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SYMPOSIUM

Glucose Monitoring in Acute Care: Technologies on the Horizon

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Abstract

Current glucose monitoring technology appears inadequate for the management of diabetic surgical and in critically ill patients requiring intensive insulin therapy. Subcutaneous sensors measure interstitial fluid glucose, and this technology has not yet been shown to provide the timely and accurate measurements necessary for intravenous insulin administration in surgical and critical care patients on intensive insulin therapy. Technologies under development that may be more suitable for surgical and intensive care unit patients are the automated intermittent type glucose monitors and central catheter glucose monitors. Improved accuracy, patient safety, incorporation of control algorithms, and alleviation of added nursing labor are important factors for consideration with future acute care glucose monitors. Hospital costs for these monitors are difficult to estimate but may be relatively low if their use can be related to better patient outcome, reduced labor costs, and increased job satisfaction for the nursing staff.

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Introduction

The deficiency in current glucose monitoring technology may be most evident during cardiac surgery in diabetics[1,2] and in critically ill patients requiring intensive insulin therapy (IIT) to maintain normoglycemia. Much like capnography and pulse oximetry emerged from the need to "think like a lung,"[3,4] this form of insulin therapy requires clinicians to "think like a pancreas," hence the need for continuous glucose information. The future of IIT will be with glucose sensors or other forms of automated blood sampling systems that will eventually feedback to a controller.[5] It is encouraging to note the recent Food and Drug Administration (FDA) approval of three subcutaneous continuous glucose monitors as significant technological developments that can spare diabetes patients the discomfort of multiple needle sticks.[6] However, subcutaneous sensors measure interstitial fluid glucose, and this technology has not yet been shown to provide the timely and accurate measurements necessary for intravenous insulin administration in surgical and critical care patients on IIT.[7,8] These needle-type sensors require equilibration and calibration procedures that make their use less practical in acute care settings.

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Abbreviations: (DTM) Diabetes Technology Meeting, (FDA) Food and Drug Administration, (ICU) intensive care unit, (IIT) intensive insulin therapy

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It is unknown how those types of sensors will perform in surgical patients experiencing rapid fluctuations in blood glucose, changes in blood flow distribution, temperature, or various pathologies (i.e., morbid obesity, burns, sepsis).[9,10] Issues such as calibration drifts from membrane fouling, measurement delays (blood to interstitial fluid), statistical handling of continuous data, and prediction of future glucose information are only beginning to receive the needed consideration in the evaluation and approval of these systems.[3] In the meantime, other related technologies have been developed to facilitate the implementation of intravenous insulin protocols in acute care patients. The Glucommander, developed in the early 1980s by Davidson and Steed, works as an open loop insulin delivery system using a glucometer and insulin infusion with delivery rates determined by a computer program receiving manually entered blood glucose information. The algorithm was shown to be helpful in assisting clinicians manage hospitalized patients on insulin infusions and has been adapted to a palm-sized device.[11,12] Other glucose monitoring technologies under development that may be more suitable to surgical and intensive care unit (ICU) patients are the automated intermittent-type glucose monitors. Via® Blood (Via Medical Corporation, Austin TX),[13] STG-22™ (Nikkiso, Tokyo, Japan),[14] OPTImus (IntelliDx Corporation, Santa Clara, CA),[15] and other similar devices offered by Cascade Metrix (Indianapolis, IN), Luminous Medical (Carlsbad, CA), and Optiscan Biomedical Corporation (Hayward, CA)[16] are envisioned to be completely automated blood glucose monitors. These devices will be capable of performing blood draws at preprogrammed intervals, or on demand, when connected to a peripheral vein or central venous catheter. Blood draws from a peripheral blood vessel require low negative pressure to avoid collapsing the blood vessel, as well as selection of an appropriate limb vein. Although gentle negative pressure is desirable, manufacturers will need to limit duration of the blood draw to avoid clotting, as routine heparin use in carrier fluids is no longer recommended in ICUs in the United States. However, vessel collapse should not be an issue when the device is connected to a central access catheter. Some foreseen advantages of those technologies are their capability to measure whole blood glucose, thereby overcoming the accuracy limitations of subcutaneous interstitial fluid sensors and reduce, if not eliminate, multiple daily finger sticks in patients receiving IIT. Another advantage of these monitors will be the significant reduction in nursing time spent implementing IIT protocols. The accuracy of some of these devices will be partly based on the selection of the strip and the meter technology used by the device manufacturer. If other non-FDA-approved glucose measurement technologies are used (e.g., optical), the accuracy of the method might require testing for validation of the method. Potential limitations of these systems are the lack of truly continuous glucose information and dependence on a peripheral venous access site, although early data from peripheral and central catheter samplings have been encouraging.[13–15] Other considerations are that blood draws from central catheters might require pausing infusions running through other catheter ports to avoid sample dilution or contamination. It is anticipated that such systems will be approved for 72 hours of use with a peripheral venous catheter in order to remain compliant with hospital infection practices.[17] When used with a central access catheter, these glucose monitors would have more extended use for as long as a central catheter is indicated.

Another type of technology specific to surgical and critically ill patients is the central catheter glucose monitor. Use of a glucose sensor incorporated into a central venous catheter is not novel, as early investigations reported some success with long-term glucose oxidase sensors placed in circulating blood.[18] The biofouling of the sensor surface was a recognized problem, requiring biomaterials research to find suitable protective membranes that would allow long-term sensor performance *in vivo*.[19–23] This approach, now being revitalized by Edwards Lifesciences (Irvine, CA) and GluMetrics Inc. (Irvine, CA), will provide continuous or periodic blood glucose measurements from a sensor built into the catheter. Early data from a European study by Verbrugge *et al*.[24] on five human subjects undergoing open heart surgery showed good correlation and low bias between the Edwards continuous glucose central catheter compared to reference. The Edwards Lifesciences sensor is described as an amperometric glucose oxidase type, whereas the GluMetrics is a fluorescent-type sensor.

The blood glucose monitors just described should facilitate the management of critically ill and surgical patients on IIT.

At present, implementation of IIT requires constant attention from the nursing staff[25] and often, as in this institution, assigning additional personnel to perform the glucose measurements. The decision to initiate, admit, or discharge a patient on IIT can be complicated by daily resource allocation considerations facing nursing supervisors.[26] These operational difficulties suggest that glucose monitors could alleviate the added nursing labor from IIT implementation. Considering the more predictable kinetics of intravenous insulin, compared to subcutaneous insulin administration,[27] it should come as no surprise if second- or third-generation hospital glucose monitors provide options for semiclosed loop feedback systems for hospitalized patients receiving IIT. Manual input/intervention might be required in situations where an algorithm may not be able to select the correct insulin infusion rate, such as with certain drug administration (e.g., steroids, epinephrine), hyperalimentation, or during surgery (e.g., cardiopulmonary bypass).[28] Measurement accuracy, reliability, ease of use, safety, and efficacy demonstrated by good studies[29,30] will determine the rate of acceptance of these technologies. The ability to reduce the risk of hypoglycemia will always be ranked as the highest patient safety concern,[31,32] although this risk can be viewed from two perspectives with respect to technology: (1) current technology limits the practice of tight glycemic control when trying to maintain a blood glucose range of 80–120 mg/dl because of an increased risk of hypoglycemia and (2) control algorithms may not initially provide the desired degree of blood glucose control, but the higher frequency of blood glucose measurements can reduce the risk of hypoglycemia. "Smart early warning" hypoglycemia alarms could be programmed based on glucose trend information and setting of safe lower glucose limits, which should increase patient safety.

The application of engineering knowledge to diabetes is of great significance,[33] as demonstrated by recent human testing of early closed loop systems[28,34,35] in critical care patients. Multidisciplinary collaborations between control theorists and biomedical scientists in academia and industry have resulted in improved algorithms, advancing the important pioneering work of Kadish[36] and Clemens and colleagues who later developed the Biostator.[37] However, progress in artificial pancreas development has been relatively slow and underfunded when considering the more than 40 years of research in the midst of a steady rise in diabetes. Increasing sensor accuracy and long-term signal stability are still major goals of artificial pancreas development.[38] An interesting concept introduced at the 2007 Diabetes Technology Meeting (DTM) in San Francisco was the use of multiple sensors to reduce errors from faulty or failed sensors. Ward and Hipszer reported on the use of multiple glucose sensors in animals and humans using voting, ranking, and averaging procedures (DTM 2007 abstracts). These interesting results demonstrated that overall accuracy may be improved, although the approach is not yet practical with current sensor designs. Perhaps microneedle sensor arrays or other microelectromechanical system-based sensors might offer more suitable platforms for improving accuracy with multiple sensing units.

The drive to develop hospital continuous glucose monitors was primarily a result of the increasing evidence that patient outcome can be improved when keeping glucose in the physiologic range.[39] One cannot help but wonder whether such revolutionary changes in the technology could be dampened if new evidence were to suggest less pronounced benefits from tight blood glucose control in critically ill and surgical patients.[40,41] The analysis of Malhotra[42] and results from other less conclusive outcome studies have raised questions regarding the blood glucose range necessary to affect outcome. Interestingly, one can still observe a decreased tolerance for elevated glucose levels across most institutions,[43] therefore making it even more difficult for future studies to show differences in outcome. It would seem logical to expect that facilitating the titration of a dangerous drug with improved monitoring will continue to be demanded by health care professionals. Hospital costs for these future monitors are difficult to estimate[44] but may be relatively low if their use can be related to better patient outcome,[45] reduced labor costs,[46] and increased job satisfaction for the nursing staff.

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References:

1. Carvalho G, Moore A, Qizilbash B, Lachapelle K, Schricker T. Maintenance of normoglycemia during cardiac surgery. Anesth Analg. 2004;99(2):319-24.
2. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg. 1999;89(5):1091-5.
3. Torjman MC, Goldberg ME, Hirsh RA, Littman J. Thinking like a pancreas: a look ahead at diabetes technology in the perioperative setting. Anesth Analg. 2007;105(2):545.
4. Martinez E, Williams K, Pronovost P. Thinking like a pancreas: perioperative glycemic control. Anesth Analg. 2007;104(1):4-6.
5. Joseph JI, Torjman MC. The Artificial Pancreas Symposium: glucose monitoring, insulin delivery, feedback control. Diabetes Technol Ther. 1999;1(3):323-8.
6. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. Diabetes Care. 2005;28(5):1231-9.
7. Corstjens AM, Ligtenberg JJ, van der Horst IC, Spanjersberg R, Lind JS, Tulleken JE, Meertens JH, Zijlstra JG. Accuracy and feasibility of point-of-care and continuous blood glucose analysis in critically ill ICU patients. Crit Care. 2006;10:R135.
8. De Block C, Manuel-Y-Keenoy B, Van Gaal L, Rogiers P. Intensive insulin therapy in the intensive care unit: assessment by continuous glucose monitoring. Diabetes Care. 2006;29(8):1750-6.
9. Samuelsson A, Steinvall I, Sjoberg F. Microdialysis shows metabolic effects in skin during fluid resuscitation in burn-injured patients. Crit Care. 2006;10(6):R172.

10. Klonoff DC. Subcutaneous continuous glucose monitoring in severe burn patients. Crit Care Med. 2007;35(5):1445; author reply 1445-6.

11. Davidson PC, Steed RD, Bode BW. Glucommander: a computer-directed intravenous insulin system shown to be safe, simple, and effective in 120,618 h of operation. Diabetes Care. 2005;28(10):2418-23.

12. Button E, Keaton P. Glycemic control after coronary bypass graft: using intravenous insulin regulated by a computerized system. Critical Care Nurs Clin North Am. 2006;18(2):257-65, xi.

13. Coss-Bu JA, Jefferson LS, Stone-McCord S, Ou CN, Watrin C, Sachdeva R, Copeland KC. Evaluation of a real-time blood glucose monitor in children with diabetic ketoacidosis. Diabetes Res Clin Pract. 1999;44(3):175-81.

14. Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M, Hanazaki K. The accuracy of a continuous blood glucose monitor during surgery. Anesth Analg. 2008;106(1):160-3.

15. Torjman MC, Goldberg ME, Marr AT, Maldonado M, Littman JJ. Evaluation of an automated blood glucose monitor in cardiac surgery and critically ill ICU patients. 2007;ASA Abstract 1127.

16. Krinsley J, Zheng P, Hall D, Magarian P. ICU validation of the Optiscanner, a continuous glucose monitoring device. Crit Care Med. 2006;34(12):A67.

17. Center for Disease Control. MMWR, recommendations and reports. 2002; 51:No.RR-10.

18. Armour JC, Lucisano JY, McKean BD, Gough DA. Application of chronic intravascular blood glucose sensor in dogs. Diabetes. 1990;39(12):1519-26.

19. Vaidya R, Wilkins E. Use of charged membranes to control interference by body chemicals in a glucose biosensor. Med Eng Phys. 1994;16(5):416-21.

20. Eisele S, Ammon HP, Kindervater R, Grobe A, Gopel W. Optimized biosensor for whole blood measurements using a new cellulose based membrane. Biosens Bioelectron. 1994;9(2):119-24.

21. Nishida K, Sakakida M, Ichinose K, Uemura T, Uehara M, Kajiwara K, Miyata T, Shichiri M, Ishihara K, Nakabayashi N. Development of a ferrocene-mediated needle-type glucose sensor covered with newly designed biocompatible membrane, 2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate. Med Prog Technol. 1995;21(2):91-103.

22. Yang S, Atanasov P, Wilkins E. A glucose biosensor based on an oxygen electrode: in-vitro performances in model buffer solution and in blood plasma. Biomed Instrum Technol. 1996;30(1):55-61.

23. Joseph JI, Torjman MC. (2004) Implantable glucose sensors. In: Wnek G, Bowlin GL, editors. Encyclopedia of biomaterials and biomedical engineering. New York: Marcel-Dekker; 2004. p. 683-92.

24. Verbrugge L, Crisis D, van Dijk J, Higgin M, van Wezel H. Accuracy of a prototype central venous continuous amperometric glucose sensor following CABG. Anesthesiology. 2007;107:A1427.

25. Gerard SO, Neary V, Apuzzo D, Giles ME, Krinsley J. Implementing an intensive glucose management initiative: strategies for success. Crit Care Nurs Clin North Am. 2006;18(4):531-43.

26. Clayton SB, Mazur JE, Condren S, Hermayer KL, Strange C. Evaluation of an intensive insulin protocol for septic patients in a medical intensive care unit. Crit Care Med. 2006;34(12):2974-8.

27. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery--the path to physiological glucose control. Adv Drug Deliv Rev. 2004;56(2):125-44.

28. Hovorka R, Kremen J, Blaha J, Matias M, Anderlova K, Bosanska L, Roubicek T, Wilinska ME, Chassin LJ, Svacina S, Haluzik M. Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. J Clin Endocrinol Metab. 2007;92(8):2960-4.

29. Ligtenberg JJ, Meertens JH, Monteban-Kooistra WE, Tulleken JE, Zijlstra JG. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. Diabetes Care. 2006;29(8):1987.

30. Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, Squire S, Haluzik M, Kremen J, Svacina S, Toller W, Plasnik A, Ellmerer M, Hovorka R, Pieber TR. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients: Response to Ligtenberg et al. Diabetes Care. 2006;29(8):1987-8.

31. Meijering S, Corstjens AM, Tulleken JE, Meertens JH, Zijlstra JG, Ligtenberg JJ. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. Crit Care. 2006;10(1):R19.

32. Ligtenberg JJ, Stemerdink A, Vogelzang M, Borggreve HF, Herngreen T, Zijlstra JG. Tight glucose control and hypoglycemia: should we bother? Crit Care Med. 2007;35(4):1218.

33. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. Diabetes Technol Ther. 2005;7(1):28-47.

34. Wintergerst KA, Deiss D, Buckingham B, Cantwell M, Kache S, Agarwal S, Wilson DM, Steil G. Glucose control in pediatric intensive care unit patients using an insulin-glucose algorithm. Diabetes Technol Ther. 2007;9(3):211-22.

35. Van Herpe T, Espinoza M, Pluymers B, Goethals I, Wouters P, Van den Berghe G, De Moor B. An adaptive input-output modeling approach for predicting the glycemia of critically ill patients. Physiol Meas. 2006;27(11):1057-69.

36. Kadish AH. Automation control of blood sugar: a servomechanism for glucose monitoring and control. Am J Med Electron. 1964;3:82-6.

37. Clemens AH, Chang PH, Myers RW. The development of Biostator, a Glucose Controlled Insulin Infusion System (GCIIS). Horm Metab Res. 1977;Suppl. 7:23-33.

38. Hovorka R. Continuous glucose monitoring and closed-loop systems. Diabet Met. 2006;23(1):1-12.

39. Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control: what is the evidence? Crit Care Med. 2007;35(9 Suppl):S496-502.

40. Van den Berghe G. Does tight blood glucose control during cardiac surgery improve patient outcome? Ann Intern Med. 2007;146(4):307-8.

41. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM, Rizza RA, McMahon MM. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med. 2007;146(4): 233-43.

42. Malhotra A. Intensive insulin in intensive care. N Engl J Med. 2006;354(5):516-8.

43. Clement S. Better glycemic control in the hospital: beneficial and feasible. Cleve Clin J Med. 2007;74(2):111-20.

44. Klonoff DC. Business and economics of diabetes. J Diabetes Sci Technol. 2008;2(1):1-3.

45. Zijlstra JG, Corstjens AM, Tulleken JE, Meertens JH, Ligtenberg JJ. Cost analysis of intensive glycemic control in critically ill adult patients. Chest. 2006;130(6):1953-4.

46. Van den Berghe G, Wouters PJ, Kesteloot K, Hilleman DE. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med. 2006;34(3):612-6.