Closed-Loop and Decision-Assist Resuscitation of Burn Patients

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Effective resuscitation is critical in reducing mortality and morbidity rates of patients with acute burns. To this end, guidelines and formulas have been developed to define infusion rates and volume requirements during the first 48 hours postburn. Even with these standardized resuscitation guidelines, however, over- and under-resuscitation are not uncommon. Two approaches to adjust infusion rate are decision-assist and closed-loop algorithms based on levels of urinary output. Specific decision assist guidelines or a **closed-loop system using computer-controlled feedback technology that supplies automatic control of infusion rates can potentially achieve better control of urinary output. In a properly designed system, closed-loop control has the potential to provide more accurate titration rates, while lowering the incidence of over- and under-resuscitation. Because the system can self-adjust based on monitoring inputs, the technology can be pushed to environments such as combat zones where burn resuscitation expertise** **is limited. A closed-loop system can also assist in the management of mass casualties, another scenario in which medical expertise is often in short supply. This article reviews the record of fluid balance of contemporary burn resuscitation and approaches, as well as the engineering efforts, animal studies, and algorithm development of our most recent autonomous systems for burn resuscitation.**

Key Words: **Closed-loop, Critical care, Decision-assist, Resuscitation, Burns.**

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Severe burn injury is costly in terms of human life, suffering and the economic investment in acute care and rehabilitation. Each year, approximately 40,000 adults are hospitalized for burns, with 4,000 dying because of complications resulting from their injuries.[1,2] In the military population deployed to combat zones, multiple injuries frequently include burns. Because acute burn care is particularly labor intensive, burn injuries sustained in mass casualties can quickly overwhelm even the best hospitals and burn centers. Critical to survival are the initial 48 hours of postburn resuscitation. During this phase, patients require prompt initiation of fluid therapy, and around-the-clock care by experienced burn surgeons and intensivists. However, advanced burn care expertise is not found in most hospitals. This limitation includes receiving centers, whether they are civilian emergency rooms, forward military facilities or ad hoc medical facilities for mass casualty. Clearly, there is a need to reduce the

workload of advanced burn centers and to impart burn expertise to less specialized medical facilities.

The pathophysiologic response to large thermal injuries [≥20% of total body surface area (TBSA)] is characterized by substantial plasma extravasation and general edema formation, leading to intravascular volume depletion and burn shock.[3] Delayed or inadequate fluid resuscitation is associated with increased morbidity and mortality.[4,5] Initial treatment currently consists of isotonic crystalloid infusion based on a regimen that is directed toward volume replenishment to obtain cardiovascular stabilization and maintain adequate renal function. However, such treatment is only partially effective because of an array of circulatory mediators and sustained fluid extravasations into the extravascular space.

CURRENT RESUSCITATION REGIMENS

Defining the best solutions, infusion rates, and volume requirements for resuscitation of burn injury has been an ongoing research focus for the last 100 years. Several formulas have been developed to guide the care provider with a predicted infusion volume for the first 24 hours and with a specific initial infusion rate based on the size of the burn injury and patient weight. Infusion rates are then adjusted hourly, based on the urinary output (UO) of the patient during the last measured period. The most common contemporary infusion formulas are the Brooke formula (2 mL/kg/% TBSA for 24 hours) and the Parkland formula (4 mL/kg/% TBSA for 24 hours). Fluids are periodically adjusted to maintain an adequate UO, within a predetermined target range. The rationale for using UO as the target endpoint to adjust fluid therapy is that if UO is normal then glomerular filtration rate,

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renal blood flow, and cardiac output are likely to be adequate. Target values are based on ranges analyzed by age (adult or pediatric), patient weight, and, sometimes, other factors that contribute to normal renal output. Adult target values are 0.5 to 1.0 mL/kg/h or 30 to 50 mL/h.[2,6] Pediatric patients often require larger volumes due to a greater surface area to weight ratio, and have a formula with a higher target UO of 1.0 to 2.0 mL/kg/h.[2,6] Maintaining UO targets is expected to normalize renal function, while avoiding excess or inadequate fluid infusion that may lead to an increase in complications or mortality. But recent reviews have suggested that this approach frequently leads to severe over-resuscitation, with many burn units administering mean volumes larger than the Parkland recommendation.[7,8]

To evaluate contemporary methods of burn resuscitation, we performed a metaanalysis of the last 26 years of burn resuscitation. We searched Medline for all clinical burn studies in which fluid resuscitation was guided by the Brooke or Parkland formula with adjustment in infusion rates to restore and maintain target UO. We extracted data from 31 studies, which included 40 groups and 1,498 patients. Figure 1 shows the total 24-hour volumes infused and the mean UOs. Mean %TBSA was $45 \pm 2\%$ and mean fluid intakes were 5.1 ± 1.3 mL/kg/%TBSA, with mean 24-hour UOs of 1.1 ± 0.4 mL/h/kg. All studies reported mean volume administration exceeding the Brooke formula and 86% of studies reported

mean values above the Parkland formula. In general, patients are resuscitated to achieve levels of UO that are at or above the high end of target level. However, 13 of 16 burn centers infused sufficient lactated Ringer solution to induce mean 24-hour UOs exceeding 1.0 mL/kg/hr. The primary conclusions from the metaanalysis are[1] total volumes infused typically exceed the Parkland formula and Advanced Burn Care Life Support (ABLS) guidelines, and[2] UOs tend to be on the high side of ABLS guidelines.

The metaanalysis did not analyze whether burn centers are infusing more fluid than is optimal, or if the Brooke and Parkland burn formulas specify inadequate volumes. A metaanalysis based on summary statistics of individual studies has limited power to analyze relationships between fluid volumes and outcomes. Detailed individual patient data from a multicenter trial are needed to accurately analyze the impact of fluid therapy on outcomes. Fluid volume requirements may have changed during the last 60 years due to changes in clinical care to include greater use of invasive monitoring, more aggressive and early surgical procedures, more liberal use of drugs for cardiovascular support, and pain control. Individual patient data are required to statistically correlate outcomes with total volumes infused and net volume retained (fluids in minus fluids out). Hourly data on infusion rates, UO, and net volume (edema) are needed to fully define the relationships between volume therapy and UO in patients with burns. The collection of such data could be facilitated using an automated monitor of IV pump function and UO as described below.

Reduced survival and more often increased morbidity are linked to suboptimal resuscitation.[5,9,10] But we do not know how many patients are harmed by under- and over-resuscitation. From the metaanalysis, case reports, and clinical experience, we know that individual burn experts resuscitate patients differently and that they usually produce clinical results deemed satisfactory. This may speak more to the physiologic reserves of the patients and the ability of their kidneys to compensate for over-resuscitation than it does to our medical knowledge or expertise. A quip often used by intensivists is "the dumbest kidney knows more than the smartest intern".[11] Patients have effective compensatory mechanisms that can often compensate for a wide range of infused volumes. "Successful clinical results", however, are not necessarily equivalent to optimal outcomes.

FLUID CREEP

The need for large volume therapy for burn shock was identified in 1968 by Charles Baxter,[12] who showed that successful resuscitation could be accomplished with a "Parkland formula" of 4 mL/kg/%TBSA of lactated Ringer's (LR) in the first 24 hours of care. Before that time, fluid therapy was largely performed with a combination of crystalloid and colloid (plasma or albumin) solutions at lower volume totals. Subsequently, Pruitt[10] provided an alternate "modified Brooke formula" of 2 mL/kg/% TBSA of LR. The ABLS guidelines established the American Burn Association accepted these formulas and recommend a 2 to 4 mL/kg/% TBSA range of total fluid volumes
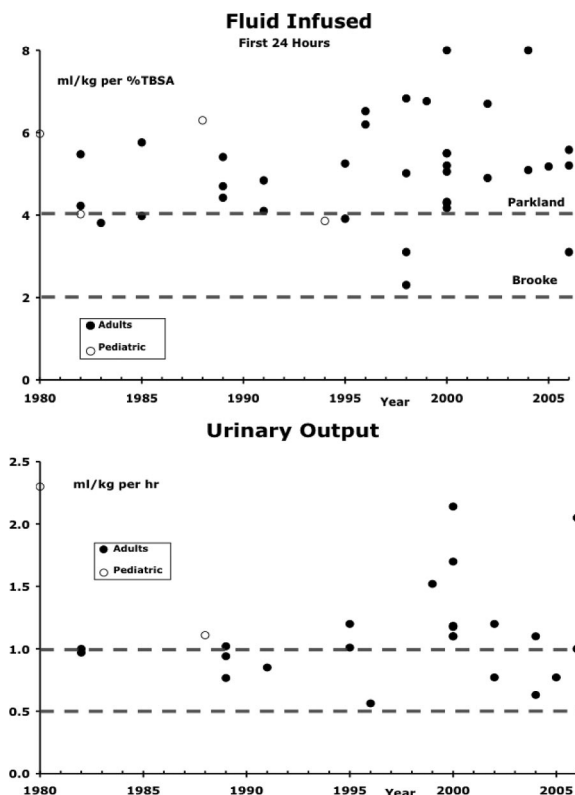

Fig. 1. *The total 24-hour total volumes infused and the mean UO reported for 40 groups of patients with burns extracted from 31 published trials from 1980–2006.*

for the first 24 hours, with the infusion rate adjusted to maintain a UO of 0.5 to 1.0 mL/kg/h or 30 to 50 mL/h.[13] Nevertheless, burn centers routinely administer 25% to 50% more fluid than Parkland formula, and more than half the fluid is given within the first 8 hours.[7,8,14] In clinical settings, physicians may accept high UOs without decreasing infusion rates and more diligently increase infusion rates when UO is low. This viewpoint is supported by our metaanalysis, which showed that mean UOs and infused volumes were typically above ABLS guidelines.[15]

The term "fluid creep" was first used by Pruitt[10] to describe the increased volume of fluid that appears to be administered by burn centers in the first 24 to 48 postburn hours. The morbidities associated with fluid overload include pulmonary edema, gastrointestinal dysfunction, abdominal and extremity compartment syndromes, delayed wound healing, increased incidents of infection, and multiorgan failure.[9,16–18] Data support the benefits of reducing total infused volumes. Recently, perioperative and intensive care unit trials of restricted fluid therapy showed improved outcomes.[17] Less net fluid accumulation has been associated with better outcomes in large burns treated with LR.[19] However, the correlation between increased survival and reduced fluid also reflects that the injury level correlates morbidity and mortality, and that patients with more severe burns require more fluid.

Taken together the above findings suggest that optimal fluid resuscitation may be achieved by minimizing fluid accumulation, while maintaining adequate UO and cardiac output. However, the clinical consequences of more tightly controlled fluid therapy and UO with less hourly variations are unknown. We suggest that a systematic means for adjusting infusion rate using either decision assist algorithm or autonomous closed-loop control may improve outcomes in patients requiring large volume fluid therapy.

FLUID THERAPY USING CLOSED-LOOP CONTROL

One approach to uniform resuscitation is to use decision assist formulas that provide specific infusion rate recommendations based on hourly UO. Another more advanced approach is a fully automated closed-loop control of infusion rates. Closed-loop resuscitation is based on a control algorithm to automatically adjust infusion rates to obtain a specific physiologic endpoint.

The concept of closed-loop control is well established for industrial applications[20–22] and its potential application to medicine has been extensively reviewed, although it has had limited utilization.[23–25] There have been clinical trials demonstrating effective closed-loop control of nitroprusside infusion for postoperative blood pressure regulation in cardiac patients.[26] Closed-loop control of ventilators and delivery of anesthetics have evolved into commercially viable products.[27,28] Experimentally, closed-loop fluid resuscitation has been used for treatment of hemorrhaged sheep using blood pressure, cardiac output, and tissue oxygen as endpoints.[29,30]

Burn resuscitation is a logical clinical application of closed-loop control of fluid therapy since a closed loop system can automatically titrate fluid therapy to changes in UO, the endpoint prescribed by the ABLS Guidelines. Closed-loop resuscitation systems could provide physicians and nurses who have limited burn experience a means to optimize the first 24 to 48 hours of burn care, even in an initial care facility. In the prehospital mass casualties environment, or in advanced burn centers such systems could be labor saving. In 1981, Bowman and Westenskow[20,31] were the first to build a closed-loop controller for fluid resuscitation of burn injury. In an era before personal computers were common, they built a specialized microprocessor for their controller. Both intake and UO were monitored with drop counters whereas a roller infusion pump was controlled with a proportional-integral-derivative (PID) algorithm. The PID algorithm was based on a mathematical model, which had been used to control resuscitation in a small number of dog experiments. They verified accurate monitoring of fluid in and urine out, but no controlled trials were performed in either animals or patients. Lack of funding, not technological problems, kept Bowman and coworkers from continuing to develop their fluid therapy system (Westenskow, personal communications, 2004). Several decision trees and mathematical models of fluid balance after burn injury have been developed,[32–35] but none has had significant clinical application.

ANIMAL STUDIES

In preparation for a series of animal studies of the first 48-hours of resuscitation we directed three surgical residents to use UO targets to adjust hourly infusion rates. We quickly realized that each surgeon translated different infusion rates out of target UOs. To provide an experimental regimen that would be reproducible we developed a detailed rule-based decision table, which defined the hourly infusion rate based on the magnitude by which UO was above or below target in the previous hour.[36] This rule-based decision table successfully guided resuscitation in a series of animal studies of different solutions to treat burn shock.[36–38] The success of strict adherence to a rule-based decision table suggested use of a computer to automatically communicate with a digital UO monitor and an infusion pump to perform automated adjustments in fluid therapy.

Hoskins and coworkers,[39,40] built a PC-based system programmed in Visual Basic that interfaced with a Bard CritiCore 926 Urine Monitor and a Baxter Flo-Gard 6201 intravenous infusion pump. This closed-loop resuscitation system used a PID controller and was tested in 10 sheep with burn injuries during 48 hours of burn resuscitation. A control group of 11 sheep with burn injuries had technician-controlled resuscitation using our published decision table.[36,41] Sheep were subjected to a 40% TBSA full-thickness burn administered resuscitation was started at an infusion rate specified by the Parkland formula and adjusted by computer control each minute or by technician hourly adjustment to achieve a
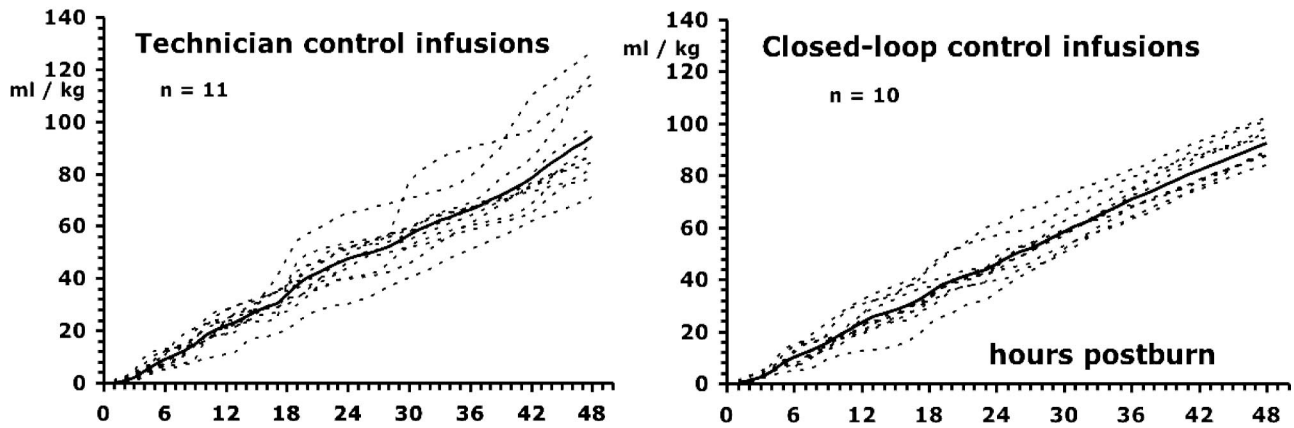
Cumulative Urinary Output

Fig. 2. *The cumulative UO plotted for each individual animal resuscitated with hourly technician adjustment of infusion rate based on a decision table is shown in the left panel. The graph on the right shows data from animals resuscitated using a closed-loop control. The thick line in both figures is the mean data. Data are from Hoskins et al.[39]*

target UO between 1 and 2 mL/kg/hr, the values correlated with restoration of cardiac output in sheep. These target values for UO are higher than ABLS guidelines for adult patients with burns, but normal for sheep.

Figure 2 shows individual data of the cumulative UO in both groups. The darker straight line represents the mean value. If UO rates were unchanged, the cumulative plot would be a straight line. The mean hourly UO was relatively constant as compared with individual data, and the mean UOs were virtually identical for both groups. Despite the mean data being similar, a greater variation in the technician group was apparent versus the closed loop group. The UO data were further examined (upper graph), which shows hourly rate of UO (mL/kg/h) plotted versus time, with parallel dotted lines representing the low and high target levels. Mean UOs were similar through the first 12 hours, but the standard deviation (SD) of the UO at each hour and the number of times that the UO was over or under target was lower with closed-loop control (Fig. 3). The highest and lowest mean hourly values, as well as higher peaks of UO, are apparent in the technician group at time points 10, 19, and 42 to 46 hours postburn.

Mean resuscitation volumes and net volume (edema) trended to be 10% to 15% lower through 48 hours, with closed-loop resuscitation versus technician control for animals resuscitated with either crystalloid or colloid, but these differences were not statistically significant ($p < 0.2$, Fig. 4). Animals in the colloid group were resuscitated for the first 25 mL/kg with dextran 70 or Hespan, These data suggest that closed loop resuscitation may result in a better ability to achieve and maintain target UOs in patients with burn injuries and reduce volume needs.

To define current standard of care (SOC) for burn resuscitation, we evaluated individual hourly records of burn patients. At Institute of Surgical Research (ISR) and University of Texas Medical Branch (UTMB), we extracted hourly fluid input and UO measurements from 20 adult patients with
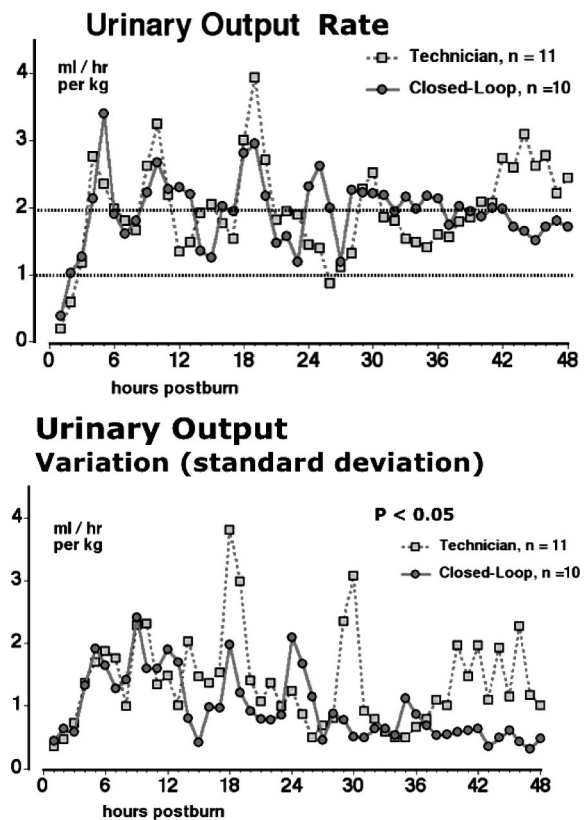

Fig. 3. *Upper graph: Mean UO for each hour of 48-hour of resuscitation is plotted for 11 sheep with infusion rate adjusted by technician control using a decision table (squares) and 10 sheep resuscitated by closed-loop control (circles). The parallel dotted lines represent the upper and lower targets for the normal UO of sheep. There was no significant treatment difference for mean rate of UO. Lower graph: The hourly SD of UO is a measure of variation and is plotted for 48-hour of fluid therapy. There was a significant treatment difference for the SD of UO,* p = 0.027.
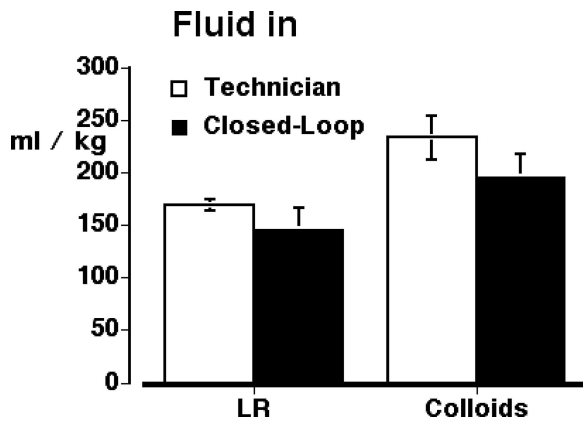
Fluid in

Fig. 4. *Total 48-hour volume requirements of 40% TBSA sheep with burn injuries resuscitated using continuous closed-loop control of infusion rate or an hourly decision table. Paired columns show two subgroups of animals in which fluids used were either crystalloid (lactated Ringer's) or colloid (Hespan and dextran). Data suggest a potential for volume sparing with closed-loop control.*

burns using the automated fluid balance monitor (FBM) described later in this review. The data shown in Figure 5 suggests great variability in UOs before and after arrival at our burn centers. Of 440 hourly in-hospital measurements in patients with burns, 41% were below the ABLS target range of 1.0 to 2.0 mL/kg and 28% were above.

The principle conclusions from the analysis of our patients and of the literature metaanalysis are that mean UO above target levels predominated with infused volumes, even in advanced burn centers, exceeding ABLS guidelines. The tendency for clinicians to over-resuscitate patients with burns may be responsible for many recognized complications such as abdominal compartment syndrome, extremity compartment syndrome, and airway edema requiring intubation, all of which are life- or limb-threatening.[19,42,43] In particular, abdominal compartment syndrome was largely unheard before 10 years ago, but is now a serious complication in many burn centers.

The clinical data contrasts with the data for decision table or closed-loop control in sheep. The animal data suggest that a decision table may be able to improve physician-controlled SOC resuscitation and that a closed-loop control could be even more effective.

DECISION-ASSIST AND CLOSED-LOOP FOR BURN RESUSCITATION

Recently ISR and UTMB collaborated on the development of automated FBMs, decision-assist and closed-loop algorithms, and the hardware systems to implement them. We have performed animal and initial clinical testing of the FBM, the first necessary component of a full burn resuscitation system.

FLUID BALANCE MONITORS

Four automated FBM resuscitation system prototypes (Fig. 6) have been assembled for initial burn unit monitoring

in patients with burns for ISR, UTMB, and the Shriners Burns Hospital, Galveston. The ISR system is implemented in the Dynamic Research Evaluation Workstation (DREW). The DREW is an integrated data acquisition platform and a modular biomedical interface engine that can acquire data from up to 16 serial devices and 16 analog channels. The DREW station is configured with a high-end single computer system, utilizing industrial standard acquisition and control card modules from National Instruments. The collection, management, control, and storage of digital, analog and multimedia data are controlled with LabVIEW software. Data retried from instrumentation is stored in a synchronous fashion and can be monitored over a network (real time), stored in a database, retrieved for analysis as discrete digital information or for wave form analysis, and played back in its original captured form. The software runs on a Windows XP platform and the UTMB system runs on a notebook personal computer (PC) with LabVIEW PCMCIA serial cards.

Data are collected from up to four commercial off-the-shelf Food and Drug Administration (FDA)-approved infusion pumps, (IMED Gemini PC-1, 2, 4) and an FDA-approved urine monitor (CritiCore, Bard, Murray Hill, NJ). The DREW's Automated Burn Resuscitation program (ABR 2.7, 4-07-07) was developed in LabVIEW and includes plug and play device drivers and subroutines for recording, and monitoring rates of fluid infusion and UO, as well as display menus with options for decision-assist recommendations and automated closed-loop control. Automated fluid balance monitoring promotes an opportunity to generate displays of fluid balance, which themselves may aid clinicians by rapidly imparting the time course of fluid balance.

Figure 7 is a screen capture showing cumulative fluid in, UO, and net fluid in (minus urine), measured with our prototype FBM from data collected in an ovine model, consisting of 40% TBSA with acute respiratory distress syndrome secondary to inhalation injury. The display is generated from 34,560 data points (infusion rate and urinary volume measured every 10 seconds for 48 hours). Per this experimental protocol steady infusion rate was set by Parkland formula with adjustments only at 8- and 24-hour postinjury time points. Clearly evident are periods of oliguria (UO = yellow negative bars) at hours 28 through 35, despite continuous LR infusion at the Parkland rate. Also observed, as indicated with arrows, are the resolutions of net fluid accumulation (green line) first occurring transiently at 6 to 12 hours and then after 36 hours.

A key question for the design of a closed-loop system is how the UO data should be analyzed and used. Standard clinical protocol is to measure total UO every hour on the hour. A continuous running average will provide more timely data since a fixed hourly UO measurement becomes "old data" as each minute postmeasurement occurs. A measurement "on" the hour or half-hour is an artificial constraint. UO calculated as running averages for 30-minute blocks or, per-
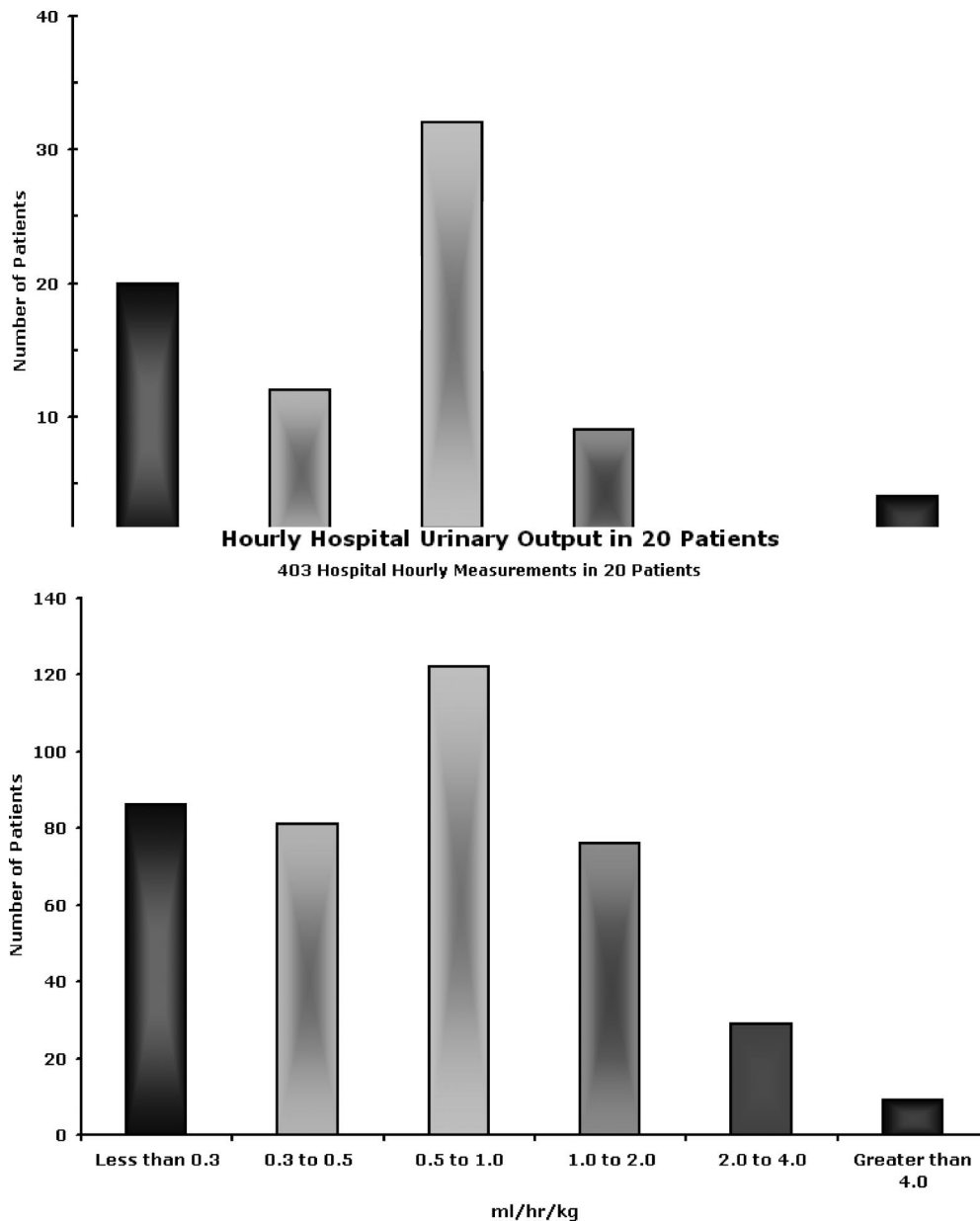
Fig. 5. *Total resuscitation in mL/kg/h of UTMB and ISR patients with burns in the prehospital (before admission) and after admission to the ICU. Graphs suggest great variability in UOs before and after arrival at the two burn centers.*

haps better, 10-minute blocks, might provide "earlier warning" of a change. At shorter time intervals of collecting UO, the increased data resolution loses meaning.

Figure 8 shows how fluid infusion rate and UO can be plotted when they are measured continuously with our fluid balance monitoring. Data are from 9 hour to 13 hour postburn for a 90% TBSA, 68 kg, female patient admitted to the UTMB Blocker Burn Unit. UO is calculated for running 10-minute (thin line) and 60-minute (thick line) averages. Infusion rate is recorded every 10 seconds, and the running averages are plotted every 2 minutes. The large arrows show that when infusion rate was increased, and then decreased, the UO responded with the expected increase or decrease within 5 to 10 minutes of the

change. Such data suggest that running a 10-minute average of UO will provide a more rapid lead time compared with standard hourly measurements to analyze changes in infusion rate adjustments. The dips in infusion rate represent when the Gemini pump was paused to change the fluid bag.

Before closed loop resuscitation technologies are distributed, it is likely that decision-assist recommendations can be derived from control algorithms. Decision assist provides an hourly recommendation to either maintain infusion rate at the current level, or to change it based on the time course of UO. In our system, decision assist is used in conjunction with the resuscitation displays, showing the time course of cumulative fluid in and UO, and the record of hourly UOs. If a 10-minute
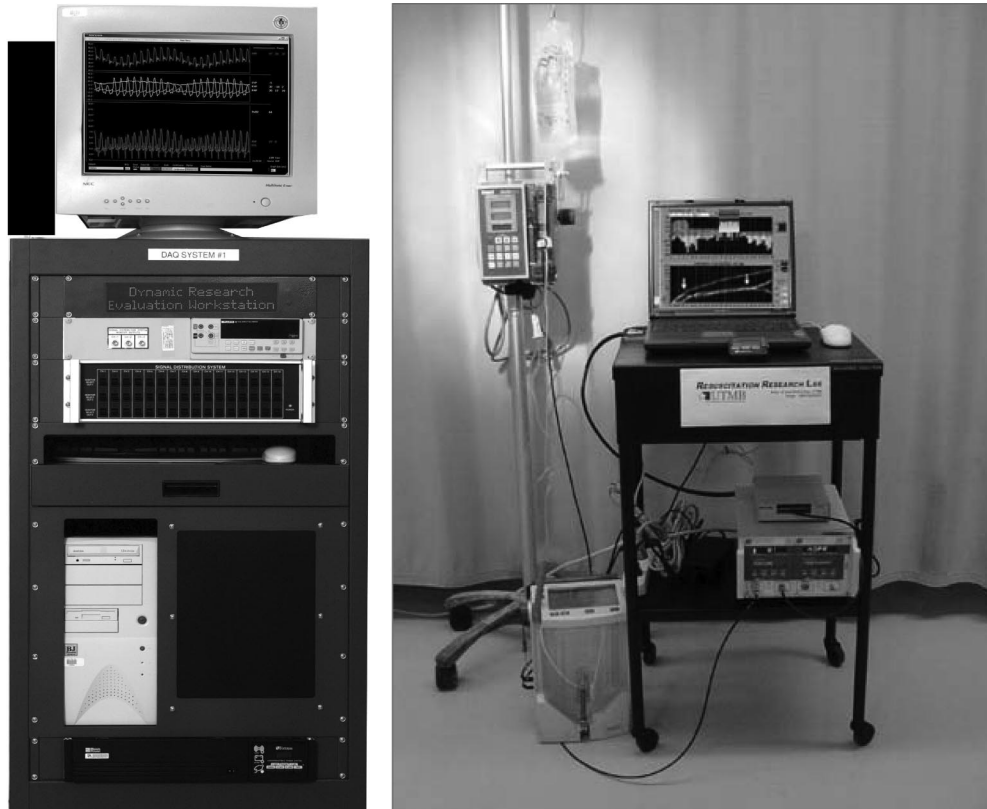
Fig. 6. *The Fluid Balance Monitor used at ISR is housed in a DREW DAQ workstation (shown on the left). On the right is the UTMB system, which runs on a Windows XP Laptop. Both systems connect to Gemini IV pumps and a Bard CritiCore urine monitors.*

period of anuria occurs, an alarm appears, and sounds, tasking the nurse to check the bladder catheter drainage tube to analyze whether it is at fault or if UO is in fact low. Decision assist would not used when automated closed-loop control is initiated. Because a closed-loop system may take several years to receive full FDA approval, we suggest that semiautonomous systems that provide decision-assist recommendations can be developed and used in near term. One version of a decision-assist system uses manual hourly data input and provides hourly recommendations of infusion rate. Versions of this system are built for tablet PCs for bedside use.[44] A version written in JAVA (Sun Microsystems, Inc., Santa Clara, CA) code has been implemented on the ISR standard clinical monitors. A mobile implementation of the software was written for use on a personal digital assistant that is field deployable and can be used in austere environments. Decision-assist protocols were implemented at ISR and UTMB in August to September 2007.

HOURLY DECISION-ASSIST ALGORITHM FOR BURN RESUSCITATION

For standard hourly measurement of UO, an hourly algorithm was developed to provide decision-assist recommendations to care providers on the infusion rates necessary to achieve a target UO. Figure 9 shows two displays of the pocket PC FBM with decision assist. The algorithm was

based on a retrospective analysis of 30 patients with burns at the ISR burn ward with greater than 20% TBSA. For the 30 patients in the study, the mean fluid rate and UO were computed for each hour postburn up to 48 hours.

Using the response input or output measures from a sample of 30 patients with burns, a modified "first order plus dead time" (FOPDT) analysis of the infusion rates and the UOs was used to define a response model based on a given infusion rate and the expected response within 1 hour after infusion. Standard FOPDT analysis defines a process for generating the necessary coefficients needed to implement a feedback control mechanism that is both stable and has good response to changes in the input parameters. These coefficients are used as part of control equation to adjust the output response based on changes to the input parameters as defined by the control parameters. FOPDT results are used to analyze the gain (K) of the system, the dead time (how long before system responds to a stimuli), and the time constant (rate of change once the process has started to respond). The process consists of stimulating the system with a test function (either a positive or negative step function) and measuring the response without additional external inputs to the system. The response curve is measured and used to derive the necessary parameters. In the case of the burn resuscitation system, the ability to "test" the system with a step function was not available. Using a retrospective analysis of the recorded pa-
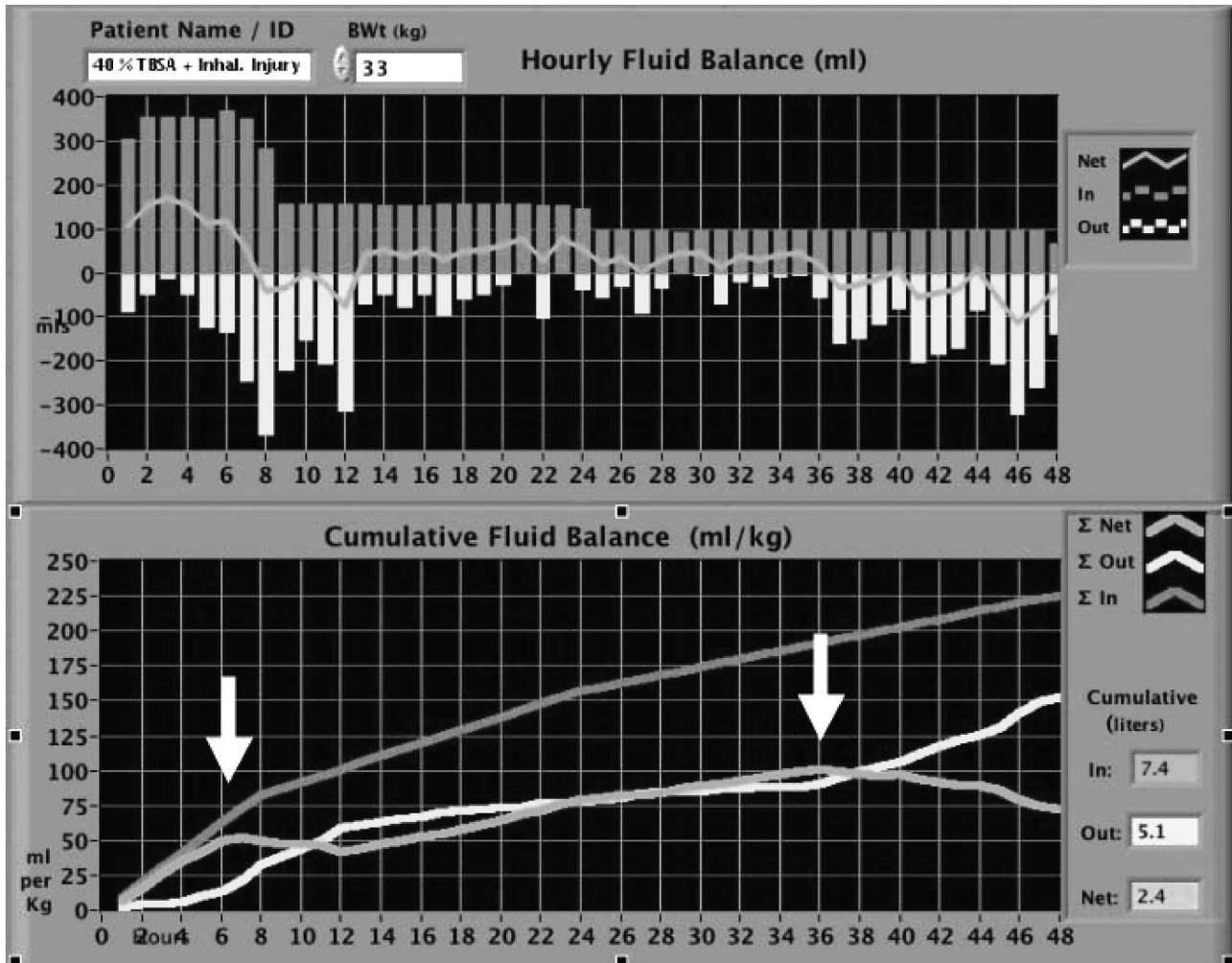
Fig. 7. *Resuscitation display of 48 hours of data recorded during resuscitation of a sheep with burn injuries. The display plots cumulative infused, cumulative UO and cumulative net in this example data are plotted in mL/kg.*

tients, the FOPDT approach was modified by using the mean response curve of the 30 patients during the first 48 hours. For each hour, the mean response measured as an increase or decrease in UO was calculated and compared with the average infusion rate of the previous hour. This resulted in hourly response model for the initial 48 hours of resuscitation and provides the expected UO for each hour for a given infusion rate. The model was generalized by curve fitting to both the hourly infusion and UO values. Best fit for infusion rate values resulted in a decaying exponential curve. UO was represented with a straight linear fit. The nonlinear relationship between the infusion and UO was mitigated by subdividing the decaying curve into three distinct phases representing initial, middle, and end infusion phases. In the initial phase (postburn hour 0–13), there is substantial variability between infusion rates and UOs as analyzed using a Poincare diagram. Thus, in the initial phase of burn resuscitation, the phase-1 algorithm recommends prompt and aggressive adjustments in infusion rates in response to changes in UO. Aggressive adjustments in phase-1 may eliminate a transient period of infusion over-

shoot that was demonstrated in most of the patients with burns. Phase-2 (postburn hours 13–34) and phase-3 (postburn hours 34–48) algorithms are similarly designed and found to be sequentially less aggressive. When fluid balance is negative with a hemodynamic stability for a consecutive 3-hour period, fluid infusion is reduced to maintenance levels. However, continuous monitoring is required because in about 30% of the patients, a period of fluid mobilization of 3 hours to 8 hours was followed by an additional period in which low UOs reoccurred and resuscitation had to be reinstituted. Using the 3-phase approach, a set of coefficients was calculated that defined the amount of fluid necessary to increase or decrease the UO at each of the phases. These coefficients were then used to modify the previous hour's infusion rate by the amount necessary to bring the UO of the patient to an acceptable target (40 mL/hr). To accommodate patients who differ significantly from the mean model, a set of modifiers for both the patient weight and the TBSA are used by the control equation to modify the recommended changes to infusion. Modifiers were based on logistic curves that change
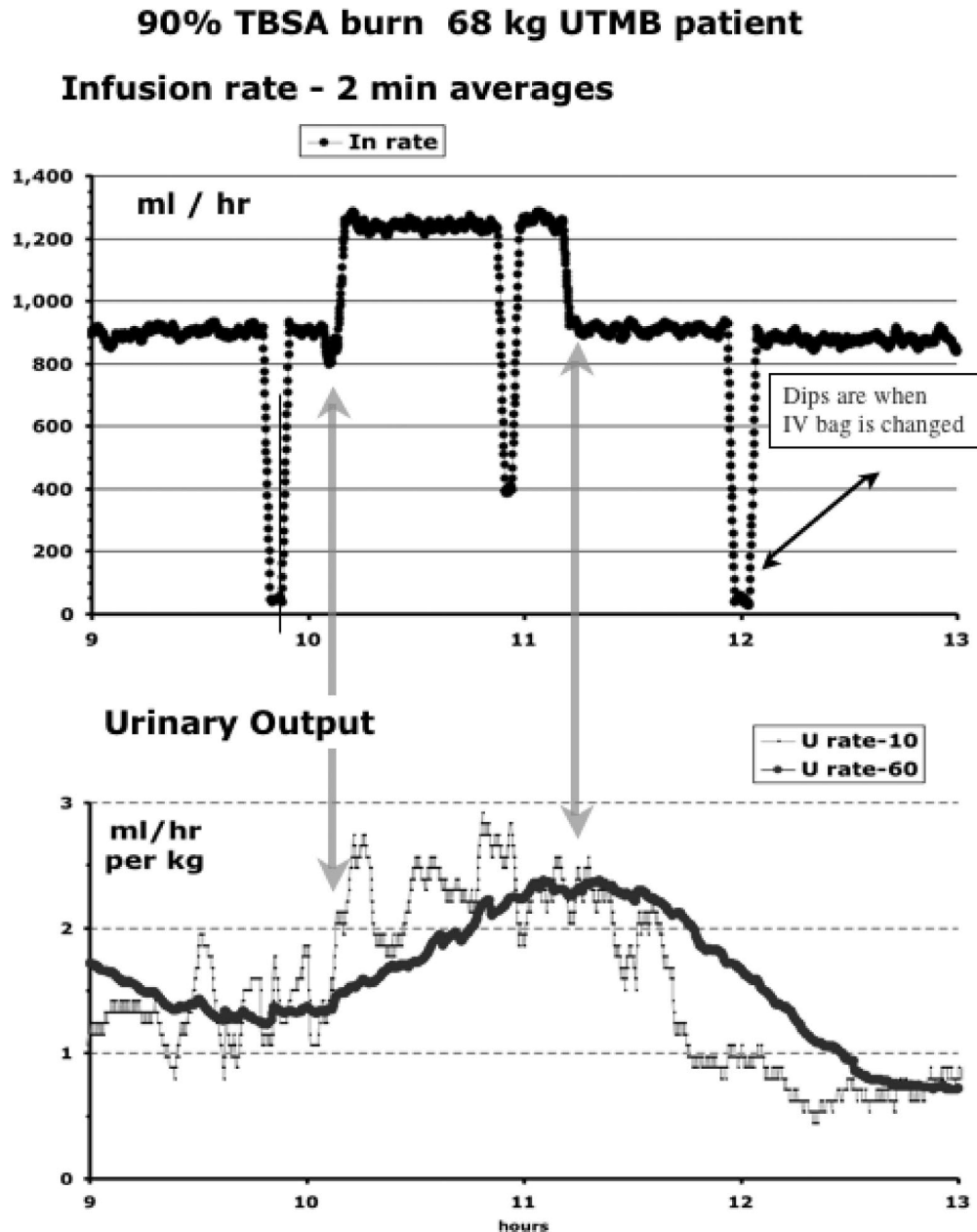
90% TBSA burn 68 kg UTMB patient

Infusion rate - 2 min averages

Fig. 8. *Continuously collected and plotted data on infusion rate and UO from a 90% TBSA patients with burn injuries from UTMB monitored with an automated Fluid Balance Monitor. Data are platted for 10 minute and 60 minute, and is compared with hourly data from nurse mates.*

the infusion recommendation by multiplying the recommended infusion rate with the modifier outputs. The resulting recommendation is further modified by multiplying the recommendation by an inverted Gaussian function that has a value of 0 at the target rate. This will guarantee the recommendation does not change when the UO is at or near the target range regardless of model values.

CLOSED-LOOP ALGORITHM

One of the main drawbacks of the hourly algorithm is the low frequency measure that is used for infusion ad-

justments. In most cases, patients with burns begin to have a response within 5 minutes of an increased infusion rate. Identifying patients who are over- or under-responders is critical in improving the mortality and morbidity rates of patients with burns. Furthermore, responses to boluses or medications may necessitate more frequent monitoring during any acute resuscitation phase. Relying on a 1-hour cycle may therefore be inadequate for an optimal resuscitation strategy. The hourly frequency of control has been dictated by the manual nature of resuscitation methodologies and is not necessary when using automated closed-

Fig. 9. *Fluid balance display and a decision-assist interface for personal digital assistant Pocket PC (Fluid Balance Monitors 1.1).*

loop systems. Using a closed-loop system interfaced with automated monitoring of UO and IV fluid pumps can provide much tighter control of the infusion rates. This will allow the control system to maintain the patient at the specified target rate, and also provide a much faster response to changes in UO rates during all resuscitation phases.

The closed-loop algorithm is a similar process to the 1-hour system.[45] However, control equations are based on a much higher sampling of the UO monitor. Using standard control modeling techniques and analysis of high frequency retrospective data, the necessary gain and time parameters required for the control equations are used. One

common approach is the use of a PID algorithm commonly used by engineers for machinery and electronic devices. It approaches control much as an expert physician intuitively analyzes clinical data. A burn expert evaluates the target levels compared with the patient's last UO (proportional), the last several measurements or history of UO (integral), and the rate of change of UO (derivative). A PID controller was used in our animal study. Infusion rate at time (t) is I_t and is calculated from the previous infusion rate and an adjustment factor or $u(t)$ where

$$I_t = I_{t-1}[1 + u(t)] \quad \text{and}$$

$$u(t) = K_p e(t) + K_i \int_0^t e(t)dt + K_d \frac{de(t)}{dt}$$

where

$$e(t) = \text{target} - \text{UO}(t)$$

is the error signal. Here, $\text{UO}(t)$ is the measured UO, the "target" is the desired UO where K_p, K_i, and K_d are the proportional gain, integral gain, and derivative gain, respectively. In our animal experiments, we tuned the controller and found that the most stable performance was achieved without the derivative control action (i.e., $K_d = 0$). As a result, the PID controller was reduced to a PI controller.

ERROR HANDLING AND FAULT TOLERANCE

Our prototype data collection systems function robustly with continuous data capture and display generation for 48 hours in several animal studies and up to 57 hours in patients. Errors have mostly occurred when cables are disconnected or the urine monitor is not level. We have developed a variety of methods to address such errors. Errors generated by the system are classified into permanent or recoverable. Permanent errors entail the shutting off and reinitialization of the system. Recoverable errors are reported to the caregiver and logged by the system. In this case, the physician will decide whether to restart the system or to continue normal operation when recovered. A system of clinical alarms provides details to assist the caregiver in deciding when to disengage the system and initiate manual pump control. Error reduction algorithms can autocorrect for a variety of errors. For example, if the Bard urine collection canister is shaken, incorrect data changes in urine volume are transiently sent to the computer. Computer-generated alarms, notes, or comments are documented in the data record log and provided to the caregiver by popup windows. The current closed-loop system version searches for devices to regain device connectivity. For example, when the connection is lost to the pump or urine monitor, an alarm and popup notifies the caregiver that the connection is lost. When the caregiver reattaches the connection, the data collection and algorithm resume. If either pump or urinary connectivity is lost for >5 minutes an alarm notifies the caregiver to assume manual control and to restart the program manually.

FUTURE ALGORITHMS

Decision assist and closed-loop control of UO to guide fluid therapy is only a first step. Our vision is that more effective and complex algorithms will some day guide all aspects of clinical care. Automated collection of multiple variables, (e.g., blood pressure, cardiac output, lactate) and multivariable algorithms are a focus of future research. A variety of control algorithms can be designed for both the closed-loop system and the decision table. Defining the op-timal algorithms will be an evolutionary process. A decision table in which infusion rate was adjusted every 30 to 60 minutes could produce an improvement from current SOC results. Most burn centers perform hourly adjustments of infusion rate, and thus hourly adjustment was chosen for our first decision assist table and to compare with experimental closed-loop control system. A decision table for manual adjustment with scheduled adjustments for less than every 30 minutes is possible, but not practical. Autonomous control would be labor saving and tirelessly diligent.

CONCLUSIONS

We hypothesize that continuous monitoring and application of control algorithms can achieve and maintain UO target levels better than human intervention. This critical ability to tightly manage fluid balance is due to the closed-loop system's ability to continuously monitor, and rapidly interpret and respond to minute systemic changes using the application of consistent rules. We have confidence that a closed-loop controller can adjust fluid infusions at least as well as typical clinical burn care teams. This in itself will be useful. Our animal studies suggest that tighter control of UO may lower total volume infused and total net fluid balance. Most importantly, we must ultimately analyze whether closed-loop resuscitation improves clinical outcomes. However, even if such systems yield outcomes no better than that of advanced burn centers, the technology would allow expertise to be "exported" to other hospitals and trauma care facilities that do not have expertise or experience in burn care.

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