Computer assisted decision support in acutely ill patients. Application in glucose management and quantification of myocardial reperfusion
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 1

General introduction and aims of this thesis
Hyperglycemia in acutely ill patients

The association of elevated blood glucose levels with trauma and injury has been well studied after it was first described by Claude Bernard in the late 19th century. Hyperglycemia is not only prevalent in injured or critically ill patients, it is also associated with adverse outcome in a number of conditions, such as stroke, myocardial infarction and general patients admitted to an intensive care unit. In 2001, a landmark trial showed benefit of treating hyperglycemia in critically ill patients by administering insulin. In a randomized open-label trial, patients were randomized to conventional treatment, aimed at keeping glucose lower than 11.1 mmol/L, or to intensive treatment, aimed at establishing and maintaining normoglycemia (4.4 - 6.1 mmol/L). The achieved glucose levels were represented by the mean morning glucose, which were 8.5 and 5.7 mmol/L for the two groups respectively. The mortality rates of patients were different between the two groups: 8.0% vs. 4.6% (P<0.04). The intensive treatment group also compared favorably on a number of morbidity aspects; systemic infection, acute renal failure, and critical illness neuropathy occurred less in the tightly controlled patients. In a post-hoc analysis, the beneficial effect was attributed to the level of glucose control, and not to the amount of insulin administered.

In addition to these very interesting results, the Leuven trial raised a number of questions. It remained unclear which category of patients would benefit from this new therapy, and whether hyperglycemia is equally undesirable for all patients admitted to an intensive care unit. The Leuven paper described the level of achieved glucose control by calculating the mean over only the morning glucose samples of the patients. Other ways to represent hyperglycemia were not studied. We hypothesized that computer assisted analysis of glucose levels may lead to an index that better reflects persistent hyperglycemia than the mean morning glucose. This would allow more precise comparisons of hyperglycemia between patients and patient groups. A number of questions pertaining to the implementation of glucose control also emerged after the Leuven study. The principal drawback of glucose control is the occurrence of hypoglycemia, which can be potentially fatal. To prevent this complication, glucose has to be sampled often, and this is a large burden on nursing time. Nurse guided protocols have been shown to improve glucose control and increase safety. We hypothesized that a computer assisted protocol may yield a safer and more efficient implementation of glucose control than conventional paper protocols.

Glucose and insulin therapy has been studied over the past decades in the form of GIK (glucose-insulin-potassium) infusion. This mixture may have a protective effect on ischemic myocardial cells, and has been proposed as an adjunctive therapy in patients with myocardial infarction. Trials in patients have shown mixed results.
We hypothesized that the fixed scheme that is used in all patients may in part be the cause why patients with myocardial infarction do not benefit from GIK infusion.

Assessment of myocardial perfusion

Primary percutaneous coronary intervention is the preferred way of treatment for acute ST-segment elevation myocardial infarction (STEMI).\textsuperscript{14,15} The success of the intervention can be assessed on the coronary angiogram. When adequate epicardial perfusion is achieved (TIMI flow 3) the most important angiographical predictor is myocardial perfusion as visually scored by the myocardial blush grade (MBG) or TIMI perfusion grade (TPG).\textsuperscript{16–18} The association between impaired myocardial perfusion and adverse clinical outcome is firmly established. However, the grading of blush requires an experienced observer, and visual assessment bears a marked variability as well as an intrinsic limited reproducibility. This limits the practical usability of blush grading in routine clinical practice. An objective analysis of the digital coronary angiogram may not only overcome these limitations, but may additionally provide a more fine-grained quantitative measure of myocardial perfusion that will facilitate the use of this parameter in future research.

Aims of this thesis

This thesis describes several projects in which computer assisted methods facilitate research or clinical practice in acutely ill patients.

Chapter 2 focuses on the development of an objective measure of hyperglycemia for assessing glucose control in acutely ill patients. The ideal index for hyperglycemia preferentially includes all available glucose measurements. This index should take measurement timing into account, as in practice there is a bias towards more frequent sampling when glucose values are out of the normal range. Additionally, conventional measures erroneously express a combination of hyper- and hypoglycemia as a normal value, whereas a correct index should reflect the hyperglycemic episodes, regardless of the occurrence of hypoglycemia. We propose a measure that meets these criteria, the hyperglycemic index (HGI), and have tested this and other indices of glucose control for correlation with adverse clinical outcome in a retrospective study design.

In chapter 3, 4 and 5 we apply the time-based analysis we developed in chapter 2 to two patient cohorts to gain more knowledge about the specifics of hyperglycemia. In chapter 3, we study a cohort of trauma patients and analyze how the pattern of hyperglycemia influences clinical outcome, and how this pattern compares with other critically ill patients. In chapter 4, a before-after study is described containing
two cohorts of patients admitted to the cardiothoracic ICU. Both cohorts received a
different dose of the potent corticosteroid dexamethasone. We analyze the influence
of this difference on persistent hyperglycemia after ICU admission. In the first part of
chapter 5 we study glucose levels in patients with acute myocardial infarction treated
with glucose-insulin-potassium (GIK) infusion in the GIPS II study. We test whether
the glucose component in the GIK solution induced hyperglycemia, and how this
relates to the outcome of the patients. In the second part of chapter 5 glucose changes
after hospital admission in patients with acute myocardial infarction are discussed.

In chapter 6 we evaluate a computer assisted method to quantify myocardial
perfusion on the coronary angiogram after reperfusion therapy in a large cohort of
patients with STEMI treated with primary angioplasty. After an operator indicates
the area of the angiogram where the infarct related vessel is, a computer application
calculates a value reflecting the amount of contrast agent that reaches the infarcted
myocardium. We analyze whether these values predict clinical outcome as reflected
by normalization of the ST segment on the ECG, enzyme levels, and death at one year.

In the second section of the thesis, focus is transferred to the application of com-
puter technology in the treatment of patients in routine practice. Chapter 7 introduces
computer assisted technology for the management of glucose metabolism. The design
and implementation of “GRIP”, a computer program to assist glucose control in the
intensive care unit is described. This computer program recommends insulin pump
rates and glucose measurement intervals to the nurse caring for a patient. The hy-
pothesis that a computer assisted protocol can deliver safe control with an optimized
number of measurements is tested on a small cohort of patients. In chapter 8 we
analyze a large cohort of patients treated with GRIP, to confirm the findings of the
small cohort study, and to refine the estimates of the rate of hypoglycemia, the quality
of glucose control, and of the level of efficiency. Chapter 9 describes the expansion of
GRIP with recommendations for potassium control, which logically extends the glu-
cose control functionality. A cohort of patients before the change is compared with
a cohort of patients admitted after GRIP was giving recommendations for potassium
infusion. The potassium levels of the two cohorts are compared to test the hypoth-
esis whether a computer protocol can reduce the number of potentially dangerous
episodes of hypo- and hyperkalemia.

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