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Strict Glucose Control Does Not Affect Mortality after Aneurysmal Subarachnoid Hemorrhage

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Background: **The effects of both hyperglycemia and hypoglycemia are deleterious to patients with neurologic injury.**

Methods: **On January 1, 2002, the neurointensive care unit at the University of Virginia Health System initiated a strict glucose control protocol (goal glucose < 120 mg/dl). The authors conducted an impact study to determine the effects of this protocol on patients presenting with aneurysmal subarachnoid hemorrhage.**

Results: **Among the 834 patients admitted between 1995 and 2007, the in-hospital mortality was 11.6%. The median admission glucose for survivors was lower (135 *vs.* 176 mg/dl); however, on multivariate analysis, increasing admission glucose was not associated with a statistically significant increase in the risk of death ($P = 0.064$). The median average glucose for survivors was also lower (116 *vs.* 135 mg/dl). This was significant on multivariate analysis ($P < 0.001$); however, the effect was small (odds ratio, 1.045). Implementation of the strict glucose protocol decreased median average glucose (121 *vs.* 116 mg/dl, $P < 0.001$) and decreased the incidence of hyperglycemia. Implementation of the protocol had no effect on in-hospital mortality (11.7% *vs.* 12.0%, $P = 0.876$ [univariate], $P = 0.132$ [multivariate]). Protocol implementation was associated with an increased incidence of hypoglycemia ($P < 0.001$). Hypoglycemia was associated with a substantially increased risk of death on multivariate analysis ($P = 0.009$; odds ratio = 3.818).**

Conclusions: **The initiation of a tight glucose control regimen lowered average glucose levels but had no effect on overall in-hospital mortality.**

ALTHOUGH glucose is the principle metabolic fuel of the central nervous system and the effects of severe hypoglycemia can be devastating, the effects of prolonged hyperglycemia may be equally deleterious, especially in patients with neurologic injury. Whether or not aggressive glucose control is beneficial to this patient population remains a matter of debate and hinges on whether glucose is a mediator or marker of critical illness.[1]

Data supporting a strong association between hyperglycemia and poor outcomes in the absence of neurologic injury are abundant and include patients with myocardial infarction,[2–8] traumatic injuries,[9,10] and postoperative wound infections.[11–14] Similarly, hyperglycemia has been associated with poor outcomes in patients suffering from stroke,[8,15–18] traumatic brain injury,[19] and subarachnoid hemorrhage.[20–23]

These data formed the impetus for a series of large, randomized, controlled trials comparing strict glucose control to more traditional means in various patient populations. In 2001, Van den Bergh *et al.* conducted a study of 1,548 predominantly surgical patients and demonstrated a statistically significant mortality reduction of 32% when patients were placed on a strict glucose control regimen (goal 80–110 mg/dl) as compared to "traditional" glucose control.[24] This often cited study led many institutions to initiate a similar glucose control regimen in their intensive care units; others were skeptical of extrapolating data based on a narrow patient population (most of Van den Bergh's patients had undergone recent cardiac surgery) and conducted their own studies.

In the prematurely terminated Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study, strict glucose control had no effect on mortality but increased the incidence of severe hypoglycemia and serious adverse events.[25] The GluControl study of 1,101 critically-ill patients similarly showed no reduction in mortality but an increased incidence of severe hypoglycemia when tight glucose control was used.[26] Repeating their study in 2006, Van den Bergh *et al.* were unable to demonstrate a benefit of strict glucose control in the medical intensive care unit.[27] Further complicating the effects of strict glucose control when Van den Bergh *et al.* reviewed a subset of neurologically injured patients from their first study, they found that strict glucose control improved outcome scores but led to an increase in mortality.[28]

Thus, in instances where hyperglycemia has been correlated with adverse outcomes, it should not be assumed that aggressive treatment is necessarily beneficial. It is known, for instance, that intraoperative hyperglycemia is an independent risk factor for perioperative complications in cardiac surgery patients.[29,30] Aggressive treatment in this population, however, does not improve mor-

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tality; in fact, it increases the incidence of stroke ($P = 0.020$).[31] Similarly, while the prognostic ramifications of hyperglycemia in subarachnoid hemorrhage patients are known, a benefit of glucose control has not been demonstrated. Indeed, a recent prospective, randomized, controlled trial of strict glucose control in 78 patients with subarachnoid hemorrhage did not show a mortality benefit, but the authors did not report glucose values for each group, making it difficult to interpret the results.[32]

On January 1, 2002, the neurocritical care unit at the University of Virginia initiated a strict glucose control regimen (90-120 mg/dl). We conducted an impact study to determine the effects this protocol had on blood glucose and in-hospital mortality in patients presenting with aneurysmal subarachnoid hemorrhage (SAH).

Materials and Methods

After approval from the institutional review board, we retrospectively reviewed the charts of 834 patients admitted to the University of Virginia Health System with aneurysmal SAH as a primary diagnosis between 1995 and 2007. This was accomplished by querying the University of Virginia's Clinical Data Repository, a structured query language database containing laboratory, mortality, and other data for all patients admitted to the University of Virginia Health System. Information not included in the Clinical Data Repository was obtained through individual chart review. For the purposes of our study, all glucose values from admission to discharge were recorded for all patients, as well as aneurysm location, number of aneurysms, type of intervention (craniotomy *vs.* interventional), whether or not vasospasm occurred, and the patient's outcome on the day of discharge (alive or deceased). A patient was considered to have vasospasm if it was noted in their discharge summary, whether diagnosis was made on clinical grounds or radiographically. Using these initial data, we then determined admission and average glucose for each patient and separated the patients on the basis of initiation of the glucose control protocol, which went into effect on January 1, 2002.

The protocol adopted by the University of Virginia neurologic intensive care unit on January 1, 2002 determines a recommended change in insulin infusion rate by taking into account the trajectory between the previous and current blood glucose readings as well as the current insulin infusion rate. This is accomplished by drawing a line between the current and previous blood glucose values on a linear scale and extrapolating this line onto a grid, stopping in the appropriate row (which is based on current infusion rate, fig. 1). The goal of this regimen is to keep glucose between 90 and 120 mg/dl.

The data were analyzed to test the primary *a priori* hypothesis that the institution of the protocol would result in less hyperglycemia and a lower average glucose and that this would result in a reduction in in-hospital mortality. The data were also analyzed to test the impact of the protocol on the incidence of vasospasm. Exploratory analyses of the other patient variables on mortality and vasospasm were also conducted.

Results are presented as percentage or means ± SD or median with 25–75% interval as appropriate. Univariate statistical analysis using version 16.0.1 of the SPSS statistical analysis software package (SPSS Incorporated, Chicago, IL) was performed using a Z-test, chi-square, Mann–Whitney rank sum test, or *t* test as indicated. Comparisons were made using two-tailed tests. Multivariate logistic regression was used to identify risk factors for death and vasospasm. Initially, all available covariates were first analyzed in the multivariate model. Then, a forward stepwise approach was taken to identify risk factors for death (or vasospasm). Only identified risk factors were put into the final model to calculate the effect size of each covariate. This analysis was performed with using SigmaStat 3.5 (Systat Software, Inc., Point Richmond, CA). A $P < 0.05$ was considered significant.

Results

Between January 1, 1995, and December 31, 2001, 343 patients were admitted with the primary diagnosis of aneurysmal subarachnoid hemorrhage (preprotocol). Between January 1, 2002, and December 31, 2007, 491 patients were admitted (postprotocol). The median average glucose for all patients before initiation of the glucose control protocol was 121 mg/dl (25–75%, 112–133 mg/dl); after the initiation of the protocol, the median average glucose decreased to 116 mg/dl (25–75%, 108–124 mg/dl) ($P < 0.001$). Furthermore, the protocol reduced the percentage of patients with an average glucose greater than 180 mg/dl from 6.4% to 0.41% ($P < 0.001$) and increased the percentage of patients with an average glucose of less than 120 mg/dl from 46.9% to 63.1% ($P < 0.001$). There are other statistically significant differences in the descriptive characteristics of the preprotocol and postprotocol groups. These results are summarized in table 1.

Of the 834 patients admitted between 1995 and 2007, 735 survived to discharge. Thus, the overall resultant in-hospital mortality for aneurysmal SAH was 11.9%. Over the entire study period, the median admission glucose for patients who survived was 135 mg/dl (25–75%, 112–170), whereas the median admission glucose for patients who died was 176 mg/dl (25–75%, 138–233) ($P < 0.001$); however, on multivariate analysis, increasing admission glucose was not associated with a statistically significant increase in the risk of death ($P = 0.064$). The median average glucose for all patients who survived was 116 mg/dl (25–75%, 109–125), whereas the median average glucose for those who died was 135

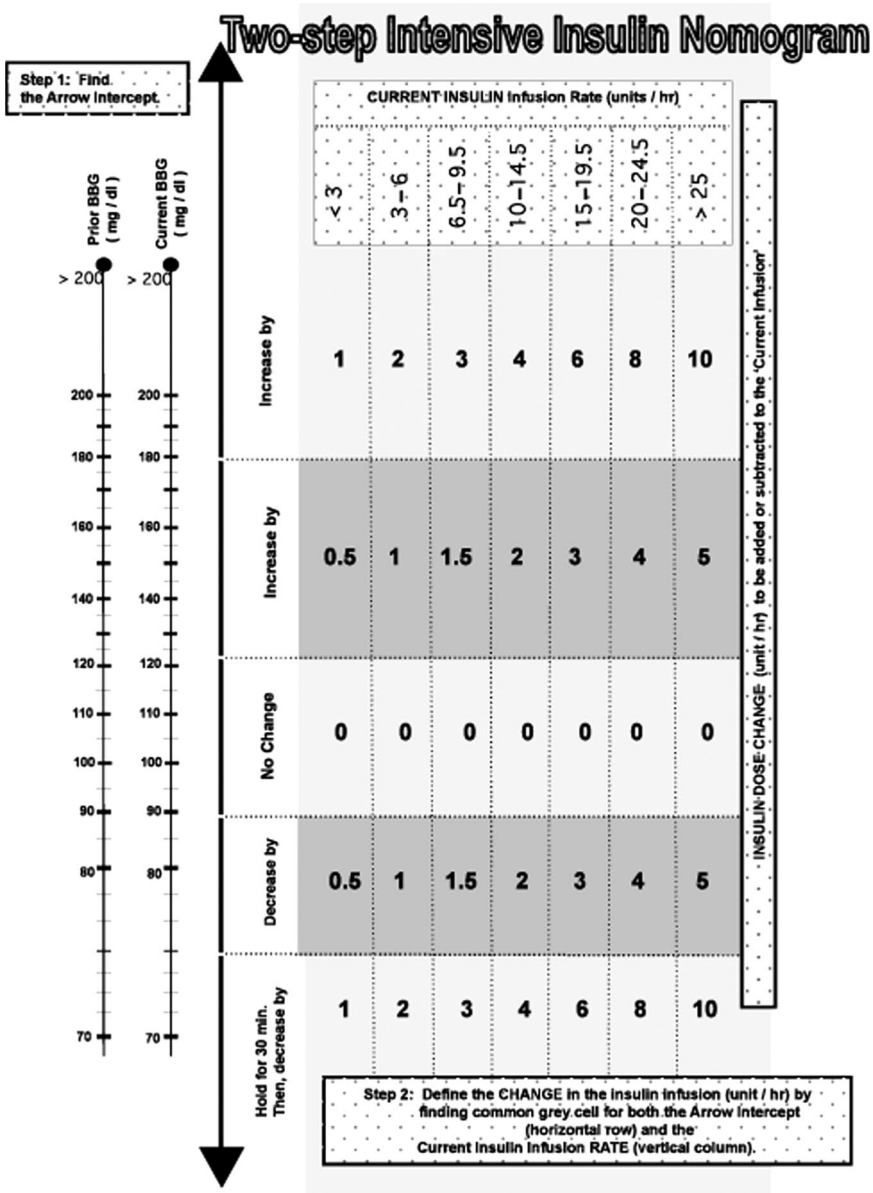

Fig. 1. Glucose control nomogram, used in the neurocritical care unit at the University of Virginia Health Sciences Center beginning on January 1, 2002.

mg/dl (25–75%, 123–157) ($P < 0.001$). On multivariate analysis, increasing average glucose was associated with a statistically significant increase in the risk of death ($P < 0.001$); however, the effect was small (OR, 1.045; 95% CI, 1.034–1.056).

Implementation of the protocol had no effect on in-hospital mortality. Mortality increased from 11.7% to 12.0% after initiation of the protocol, which did not reach statistical significance on univariate ($P = 0.876$) or multivariate ($P = 0.132$; OR, 1.602; 95% CI,: 0.868–2.956) analysis.

Other factors associated with an increase in mortality on multivariate analysis include the presence of either an intraventricular or intraparenchymal hemorrhage ($P = < 0.001$; OR, 2.658; 95% CI, 1.603–4.407) and an incident of moderate (defined as < 60 mg/dl) hypoglycemia ($P = 0.009$; OR, 3.818; 95% CI, 1.396–10.441). Obviously, in-hospital mortality was associated with a decreased length of stay on multivariate analysis ($P < 0.001$; OR, 0.876; 95% CI, 0.840–0.915). These results are summarized in table 2.

Vasospasm (clinical or radiographic) was documented in 22.4% of patients before initiation of the protocol, as compared to 34.0% of patients after initiation of the protocol ($P < 0.001$). On multivariate analysis, this association was also statistically significant ($P = 0.003$; OR, 1.784; 95% CI, 1.220–2.610). Other factors associated with an increase in the incidence of vasospasm on multivariate analysis included a craniotomy and clipping of the aneurysm (*vs.* endovascular coiling) ($P = 0.004$; OR, 1.757; 95% CI, 1.195–2.582), the presence of either an intraventricular or intraparenchymal hemorrhage ($P = 0.016$; OR, 1.541; 95% CI, 1.084–2.190), and increased length of stay ($P < 0.001$; OR, 1.057; 95% CI, 1.039–

Table 1. Comparison between Preprotocol and Postprotocol Groups

	Preprotocol	Postprotocol	*P* Value
Patient characteristics			
Number of patients	343	491	N/A
Male	31.8%	24.8%	0.028†‡
Caucasian	81.6%	55.2%	< 0.001†‡
Anterior circulation aneurysms	74.6%	80.2%	0.346†
Multiple aneurysms	12.2%	14.1%	0.449†
Other bleed (IVH, IPH)	27.4%	58.3%	< 0.001†‡
Craniotomy	79.3%	61.5%	< 0.001†‡
Median admission glucose	137 (112–174)	140 (114–175)	0.408
Outcome variables			
Median glucose	121 (112–133)	116 (108–124)	< 0.001*‡
Average glucose > 180	6.4%	0.41%	< 0.001†‡
Average glucose < 120	46.9%	63.1%	< 0.001†‡
Median length of stay	13 (9–19) days	13 (10–18) days	0.590*
Moderate hypoglycemic events	2.04%	9.17%	< 0.001†‡
Severe hypoglycemic events	0.583%	0.611%	0.95†
Documented vasospasm	22.5%	34.0%	< 0.003†‡
Mortality	11.7%	12.0%	0.876†

Results are median (25–75%).

* *P* values based on Mann-Whitney rank sum test. † *P*values based on chi-square. ‡ Statistically significant.

IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage; N/A = not applicable.

1.076). Factors associated with a decrease in the risk of vasospasm included a lower average glucose ($P = 0.004$; OR, 0.984; 95% CI, 0.972–0.995). These results are summarized in table 3.

Initiation of the protocol was associated with an increase in the incidence of hypoglycemia; 1.46% of patients experienced an episode of moderate hypoglycemia (defined as a glucose value < 60 mg/dl) before initiation of the protocol compared to 7.13% of patients after initiation of the protocol ($P < 0.001$). Differences in the incidence of severe hypoglycemic events (defined as a glucose value < 40 mg/dl) were not significant (0.292% *vs.* 0.611%; $P = 0.511$). These data are summarized in table 4. As noted above, hypoglycemia was associated with an increased risk of death on multivariate analysis ($P = 0.016$; OR, 3.43; 95% CI, 1.256–9.386; table 2).

Table 2. Multivariate Comparison of Factors Related to Mortality

	Odds Ratio	5% Confidence Lower	95% Confidence Upper	*P* Value
Significant predictors				
Other bleed (IVH, IPH)	2.658	1.603	4.407	< 0.001
Moderate hypoglycemia	3.818	1.396	10.441	0.009
Average glucose	1.045	1.034	1.056	< 0.001
Length of stay	0.876	0.840	0.915	< 0.001
Other factors				
Male	0.974	0.554	1.711	0.926
Caucasian	1.327	0.680	2.590	0.407
Multiple aneurysms	0.993	0.450	2.192	0.987
Craniotomy	0.817	0.469	1.425	0.477
Posterior circulation	1.398	0.743	2.628	0.299
Admission glucose	1.004	1.000	1.009	0.064
Vasospasm	1.397	0.754	2.588	0.288
Protocol	1.602	0.868	2.956	0.132

IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage.

Discussion

Our data show that the glucose control protocol initiated in 2002 effectively reduced average blood glucose, reduced the incidence of hyperglycemia, and increased the number of patients with an average blood glucose less than 120 mg/dl. Unfortunately, the protocol was associated with a substantial increase in the number of hypoglycemic events. On univariate analysis, increased admission and average glucose were strongly correlated

Table 3. Multivariate Comparison of Factors Related to Vasospasm

	Odds Ratio	5% Confidence Lower	95% Confidence Upper	*P* Value
Significant Predictors				
Craniotomy	1.757	1.195	2.582	0.004
Other bleed (IVH, IPH)	1.541	1.084	2.190	0.016
Average glucose	0.984	0.972	0.995	0.004
Length of stay	1.057	1.039	1.076	< 0.001
Protocol	1.784	1.220	2.610	0.003
Other factors				
Male	0.775	0.535	1.123	0.178
Caucasian	1.180	0.786	1.774	0.425
Multiple aneurysms	1.128	0.700	1.816	0.621
Moderate hypoglycemia	1.396	0.666	2.924	0.377
Admission glucose	1.001	0.998	1.005	0.472
Death	1.386	0.716	2.683	0.333

IPH = intraparenchymal hemorrhage; IVH = intraventricular hemorrhage.

Table 4. Hypoglycemic Incidents

	Incidents	Incidence (per Patient)	*P* Value*
Before January 1, 2002			
< 60	5	0.0146	
< 40	1	0.00292	
Beginning January 1, 2002			
< 60	35	0.0713	< 0.001
< 40	3	0.00611	0.511

* Comparing incidence of hypoglycemia preprotocol and postprotocol, chi-square.

with mortality; however, only increased average glucose was found to be associated with mortality on multivariate analysis. Although the effect of higher average blood sugar was statistically significant ($P < 0.001$), the impact of hyperglycemia appears to be fairly small, evidenced by the OR of 1.045 (95% CI, 1.031–1.059; table 2). Given the small contribution of hyperglycemia to in-hospital mortality, it is not surprising that implementation of the protocol did not affect patient mortality on either univariate or multivariate analysis. Taken together, these data suggest that hyperglycemia is powerful predictor of mortality but contributes little to mortality in and of itself.

Hyperglycemia is a known component of the stress response[33]; similar to Glasgow Coma Scale scores, it may simply be an indication of injury severity. The prospective, observational study by Finney *et al.* of 531 heterogeneous critical care patients found a statistically significant relationship between likelihood of death (OR) and amount of insulin administered in each subgroup (categorized on the basis of average glucose), but it did not find a relationship between mortality and glucose level.[34] These findings are compatible with the idea that elevated glucose is simply a marker for injury and that treating it does not provide any recognizable benefit.

Another important observation is the increase in hypoglycemic events after implementation of the protocol and the strong association of hypoglycemia and mortality. Indeed, we were unable to identify a factor more powerfully associated with mortality than moderate (< 60 mg/dl) hypoglycemia (OR, 3.818; 95% CI, 1.396–10.441). It is possible that any positive impact of the protocol and aggressive glucose management may have been eclipsed by the negative impact of hypoglycemia. In the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis study, which was terminated early due to lack of benefit and in increased incidence of severe (< 40 mg/dl) hypoglycemia, Cox regression analysis identified hypoglycemia as an independent risk factor for death from any cause.[25] A recent meta-analysis of 34 randomized trials in critically ill adult patients suggested that tight glucose control is not associated with significantly reduced in-hospital mortality and is associated with an increased risk of hypoglycemia.[35] Whether or not hypoglycemia itself is dangerous or a marker for injury or difficult glucose control cannot be determined from these data.

Vespa *et al.* recently studied parenchymal glucose values by placing intracerebral microdialysis catheters in 47 patients with severe traumatic brain injuries (33 of whom received intensive insulin therapy with a target glucose 120–150 mg/dl, and 14 of whom did not) and found that markedly low levels of intraparenchymal glucose could occur in the intensive insulin therapy group despite relatively normal systemic blood glucose levels.[36] While upregulation of the blood brain barrier *GLUT1* transporter in hypoglycemic states is well established in animal models,[37–39] evidence of downregulation of the *GLUT1* in animal models is mixed.[40,41]

On the basis of the data from Vespa *et al.*, it seems possible that patients who had chronically elevated serum glucose levels have less native *GLUT1* and therefore low glucose levels in the central nervous system after rapid normalization of chronic hyperglycemia. If this were the case, response to intensive insulin therapy would depend heavily on the level of pre-SAH glucose control. In patients who have poorly controlled diabetes before their SAH, abrupt normalization of blood glucose could lead to cerebral hypoglycemia that would not be detected by standard laboratory measures. Unfortunately, it is impossible to determine each patient's pre-SAH glucose control in this retrospective study.

A third explanation for the protocol's lack of benefit despite an association between hyperglycemia and mortality is that the hyperglycemic response to stress may be adaptive and beneficial, making attenuation harmful.[42] Indeed, a review of 12 glucose control studies by Wilson *et al.* suggested that the 80–110 mg/dl range may not be ideal because it is based on a trial of predominantly postsurgical patients,[43] all of whom received 200–300 g of IV glucose daily in the intensive care unit.[24,25] While Wilson *et al.* acknowledge that it is difficult to make comparisons across studies, a retrospective study of 1600 consecutive critically ill patients by Krinsley *et al.* showed a mortality reduction when glucose was kept below 140 mg/dl with no appreciable change in hypoglycemia, suggesting that the upper limit of glucose with regards to mortality may be need to be revised.[44]

Wilson *et al.* further point out that, in addition to differences in target glucose levels, there is no standardized dosing regimen across studies; different infusion algorithms lead to substantial variation in treatment efficacy as well as the incidence of hypoglycemia. In addition, not all regimens take into account insulin sensitivity,[45] which can also affect efficacy. Finally, it may be that insulin variability is just as important as mean values in determining outcome,[46] a possibility that is neglected by most current protocols (including ours).

Given the uncertainty surrounding glucose control in various patient populations, it seems prudent to study

SAH patients specifically. Bilotta *et al.* recently published a prospective, randomized, controlled trial of strict glucose control in 78 patients with SAH that did not show a mortality benefit. Unfortunately, the authors did not disclose the mean glucose values or the SD in either study group, making it difficult to interpret the results.[32]

Vasospasm is the leading cause of death in patients who survive the initial insult of aneurysm rupture; therefore, we felt it reasonable to study the effect of our protocol on vasospasm. After multivariate analysis, the protocol was associated with an increase in the incidence of vasospasm (table 3). It is important to note that an increase in the apparent incidence of vasospasm was also noted over the study period (table 1). These results can most likely be explained by the increase in computed tomography angiography resolution that accompanied the adoption of a strict glucose protocol. If a strict glucose protocol or differences in average glucose had a true, clinically significant effect on the second overall leading cause of death in the SAH population, this would be reflected in the mortality data; however, it is not.

Finally, this retrospective review was conducted by examining all available data over a defined study period and was not powered to detect clinically significant differences. Indeed, the incidence of in-hospital mortality postprotocol would have to be 6.1% for the study to have had 80% power to detect statistically significant differences. This would have amounted to a 49% reduction in mortality, as compared to the 32% reduction observed in Van den Bergh's initial study.[24] Thus, our data must be interpreted in the context of the available statistical power.

Our study has several limitations. First, it is retrospective, which introduces potential differences in baseline patient population characteristics, potential differences in medical practice, and potential biases with regards to treatment. The study period has seen tremendous differences in the way patients with SAH are treated. The advent of interventional neuroradiology, for instance, has had a profound effect on the treatment of patients with aneurysmal subarachnoid hemorrhage, although the effects on outcome are less certain. Data from the International Subarachnoid Aneurysm Trial study, which included a much narrower patient population than ours (less than 25% of eligible patients were randomized, 97% were anterior circulation aneurysms, and 80% were Hunt and Hess grade 2 or better), took place outside of the United States and showed a mortality difference of 7.0 *versus* 7.9% at 2 months in favor of endovascular surgery, may not be applicable to our study.[47] This is not to say that there is no difference between traditional (craniotomy) or interventional treatment of aneurysms, only that in terms of our study variables (in-house mortality, vasospasm), differences have not been firmly established. Also important, the constantly increasing resolution and decreasing scan time of computed tomography angiography has enhanced the ability of physicians to detect radiographic vasospasm, which can lead to a perceived increase in the incidence of vasospasm when in fact, no change has occurred.

Another limitation of the study is that glucose was treated as a continuous variable in the multivariate model, and the effect of glucose was considered to be linear; however, any effect of glucose on mortality or vasospasm may indeed not be linear. Unfortunately, there are no human clinical data to suggest an optimal blood glucose in patients with SAH. Thus, coding the data would be somewhat arbitrary.

Our analysis is also weakened because is does not stratify patients on the basis of all known prognostic variables, most notably World Federation of Neurosurgeons score, Hunt & Hess score, or Fisher grade. Unfortunately, World Federation of Neurosurgeons score and Hunt & Hess score were not included in the Clinical Data Repository database dataset and are inconsistently recorded in the paper charts. Any attempt on the part of the study team to reconstruct a World Federation of Neurosurgeons score or Hunt & Hess score would introduce significant bias.

To minimize these potentially confounding factors, we studied a large number of patients (834 total), with the expectation that most or all of the prognostic variables not available in our database would be averaged out over such a large population. In addition, our hospital is the only medical facility that treats aneurysmal subarachnoid hemorrhage in a large, stable catchment area, making it unlikely that the injury severity in patients admitted to our hospital with the diagnosis of subarachnoid hemorrhage changed over the course of this study.

Our findings are important for several reasons. First, as has previously been described, they confirm that the mortality rate of SAH patients as a population is associated with their admission glucose. Second, they fail to demonstrate a statistically significant relationship between mortality and intensive glucose control. Third, they support the hypothesis that while hyperglycemia is detrimental and intensive insulin therapy may reduce mortality above a certain threshold, there is a point below which increasing glucose control may no longer beneficial, and, may be harmful, especially if associated with hypoglycemia. In light of this and other published data, the design of more sophisticated insulin protocols that reduce the incidence of hyperglycemia while preventing hypoglycemia should be a priority.

Conclusions

Patients who survive SAH have lower admission and average blood glucose levels as compared to those who die. The initiation of a strict glucose control

regimen in the neurologic intensive care unit at the University of Virginia Health System decreased median average glucose levels, decreased the number of hyperglycemic patients, and increased the number of patients with blood glucose less than 120 mg/dl, but it had no effect on overall in-hospital mortality. The protocol was also associated with an increase in the incidence of hypoglycemia, which was powerfully associated with mortality.

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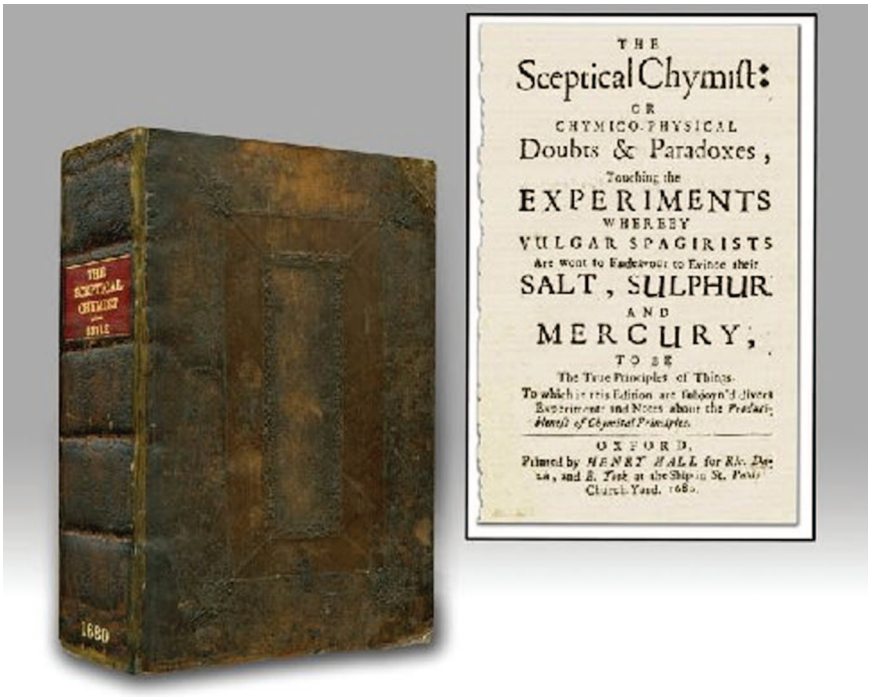
ANESTHESIOLOGY REFLECTIONS

Boyle, a Most Skeptical Chemist



In 1659 the future "Sir Christopher Wren" and Anglo-Irish chemist Robert Boyle (1627–1691) pioneered intravenous therapy by injecting opium through a goose quill into a dog's vein. By November of 1660, Wren and Boyle were meeting with 10 other scientists, gatherings that would lead to the formal chartering of the "Royal Society of London for the Improvement of Natural Knowledge." Not surprisingly, the Royal Society's motto *Nullius in Verba* ("Nothing in Words") would reflect Boyle's emphasis on the experimental method. Boyle's masterwork *Sceptical Chymist* was first published from London in 1661. He published what we call "Boyle's Law" the following year. Pictured here is the Wood Library-Museum's first complete English edition of *Sceptical Chymist* published from Oxford in 1680. That same year Boyle was elected to the presidency of the Royal Society, but the "Father of Modern Chemistry" declined the honor, citing his religion's prohibitions against taking oaths. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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