervention decision-making in these systems is based on the algorithms that are supposed to comply with conventional clinical practice. However, even the most trustworthy consensus guidelines for interventions in specific clinical settings are constantly debated and, therefore, compliance with them is not mandatory for a physician. Moreover, there are no validated hemodynamic management algorithms that would be both applicable in closed-loop systems and fit in the majority of everyday clinical settings. Installation of multiple algorithms designed for specific clinical cases can only partially solve the problem because the main conceptual deficiency will remain. This is a missing option for a care provider to be able to not only shut down a closed-loop system, but also to adjust the automated interventions, e.g., manually change the dose of vasopressor or volume of a fluid bolus, or even adjust an algorithm itself. There is also an obvious need to have a possibility to suspend the action of a closed loop and immediately switch to the manual delivery of commands to intervention devices by using the same command center. That can be lifesaving when unexpected severe changes in the patient’s condition occur, e.g., deterioration of vital signs related to the cement implantation syndrome during the major joint replacement surgery. Since such conditions are usually short lasting it is important to be able to return to the previous – closed loop – operation without restarting the system. Addition of these functions turns the closed-loop system into a semi-closed loop (SCL).

II. IN VIVO TESTING OF A SCL INFUSION SYSTEM

We developed a prototype SCL infusion system that does not have an option of a closed-loop mode. Its PC-based command center deploys an automated clinical decision support system (ACDSS) that assists care providers in decision-making. The suggested interventions – vasopressor injection, fluid infusion, and transfusion of blood components – require physician’s approval [4], [5]. The ACDSS generates clinical advice in compliance with an algorithm that was developed by orthopedic surgeons and anesthesiologists from our research team. One part is a goal-directed optimization algorithm which implies evaluation of
hemodilution responsiveness during stepwise fluid loading. According to a mini volume loading test (mVLT), further fluid loading is not any longer justifiable when plasma dilution is not any longer enhanced [6]. Vasopressors are then considered. Red cell transfusion is considered if signs of anemia persist after the optimization. To achieve flexibility of our SCL infusion system in dynamically changing clinical settings, some parts of the algorithm may be activated both automatically and manually. These are administration of adrenalin infusion and goal-directed fluid loading. Adrenalin infusion dose is semi-automatically titrated according to the feedback from a device for continuous noninvasive measuring of arterial pressure (CNAP™) using the finger cuff method (Draeger Medical, Germany). Goal-directed fluid loading – a stepwise infusion – is performed with a high-volume pump (Belmont Rapid Infuser™, Belmont Instrument Corp., USA) according to the mVLT protocol. This requires the feedback from a device for continuous noninvasive measuring of total hemoglobin (Radical-7; Masimo Corp., USA), as well as automated analysis and visual display of pertinent trends.

Before starting the ongoing clinical trial, we developed a simulator – “Virtual Patient” – and tested the prototype SCL infusion system in silico [6]. Several amendments to the algorithm were made on the basis of deficiencies revealed during the simulation sessions, and the design of a computer screen of a command center was improved and modification of noninvasive readings was developed.

III. CHANGES IN ALGORITHM

The initial version of the algorithm was designed by using the serial method. It resulted in limitations and challenges when amendments to the algorithm had to be applied. An in silico testing revealed that the serial algorithm required prioritization of vital signs when they fell below the preset critical levels. The algorithm was branching as soon as one of these parameters – blood pressure (CNAP and ABP) or hemoglobin (SpHb and aHb) – reached the critical level. Different therapeutic interventions are required to restore clinically acceptable values of these parameters. The pre-programmed choice of treatment of arterial hypotension is infusion of vasopressors by a syringe pump, while treatment of anemia may require fluid infusion according to the mVLT algorithm and/or considering transfusion of blood components. Thus, in case when both target parameters fall below critical limits, a combination of therapeutic interventions from different arms of the algorithm may be required. In addressing such a clinical situation, amendments to the algorithm were needed but appeared to be nearly impossible to implement. Thus, we made a decision to split the algorithm into two independent parts, one for hemoglobin and another for blood pressure tracking related generation of advice by the ACDSS. In order to run both parts concurrently, the system was redesigned to use software threads. The testing of synchronization as well as thread safety and reentrancy had to be performed thereafter.

In silico testing also revealed another fully realistic but previously unaddressed clinical situation when blood pressure falls below the critical level during the mVLT guided fluid loading. The algorithm was designed so that automated clinical advice to start vasopressor infusion was suspended during the mVLT. Thus, another amendment to the algorithm was required to allow the initiation of vasopressor injection during any other algorithmic processes. This objective introduced an implicit state to the algorithm. Our attempts to further redesign an algorithm showed that such an implicit state broke the declarative implementation and required an imperative approach. Technical analysis revealed that with vasopressor injection tracking separated from blood pressure tracking the algorithm yielded four distinct parts of tracking – arterial blood pressure and hemoglobin, vasopressor injection and mVLT fluid loading protocol. Since each part is implicitly stateful, the algorithm was redesigned into four distinct state diagrams (Fig. 1) and later implemented as a finite state machine (FSM).

Fig. 1. The state diagrams of the redesigned algorithm (aHb – invasive arterial and SpHb noninvasive capillary hemoglobin, ABP – arterial blood pressure, CNAP – noninvasive arterial pressure).
IV. THE SITUATION DESCRIPTION

In the intervention group of patients undergoing elective primary total hip replacement, our prototype SCL infusion system was applied continuously for 12 perioperative hours. The system’s operation faced unexpected failures due to malfunction of sensor devices connected to the command center. More specifically, the CNAP measuring device sometimes failed to restart continuous measurements after the calibration, which was automatically done every 15 min. by using the arm cuff oscillometry. The device had to be restarted to troubleshoot the problem. However, that takes time and it is a serious problem if that happens during the adrenalin infusion because it is titrated according to the CNAP readings. These events did not cause any risk for the patients because for safety reasons during the experiment we had an invasive measurement of arterial pressure and our SCL system allows switching to manual adjustment of the syringe pump’s operation by using the SCL command center computer. If CNAP readings were available, every 5 min. ACDSS would generate a pop-up window with a suggestion to increase the dose of adrenalin if hypotension persisted. Accuracy of CNAP measurements is also clinically unacceptable because in many cases CNAP did not show a significant decrease in systolic pressure to the limit where the adrenalin infusion had to be started. Thus, an ACDSS did not generate a pop-up window with a suggestion to start the adrenalin infusion. Similarly to the situation described above when the CNAP signal was lost during hypotension, we had to titrate the infusion manually. When choosing a device for continuous noninvasive measuring of ABP we relied on literature reports that CNAP was superior to intermittent oscillometric measurements and comparable in precision and accuracy to invasive arterial pressure measurement from radial artery catheter in patients undergoing anesthesia and surgery [7]. Moreover, the same model of a CNAP device (Draeger Medical, Germany) was previously applied in a closed-loop system for the management of arterial blood pressure (ABP) during surgery, and authors did not report similar kind of malfunctioning [1]. We discussed these issues with our colleagues who have a long term experience of using that device in their everyday clinical practice during surgery. They also experience similar malfunctions rather frequently. To the best of our knowledge, that device is one of the first to enter the market in the last decade. There is evidence that a new generation of CNAP devices is more reliable [8]. New techniques such as radial arteryplanation tonometry [9] are also promising. Future studies should consider the use of the newest devices with widely proven reliability.

We used the Radical-7 Pulse CO-Oximeter (software V7.9.1.0 and SpHb averaging time 1 min.) with ReSposable R2-25a sensors (version k). The problems were related to the lengthy periods (>5 min) when the noninvasive SpHb readings could not be obtained. These episodes were associated with both low (<0.5) and high (>1) perfusion index (PI). There was no association with adrenalin infusion or movement because the limb was immobilized. Change of sensitivity modes sometimes helped to restart readings. During the periods when SpHb was not available, the SCL command center could not evaluate hemodilution and ensure the anemia-watch. Moreover, sometimes Radical-7 device automatically started its re-calibration. It was by initializing the sensor as if it was a new sensor and a new patient, which resulted in a loss of in vivo adjustment that was made at the start of the protocol. If you see re-initializing happening you can simply repeat the in vivo adjustment procedure by using the previously applied adjustment value. However, such auto re-calibration may be unnoticed in conventional clinical environment. Moreover, it is unclear if the SpHb reading obtained after the self re-calibration of the device can be considered equivalent in accuracy to previous readings. In our everyday clinical practice we have observed similar re-initializing of a sensor when oscillometric ABP measurement with an arm cuff was used on the same limb. The sensor was re-initializing after each disruption of the blood flow during cuff inflation. In the present trial, we used the arm cuff on a different limb. Another issue was occasional, rather fast decrease in the SpHb value below a pre-set anemia limit. According to the study protocol, if the SpHb value remained at >10 g l⁻¹ below that threshold for >5 min, invasive Hb measurement had to be made for verification. Noninvasively detected anemia was never confirmed invasively. These episodes were not associated with arterial hypotension or adrenalin infusion, but the PI was usually low (<1.0).

The above-mentioned problems cannot be fixed without improvements in technologies. However, there was a problem that we managed to fix, at least partially. We had to minimize invasive and noninvasive Hb measurements related error on the derivative variables that are crucial in the application of the mVLT protocol. More specifically, the stepwise fluid loading has to be stopped when invasively and noninvasively measured capillary plasma dilution efficacy of a fluid challenge is minimized and arterio-capillary plasma dilution efficacy difference becomes negative [6]. These variables are displayed as graphs on the screen of the SCL command center computer. The measuring errors related fluctuations in these trends make it difficult to detect the above-mentioned criteria that serve as indication to stop fluid loading. Thus, we developed and applied a modification of the noninvasive readings.

V. MODIFICATION OF NONINVASIVE VARIABLES

Fluid challenge induced plasma dilution (PD) during the mVLT is calculated from a change of hemoglobin concentration (Hb). Since we are considering the dilution of plasma, we need to adjust for the hematocrit

\[ PD_t = \left( Hb \times Hb_i^{-1} - 1 \right) \times (1 - Hct)^{-1}, \]  

where PD_t is the plasma dilution after the fluid challenge number t, Hb is the initial hemoglobin concentration obtained before the first fluid challenge, Hb_i is the hemoglobin concentration obtained after the fluid challenge number i, and Hct is the initial hematocrit value obtained before the first fluid challenge (since noninvasive Hct is not available during the noninvasive determination of the PD, the initial Hct is derived by dividing the noninvasive initial Hb by 330, which is the mean value of the normal range for the mean cell hemoglobin concentration).

The plasma dilution efficacy (PDE) is used to evaluate the ability of a fluid challenge to increase the PD from a preceding fluid challenge. The PDE is calculated as follows:
\[ PDE_i = (PD_i + 1) \times (PD_{i-1} + 1)^{-1} - 1, \]  

where \( PDE \) is the **plasma dilution efficacy** of the fluid challenge number \( i \), \( PD_i \) is the plasma dilution at the end of the fluid challenge number \( i \), and \( PD_{i-1} \) is the plasma dilution at the end of the preceding fluid challenge.

According to the mVLT, a decision to make an additional fluid bolus is based on a difference between invasively (arterial) and noninvasively (capillary) measured plasma dilution efficacies, \( aPDE \) and \( cPDE \), respectively. These are calculated from plasma dilution. The **plasma dilution efficacy difference** (PED) is calculated as follows:

\[ acPED_i = aPDE_i - cPDE_i, \]

where \( acPED_i \) is the **arterio-capillary plasma dilution efficacy difference** of the fluid challenge number \( i \), \( aPDE_i \) is arterial plasma dilution efficacy of the fluid challenge number \( i \), and \( cPDE_i \) is capillary plasma dilution efficacy of the fluid challenge number \( i \).

It is clear from the equations above, that \( acPED \) is a function of two one after the other consequent measurements difference of hemoglobin values

\[ acPED_i = f \times \left( \frac{aHb_{i-1}}{aHb_i} \right) - f \times \left( \frac{cHb_{i-1}}{cHb_i} \right), \]

Accuracy of invasive and noninvasive hemoglobin measurements depends on errors related to the measuring equipment and method, as well as on the invasive blood sampling technique or the positioning of a sensor for noninvasive measurements. Finally, individual anatomy and physiology contributes to measured variable’s deviation from the actual value.

The most reliable decision regarding clinical usefulness of an additional fluid bolus during stepwise fluid loading is based on the difference between hemodilution responsiveness in large vessels (\( aPDE \)) and capillaries (\( cPDE \)), referred to as \( acPED \). According to the mVLT method, an additional fluid bolus is necessary only when \( acPED \) is positive. However, a relatively insignificant fluctuation in the Hb trend leads to a much more pronounced fluctuation in the \( acPED \) trend (Fig. 2). Thus, it challenges the reliable decision-making.

Retrospective analysis of the data obtained from 48 patients during a 6-step mVLT protocol in our previous RCT revealed that fluctuation amplitude of noninvasive variables was much higher than of invasive.

Despite the lack of evidence, there is a hypothesis that this is related to the unique anatomy and physiology of the blood vessels where noninvasive measurements are performed, as well as the influence of neuro-humoral stimulation of capillaries under the sensor.

We propose a method for the amelioration of the impact of random factors in order to increase the precision of noninvasive estimates of \( cPDE \) and reduce the fluctuation in \( vcPED \) trends. That would enable more reliable and simplified decision-making during the mVLT. We made an empirical assumption that a change in SpHb by \( < (+/-2) \, g/l \) is due to an error, but a change by \( > (+/-2) \) is due to an actual change in Hb. An algorithm for data modification:

1. Baseline values of aHb ir SpHb (cHb) are obtained.

2. These variables are normalized after the first fluid load, but no data adjustment is performed at that point.

3. Since the tendency is apparent after the first fluid load, the aHb ir cHb variables are normalized after all the following fluid loads:

\[ aHb_i = aHb_0 + (aHb_i - aHb_{i-1}) \times Ka, \]

\[ cHb_i = cHb_0 + (cHb_i - cHb_{i-1}) \times Kc, \]

where \( i \) is a number of fluid challenge, \( Ka \) and \( Kc \) are the modification coefficients for the correction of arterial and capillary Hb readings, which values are unknown at this moment.
Moreover, it must be borne in mind that clinical research is performed to improve outcomes of treatment and not solely to compare one device with another. Our previous RCT showed that perioperative application of the mVLT fluid protocol was associated with better outcomes in patients after elective unilateral total knee replacement compared with our institution’s standard of care fluid therapy [12]. Even more, changes in Hb and the gap between invasive and noninvasive measurements during the mVLT are predictable by the transcapillary reflux model [6]. The mVLT has evolved from a precursor method [13] proposed nearly a decade ago but still needs further investigation, and especially in an SCL application.

VII. CONCLUSIONS

The in vivo testing of a novel SCL system revealed several deficiencies related to occasional malfunction of noninvasive devices for measuring arterial pressure and hemoglobin. Improvement of these techniques is needed.

VIII. ACKNOWLEDGEMENTS

Conflicts of interest:


REFERENCES


