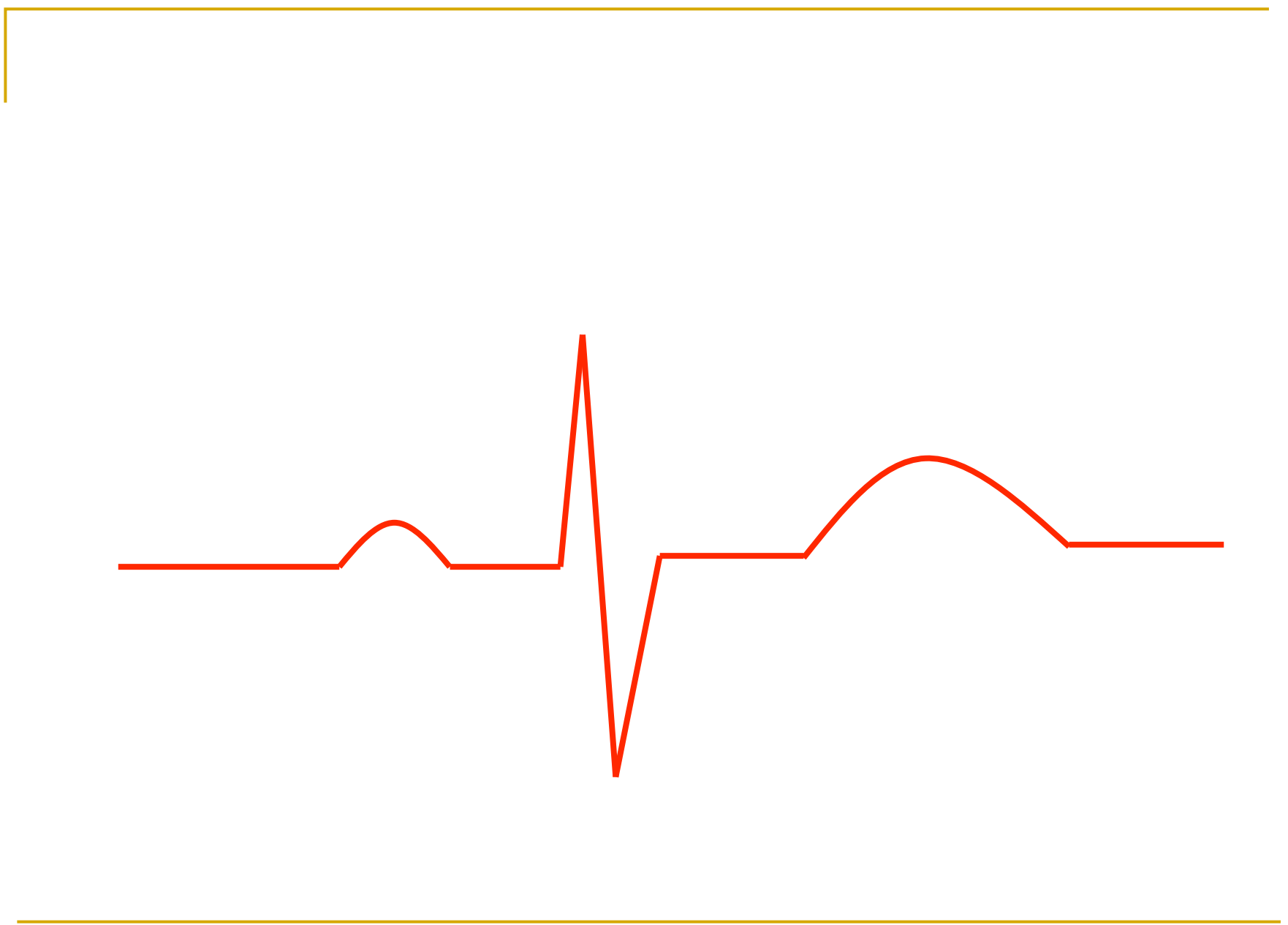
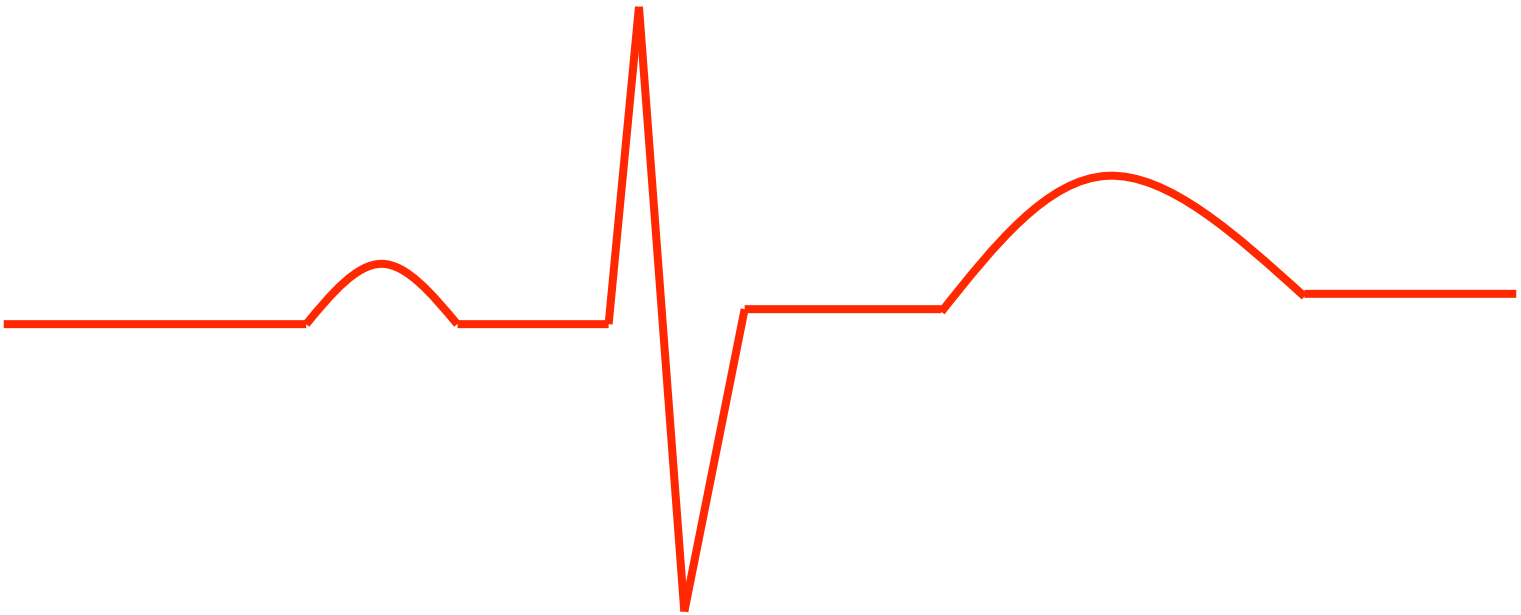
Limiter ou respecter la variabilité glycémique?

Jean-Charles Preiser

JFN 2010

10 décembre 2010





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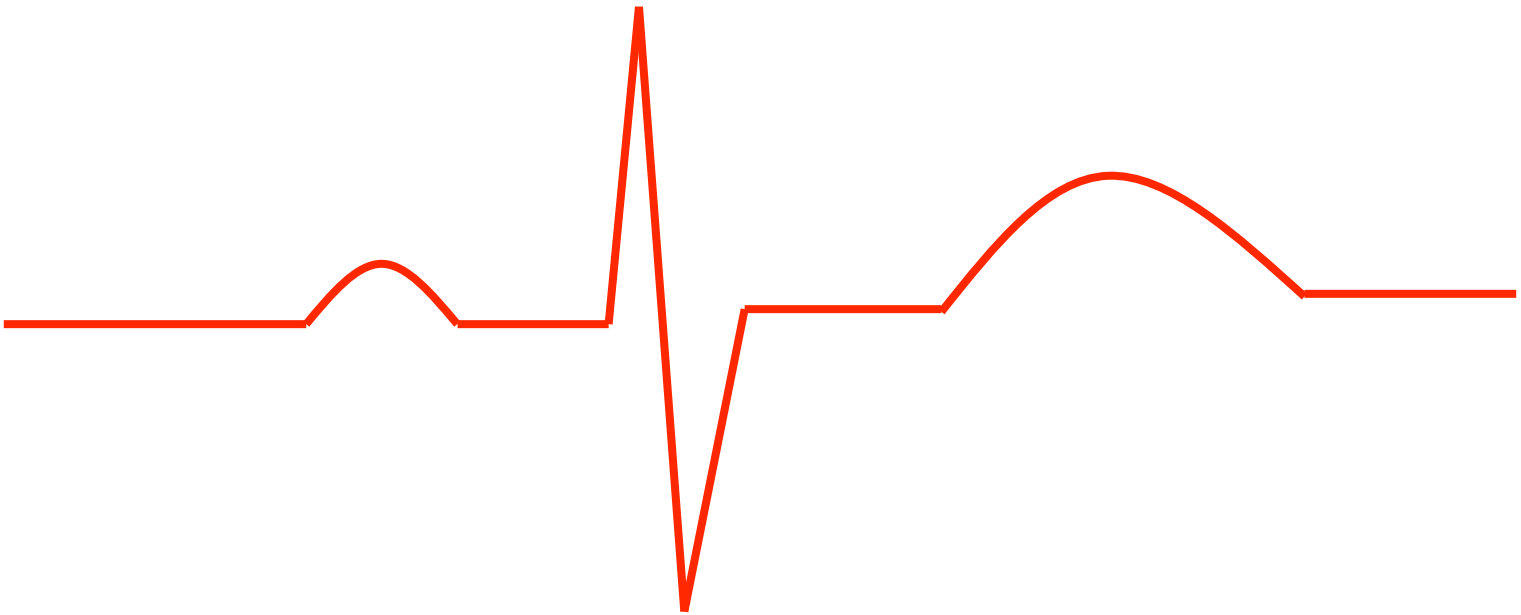

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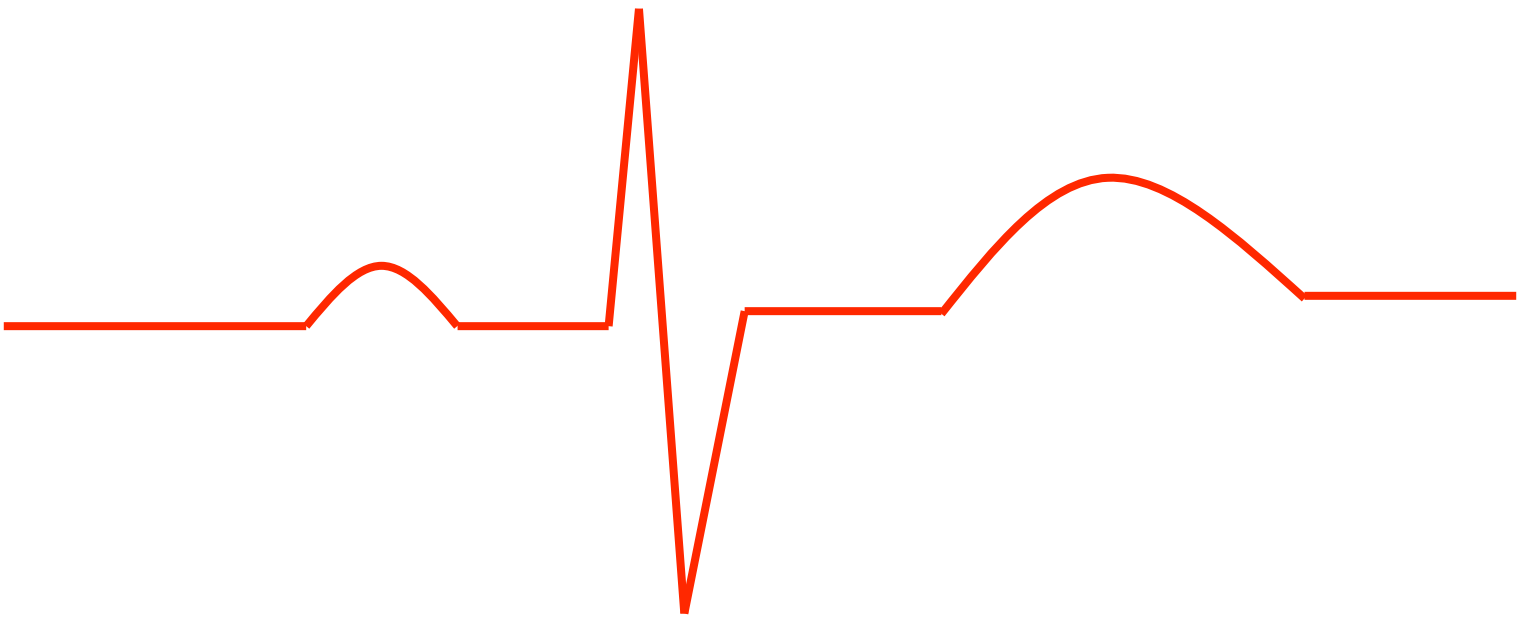

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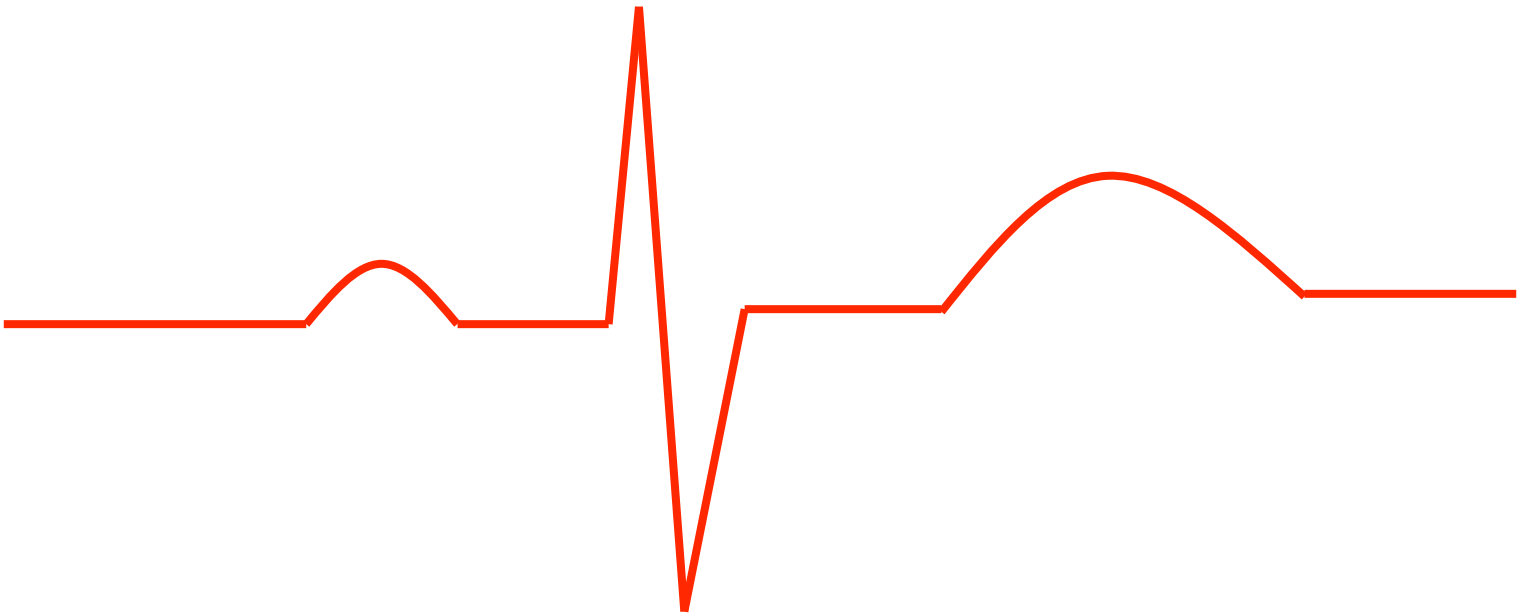
2006-2009



Period 4
2009-


Walt Disney
Pictures Presents
Cinderella II
Dreams Come True
DVD


By far the most terrifying film
you will ever see.
aninconvenienttruth
A GLOBAL WARNING

CLINICAL EXPERIENCE WITH TIGHT GLUCOSE CONTROL BY INTENSIVE INSULIN THERAPY

Preiser Devos Crit Care Med 2007

- How does IIT work?
- Optimal target for blood glucose
- **Is the absolute level or the variability of blood glucose the most detrimental factor?**
- Is hypoglycemia life-threatening?
- Associated workload

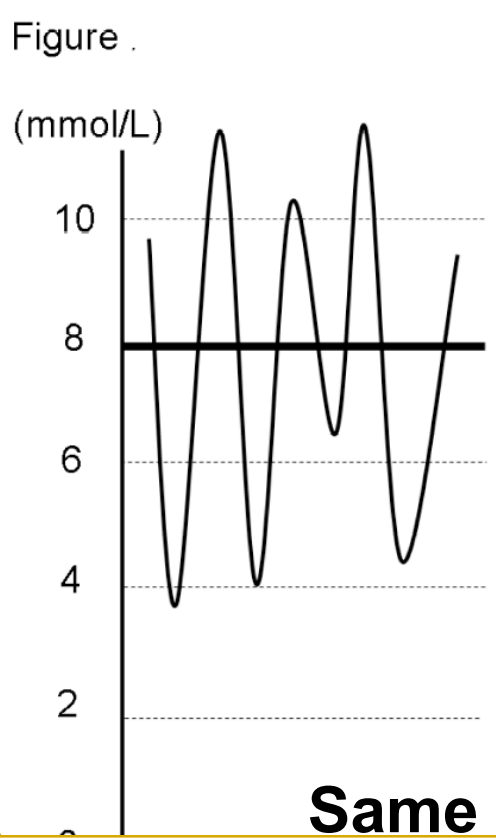
An unexplored hypothesis is left and appealing !

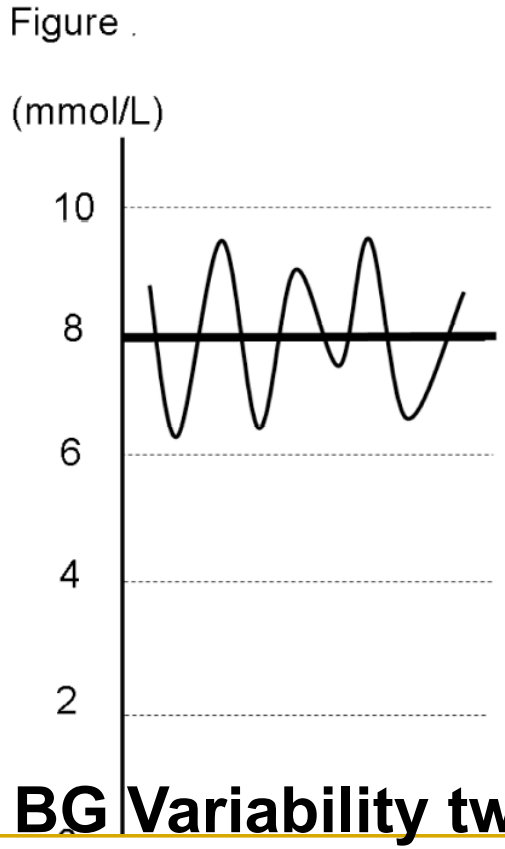
- Hypothesis : high glucose variability is possibly detrimental for critically ill patients
- Supporting data : retrospective cohort study
- Biological plausibility

Is reducing variability of blood glucose the real but hidden target of intensive insulin therapy?

M Egi R Bellomo M Reade

Crit Care 2009 (in press)





Same average BG Variability twice lower

Anesthesiology 2006; 105:244–52 © 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

Moritoki Egi, M.D., Rinaldo Bellomo, M.D., F.J.F.I.C.M.,† Edward Stachowski, M.D.,‡ Craig J. French, M.D.,§ Graeme Hart, M.D.‖*

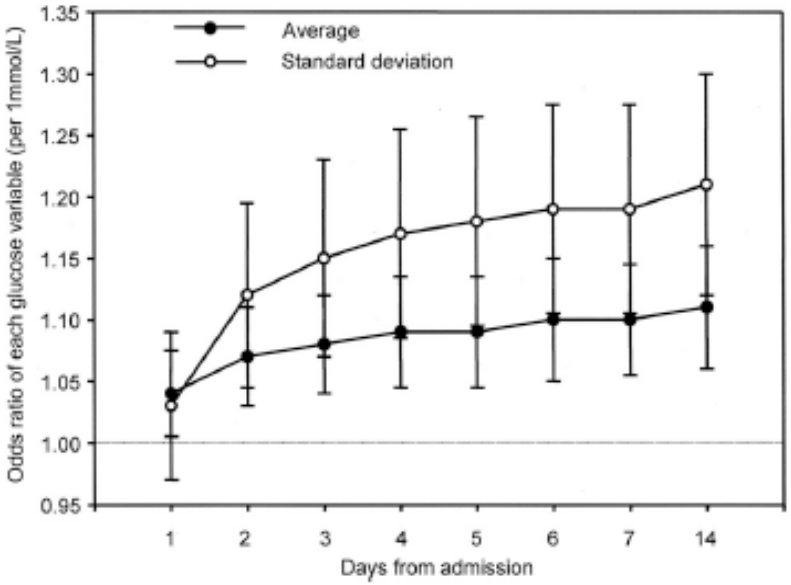


Fig. 4. Time course of the predictive ability of average and SD of blood glucose. Odds ratios (expressed with 95% confidential intervals) for glucose indexes indicate the risk change of intensive care unit mortality per 1-mmol change in each index. For example, average of blood glucose on 7 days from admission means average of entire glucose measurements during 7 days from admission. As time in intensive care unit increased, so did the ability of glucose control indices to predict outcome.

Glycemic variability: A strong independent predictor of mortality in critically ill patients

James S. Krinsley, MD, FCCM, FCCP

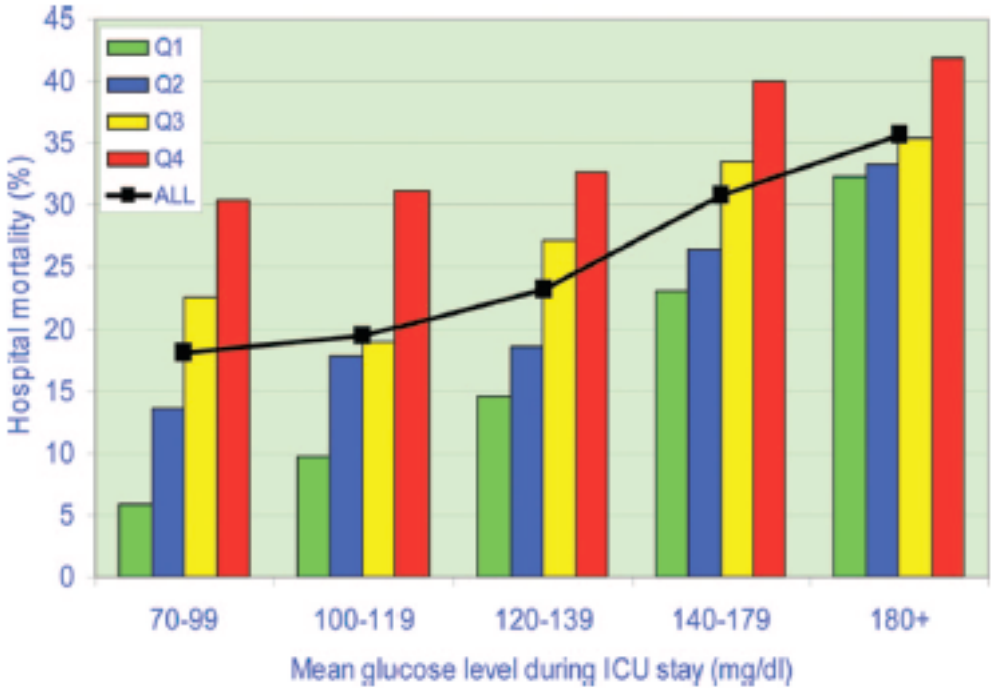
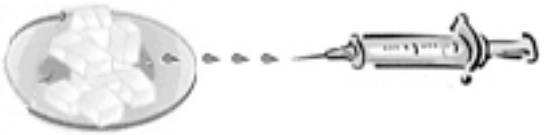
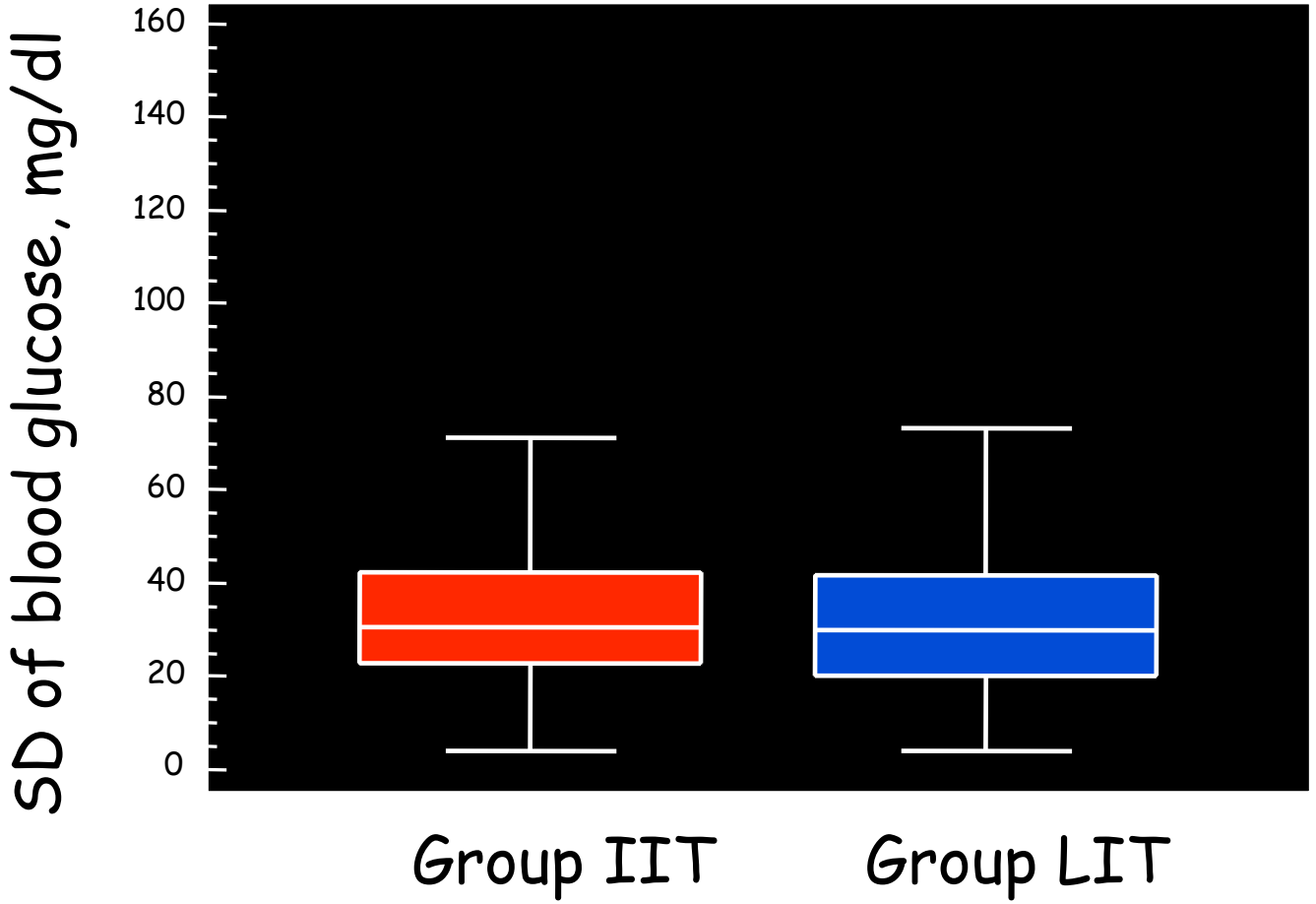


Figure 1. Each of the increments of MGL is subdivided into four quartiles of glycemic variability. Q1 represents the lowest quartile; Q4 represents the highest quartile. *MGL,* mean glucose level.

Glycemic Variability Assessed From SD



GLUCONTROL



p NS

Variability of blood glucose

NICE-SUGAR

N Engl J Med 2009

	n =	IIT	Ctrl			
Morning blood glucose — mg/dl						
From randomization to cessation of study treatment	6001	118±25	145±26	−27 (−28 to −25)	Welch's test	<0.001
From randomization to ICU dis-charge	5987	118±25	145±26	−27 (−28 to −25)	Welch's test	<0.001
Time-weighted blood glucose — mg/dl						
From randomization to cessation of study treatment	6014	115±18	144±23	−29 (−30 to −28)	Welch's test	<0.001
From randomization to ICU dis-charge	6000	115±19	144±23	−29 (−30 to −28)	Welch's test	<0.001

Which « index » of GV is better ?

Indices of glucose variability

Ali, Krinsley, Preiser Yearbook ICEM 2009

Expression	Calculation	Population studied	Description
Standard Deviation[21,22]		Diabetics, Sepsis, mixed ICU patients	Measure of the range of glucoses measured from the median
MAGE[26]	$\cdot N^{-1}$ if (Yi-Yi-1)≥ 1SD of a subjects glucose values	Diabetics, sepsis	**Mean amplitude of glycemic excursions** In assessing serial glucose values any continuous excursion that exceeds 1 SD of the range of glucose values is averaged.
GLI[19,26]		Sepsis, Diabetes	**Glycemic lability index** Quantification of all rates of change between consecutive glucose measures

Indices of glucose variability

Ali, Krinsley, Preiser Yearbook ICEM 2009

Maximal glucose change ($BG\Delta_{max}$)[23]	for all sequential values in the dataset	Surgical ICU	Maximum glucose change between any 2 consecutive glucose values
Variability Index (VI) [25]	$\cdot N^{-1}$	Pediatric ICU	Average of sequential rates of change between all consecutive glucose values
Glucose variability[24]	Any blood sugar $\geq$ 150 mg/dl *and* $\leq$ 60 mg/dl *at anytime*	Pediatric ICU	Presence of both a hyperglycemic *and* hypoglycemic event during a single hospitalization

Comparison of the relationship between glucose variability expression and mortality in patients with a diagnosis of sepsis

Glucose Characteristic	Logistic Regression			Comparison of Mortality Discrimination		
	Mortality Crude Odds Ratio[1]	p-value	95% CI	Area under the ROC	p-value[2]	95% CI
GLI	1.25	< 0.001	1.20 – 1.32	0.67		0.64 – 0.71
MAGE	1.12	< 0.001	1.07 – 1.18	0.59	< 0.001	0.56 – 0.63
MEAN	1.17	< 0.001	1.12 – 1.23	0.63	0.003	0.59 – 0.66
Standard Deviation	1.16	< 0.001	1.11 – 1.21	0.62	< 0.001	0.58 – 0.65

Ali et al Crit Care Med 2008

Glucose variability and mortality in patients with sepsis

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD

Table 2. Demographics and glucose data for the sepsis cohort by patient group

Characteristic	Total	GLI Below Cohort Median		GLI Above Cohort Median		p
		Group I (Average Glucose Below Cohort Median)	Group II (Average Glucose Above Cohort Median)	Group III (Average Glucose Below Cohort Median)	Group IV (Average Glucose Above Cohort Median)	
N (%)	1,246	499 (40.0)	124 (9.9)	117 (9.5)	506 (40.6)	
Age (mean)	60.5	57.4	62.7	58.9	63.4	<0.001
Male (%)	52.7	53.9	58.1	49.6	51.4	0.472
Race (%)						0.691
White	66.2	65.5	68.6	61.5	66.8	
African-American	29.2	30.7	25.8	34.2	28.1	
Other	4.6	3.8	5.6	4.3	5.1	
Admission source (%)						0.135
ED	35.3	39.9	37.1	32.5	31.2	
Hospital transfer	33.8	30.4	30.6	36.7	36.6	
Diabetes (%)	31.8	9.4	19.4	36.8	56.5	<0.001
Charlson score, median (IQR)	2 (1–3)	1 (0–3)	2 (1–3.5)	2 (1–3)	2 (1–3)	<0.001[a]
Mean glucose (±SD)	143 (41)	111 (13)	155 (21)	117 (13)	177 (37)	<0.001
Glucose variability [GLI, median (IQR)]	27.4 (2–134)	1.6 (0.5–5.6)	8.1 (2.7–16)	77 (45–157)	152 (73–332)	<0.001[a]
Glucose measures per day, mean (±SD)	4.8 (5.1)	2.1 (2.0)	3.0 (3.0)	5.5 (3.4)	7.8 (6.3)	<0.001[a]
Continuous IV insulin treatment (%)	25.7	7.0	10.5	28.2	48.0	<0.001
Hypoglycemia (%)	31.4	13.2	6.5	65.0	48.4	<0.001

ED, emergency department; GLI, glycemic lability index; IQR, interquartile range.

Unless otherwise stated, comparisons of proportion were analyzed with χ^2 analysis and means with the two-sample t-test. Hypoglycemia was defined as any glucose value <60 mg/dL. Population median for GLI, 27.4; population median for average hospital glucose, 133 mg/dL.

[a]p-value from Kruskal-Wallis test.

Glucose variability and mortality in patients with sepsis

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD

Table 3. Sepsis and outcome data for the cohort by patient group

Characteristic	Total	GLI Below Cohort Median		GLI Above Cohort Median		p
		Group I (Average Glucose Below Cohort Median)	Group II (Average Glucose Above Cohort Median)	Group III (Average Glucose Below Cohort Median)	Group IV (Average Glucose Above Cohort Median)	
Sepsis-associated organ failure (%)						
Respiratory	32.3	22.6	34.7	39.3	39.9	<0.001
Cardiovascular	15.5	11.8	11.3	19.7	19.0	0.004
Renal	54.8	42.7	43.5	65.8	68.0	<0.001
Hepatic	8.3	4.2	8.1	15.4	10.7	<0.001
Hematologic	24.0	21.8	22.6	29.1	25.9	0.264
Metabolic	21.5	16.0	23.4	29.9	24.7	0.001
Neurologic	7.4	7.0	11.3	11.1	6.1	0.096
Organ failure No. (%)						
0	25.0	34.7	33.0	15.4	14.8	<0.001
1	28.8	30.3	21.8	23.9	30.4	
2	19.3	18.0	15.3	25.6	20.2	
3+	26.9	17.0	29.8	35.0	34.6	
Hospital LOS, mean (±SD)	17.7 (21.3)	15.6 (18.2)	13.0 (14.0)	17.6 (18.8)	21.1 (25.3)	<0.001[a]
ICU admit (%)	62.9	51.9	66.1	65.8	73.1	<0.001
ICU LOS, mean (±SD)	12.8 (17.7)	10.0 (13.2)	9.7 (13.0)	13.7 (18.6)	15.3 (20.6)	<0.001[a]
Mortality (%)	27.6	13.2	39.5	35.9	36.4	<0.001

ICU, intensive care unit.

p value represents the significance of changes across the four descriptive groups. (GLI, glycemic lability index; population median for GLI, 27.4; population median for average hospital glucose, 133 mg/dL).

[a]p value is based on natural log transformation.

Alterations in glucose homeostasis in the pediatric intensive care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity*

Eliotte Hirshberg, MD; Gitte Larsen, MD, MPH; Heather Van Duker, MS

(Pediatr Crit Care Med 2008; 9:361–366)

Table 4. Clinical bivariate outcomes by blood glucose category

Blood Glucose Group (mg/dL)[mmol/dL]	Total n (%)	Mortality, n (%) OR (CI)[a] $p < 0.001$	Nosocomial Infections, n (%) OR (CI)[a] $p = 0.01$	Hosp LOS (days) Median, IQR[b]
Normoglycemia (61–149) [3.4–8.3]	354 (41.0)	1 (4.4) Reference group	11 (23.4) Reference group	5.9 (3.5, 10)
Isolated hyperglycemia (≥150) [≥8.3]	425 (49.2)	13 (56.5) 11.1 (1.5–85.6)	26 (55.3) 2.0 (1.0–4.2)	7.2 (4.2, 13.5)
Isolated hypoglycemia (≤60) [≤3.3]	25 (2.9)	0 (0.0) Cannot estimate	2 (4.3) Cannot estimate	8.5 (4.0, 18.0)
Glucose variability (≥150 and ≤60) [≥8.3 and ≤3.3]	59 (6.8)	9 (39.1) 63.6 (7.8–512.2)	8 (17.0) 4.9 (1.9–12.7)	18.8 (10.4, 37.3)

Hosp LOS, hospital length of stay.

[a]Bivariate odds ratio (OR) with 95% confidence interval (CI). [b]Interquartile range (IQR) summarizes the 25th and 75th percentiles.

Blood Glucose Variability Is Associated with Mortality in the Surgical Intensive Care Unit

LESLY A. DOSSETT, M.D.,* HANQING CAO, PH.D.,*‡ NATHAN T. MOWERY, M.D.,*
MARCUS J. DORTCH, PHARM.D.,*† JOHN M. MORRIS JR., M.D.,* ADDISON K. MAY, M.D.*

*From the *Division of Trauma and Surgical Critical Care, The Department of Surgery and †The Department of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee and ‡Philips Research North America, Briarcliff Manor, New York*

Intensive insulin therapy has widely and rapidly been adopted as the standard of care for the treatment of hyperglycemia in the intensive care unit (ICU). Variability in blood glucose is increasingly recognized as an important factor in outcomes in the chronic diabetic in addition to hemoglobin A1C. We tested the hypothesis that measures of blood glucose variability would be associated with mortality in the surgical ICU. A retrospective analysis of a cohort of ventilated, critically ill surgical and trauma ICU patients placed on an automated insulin protocol was performed. Blood glucose (BG) variability was measured by comparing standard deviation, percentile values, successive changes in blood glucose, and by calculating the triangular index for various glucose-related indices. Eight hundred and fifty-eight patients had 46,474 blood glucose and insulin dose data points. One hundred and twenty-one patients died for an overall mortality rate of 14 per cent. Several measures of blood glucose variability (maximum successive change in BG and the triangular index) were different between the groups despite similar mean BG between survivors (117 mg/dL) and nonsurvivors (118 mg/dL). Increased blood glucose variability is associated with mortality in the surgical ICU. Further studies should focus on the demographic, clinical, and genetic factors responsible for this observation and identify strategies to minimize BG variability.

An unexplored hypothesis is left and appealing !

- Hypothesis : high glucose variability is possibly detrimental for critically ill patients
- Supporting data : retrospective cohort study
- **Biological plausibility**

Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture

A. RISSO,[1] F. MERCURI,[2] L. QUAGLIARO,[2] G. DAMANTE,[1] AND A. CERIELLO[3]
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Am J Physiol Endocrinol Metab
281: E924–E930, 2001.

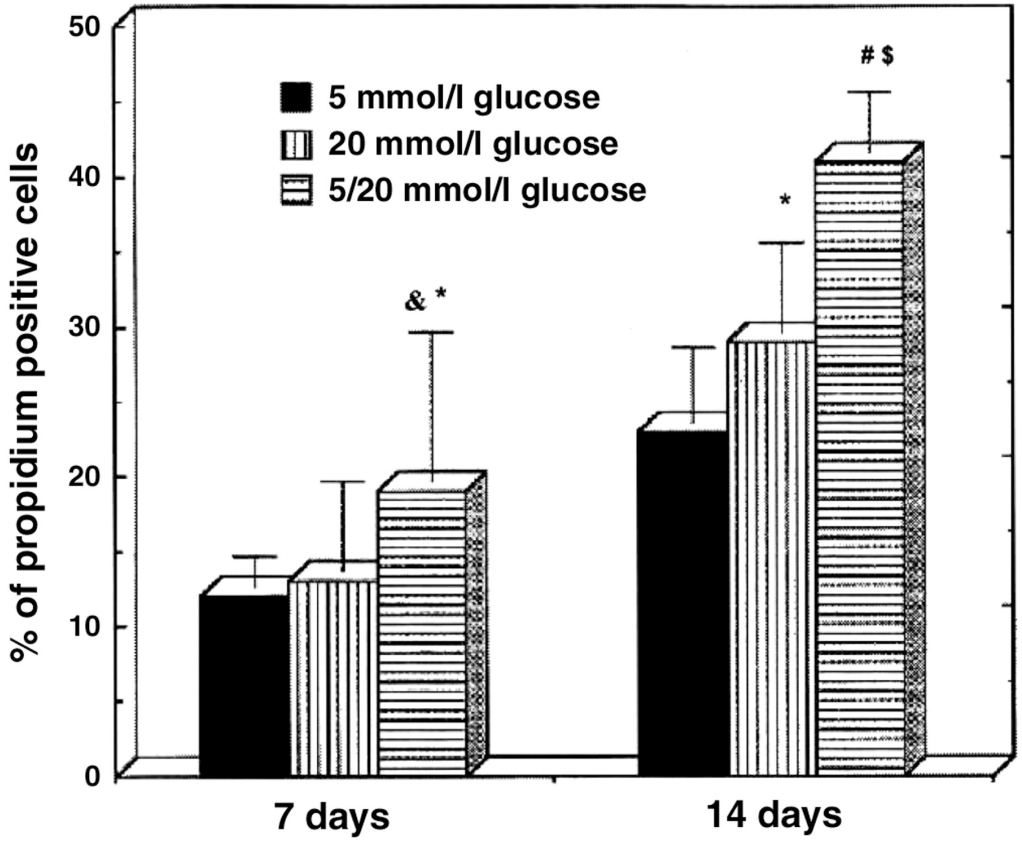

Fig. 1. Cell death of human umbilical vein endothelial cells (HUVECs) cultured with different concentrations of glucose. HUVECs were cultured in the presence of normal (5 mmol/l), high (20 mmol/l), or alternating normal/high concentrations, as described in MATERIALS AND METHODS. After 7 and 14 days, they were detached from Petri dishes, stained with 20 μg/ml of propidium iodide, and analyzed with the cytofluorimeter. Data are means ± SD of 6 independent experiments. **P* < 0.05 vs. glucose 5 mmol/l; &*P* < 0.05 vs. glucose 20 mmol/l; #*P* < 0.01 vs. glucose 5 mmol/l; $*P* < 0.01 vs. glucose 20 mmol/l.

Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture

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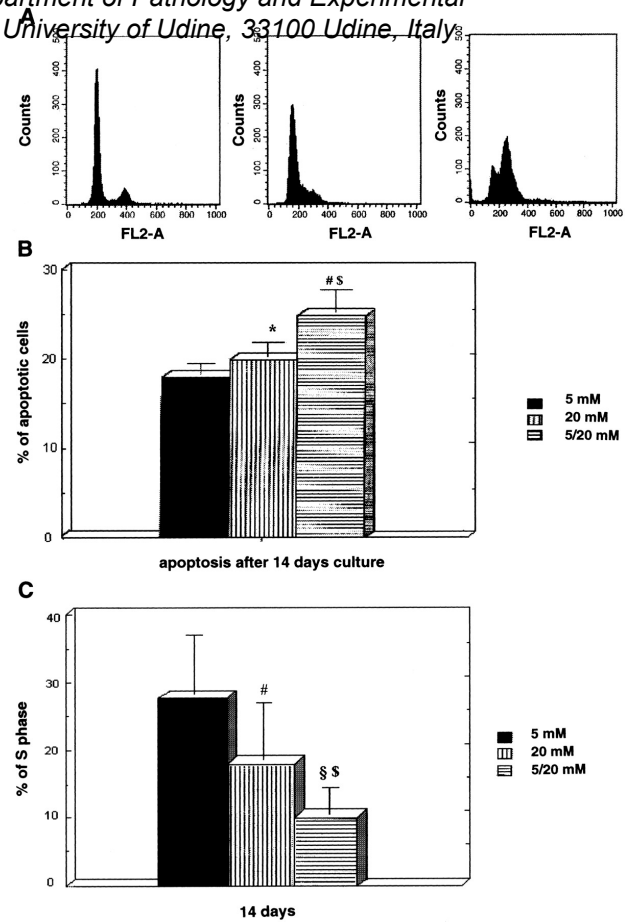

Cell cycle analysis of HUVECs. HUVECs were cultured in the presence of normal (5 mmol/l), high (20 mmol/l), or alternating normal/high concentrations and were stained for 1 h with 50 μg/ml of propidium iodide in 0.2% sodium citrate containing 12.5 μg/ml RNase. DNA content of the different cell populations was analyzed as described in MATERIALS AND METHODS. *A*: histograms representing DNA content of HUVEC populations cultured for 14 days with different concentrations of glucose (5, 20, and 5/20 mmol/l, from *left* to *right,* respectively). Cytofluorimetric analysis is from 1 of 6 separate experiments. *B* and *C*: quantitative assessment of apoptosis and S phase in HUVECs. Values are means ± SD of 6 separate experiments. **P* < 0.05 vs. glucose 5 mmol/l; #*P* < 0.01 vs. glucose 5 mmol/l; $*P* < 0.01 vs. glucose 20 mmol/l; §*P* < 0.001 vs. glucose 5 mmol/l.

Risso, A. et al. Am J Physiol Endocrinol Metab 281: E924-E930 2001

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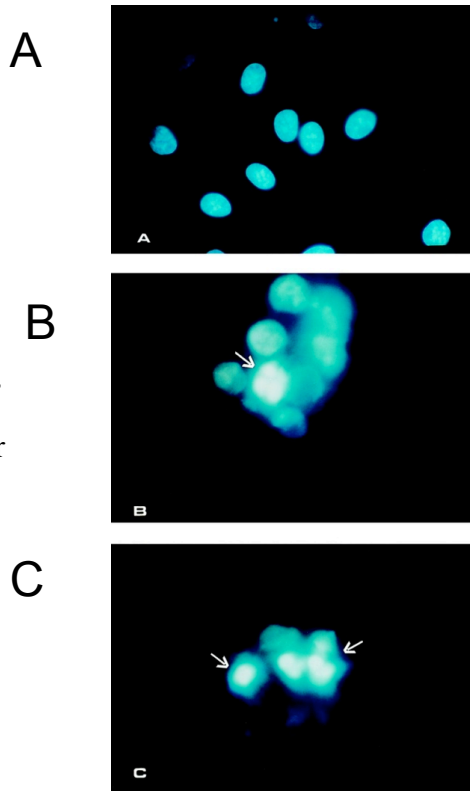
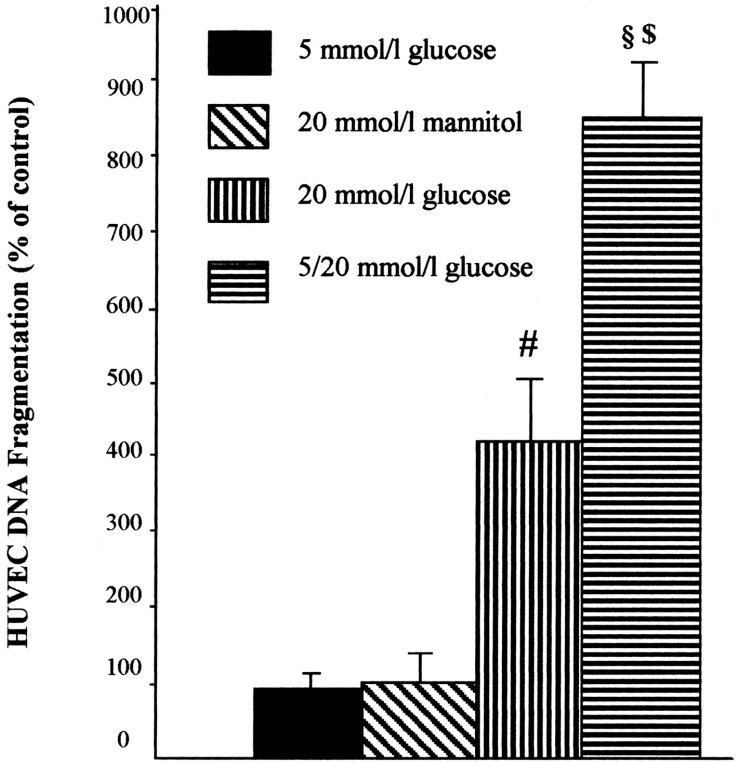


Fig. 3. Morphological analysis of HUVECs cultured for 14 days with normal (*A*), high (*B*), or alternating low/high (*C*) glucose. Cells were cultured on gelatin-coated slides, fixed, and stained as described in MATERIALS AND METHODS. Arrows, nuclear piknosis

Fig. 4. DNA fragmentation of HUVECs by ELISA. Values are means ± SD of 6 separate experiments. #$P <$ 0.01 vs. glucose 5 mmol/l; \$$P < 0.01$ vs. glucose 20 mmol/l; §$P < 0.001$ vs. glucose 5 mmol/l.



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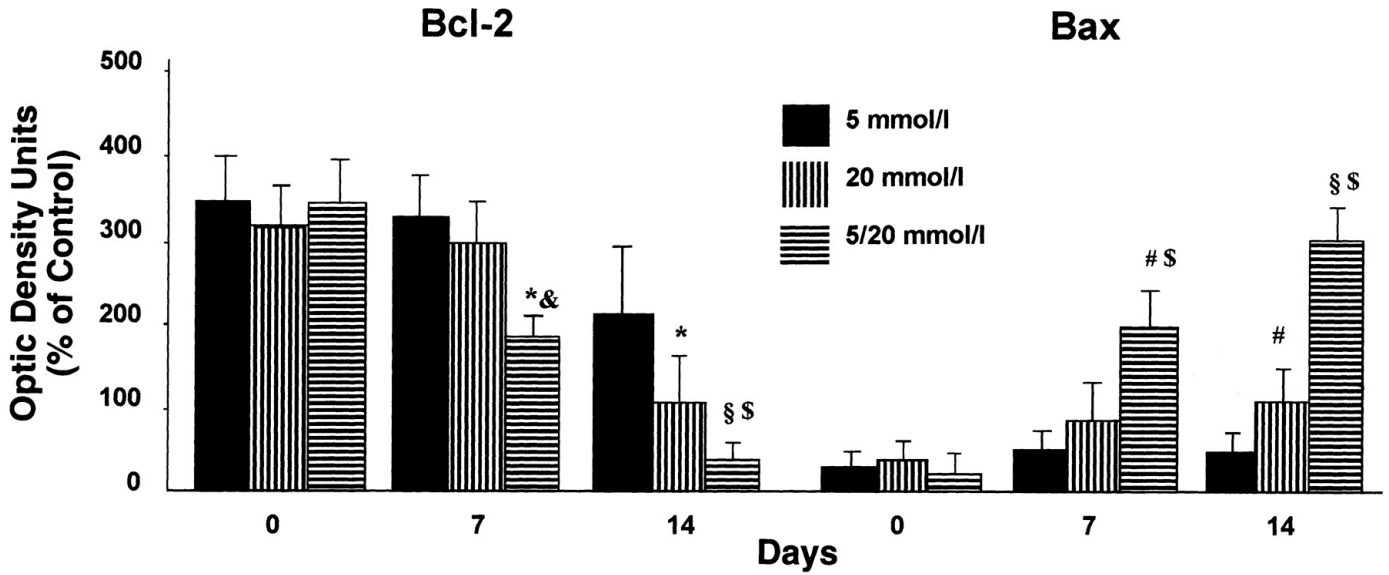

Risso, A. et al. Am J Physiol Endocrinol Metab 281: E924-E930 2001

Fig. 8. Time course of Bcl-2 and Bax proteins expressed as optical density units measured by Western blot analysis. Values are means ± SD of 6 separate experiments. *$P < 0.05$ vs. glucose 5 mmol/l; &$P < 0.05$ vs. glucose 20 mmol/l; \$$P < 0.01$ vs. glucose 20 mmol/l; #$P < 0.01$ vs. glucose 5 mmol/l; §$P < 0.001$ vs. glucose 5 mmol/l.

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DIABETES/METABOLISM RESEARCH AND REVIEWS
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RESEARCH ARTICLE

Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction

Ludovica Piconi[1]

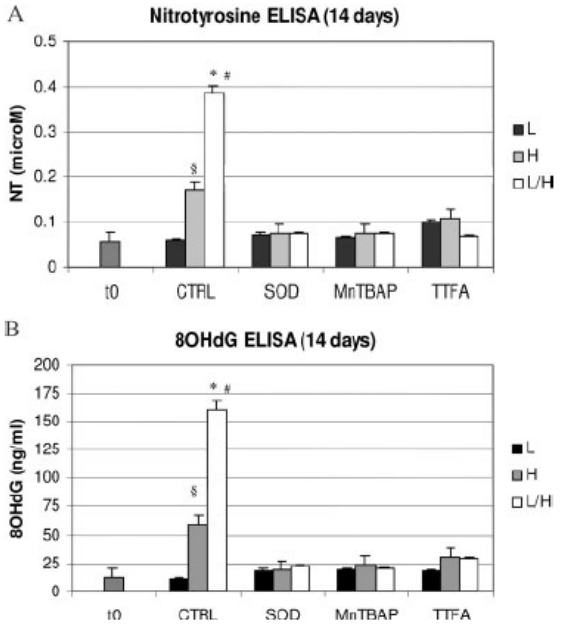


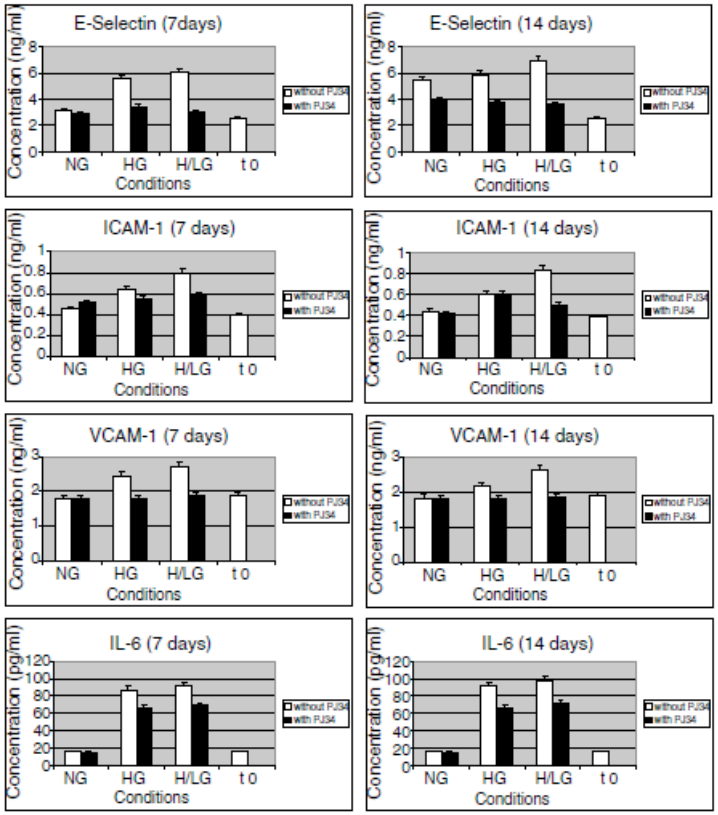
Figure 3. (A) Nitrotyrosine ELISA of HUVEC lysates, $N = 5$ nM glucose; H = 20 nM glucose; H/L = 5/20 nM glucose. (B) 8OHdG content in HUVEC DNA measured with ELISA technique. § = $p < 0.01$ normal *versus* high glucose; # = $p < 0.001$ intermittent *versus* normal glucose; * = $p < 0.01$ intermittent *versus* high glucose. Bars indicate ±SD

Journal of Thrombosis and Haemostasis, **2**: 1453–1459

ORIGINAL ARTICLE

Intermittent high glucose enhances ICAM-1, VCAM-1, E-selectin and interleukin-6 expression in human umbilical endothelial cells in culture: the role of poly(ADP-ribose) polymerase

L. PICONI, L. QUAGLIARO, R. DA ROS,* R. ASSALONI,* D. GIUGLIANO,‡ K. ESPOSITO,† C. SZABÓ§ and A. CERIELLO*



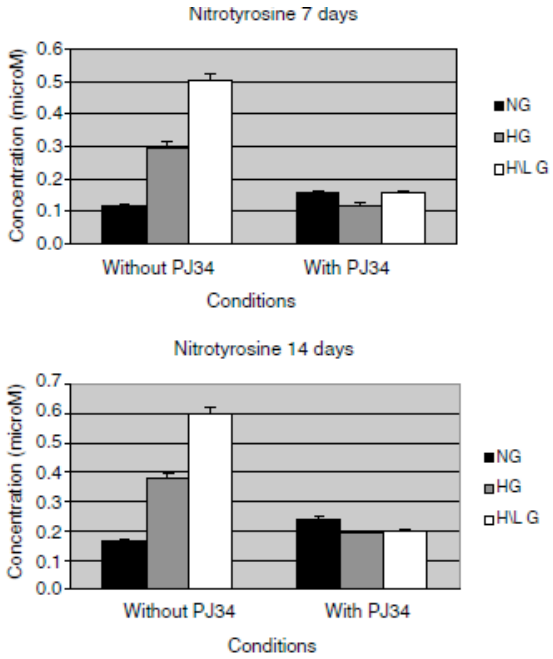


Fig. 4. Nitrotyrosine content in human umbilical vein endothelial cell (HUVEC) lysates after 7 and 14 days of experiment, when cells were exposed to 5 mM glucose (N), 20 mM glucose (H), 20/5 mM glucose (H/L), without poly ADP ribose polymerase (PARP) inhibitor or with the addiction of PJ34 (1 mM). Bars indicate SE.

Diabetologia (2007) 50:1523–1531
DOI 10.1007/s00125-007-0684-2

ARTICLE

Reactive oxygen species mediate a cellular 'memory' of high glucose stress signalling

M. A. Ihnat · J. E. Thorpe · C. D. Kamat · C. Szabó · D. E. Green · L. A. Warnke · Z. Lacza · A. Cselenyák · K. Ross · S. Shakir · L. Piconi · R. C. Kaltreider · A. Ceriello

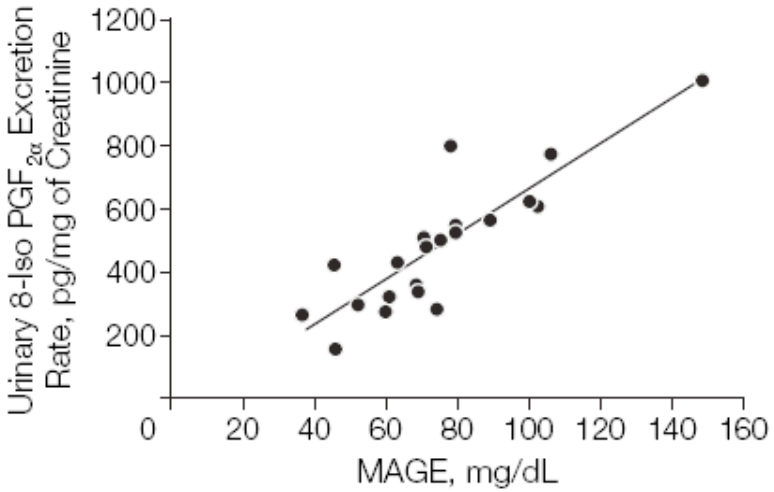
Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes

Louis Monnier, MD
Emilie Mas, PhD

Context Glycemic disorders, one of the main risk factors for cardiovascular disease, are associated with activation of oxidative stress.

JAMA 2006 ; 295 : 1681

Figure 2. Linear Correlation Between 24-Hour Urinary Excretion Rates of 8-Iso Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and Mean Amplitude of Glycemic Excursions (MAGE)

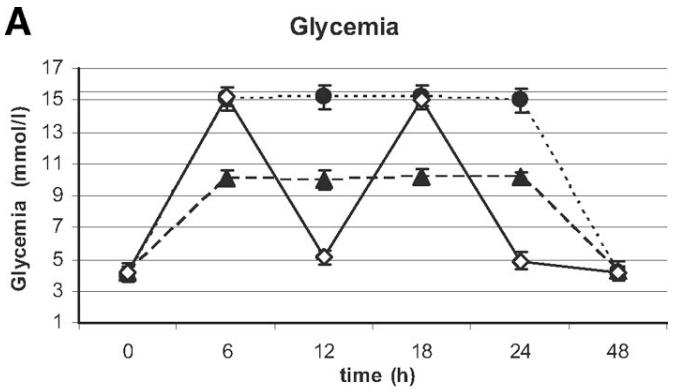


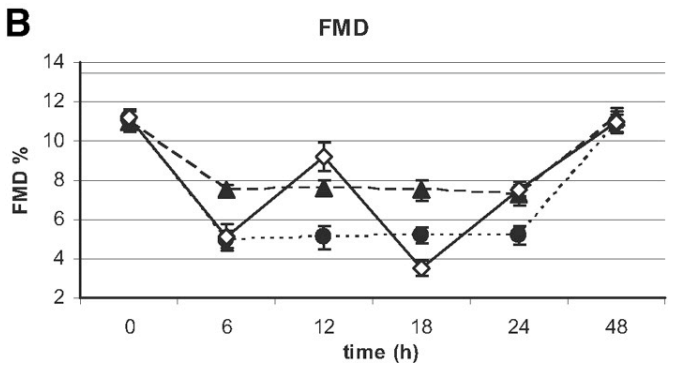
r=0.86; P<.001.

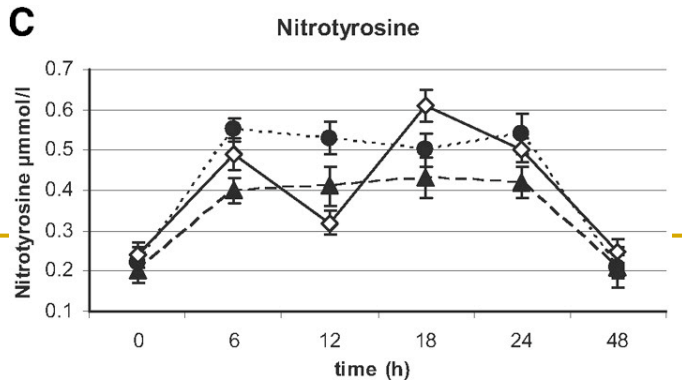
OSCILLATING GLUCOSE IN VOLUNTEERS

Ceriello et al
Diabetes 2008;57:1349

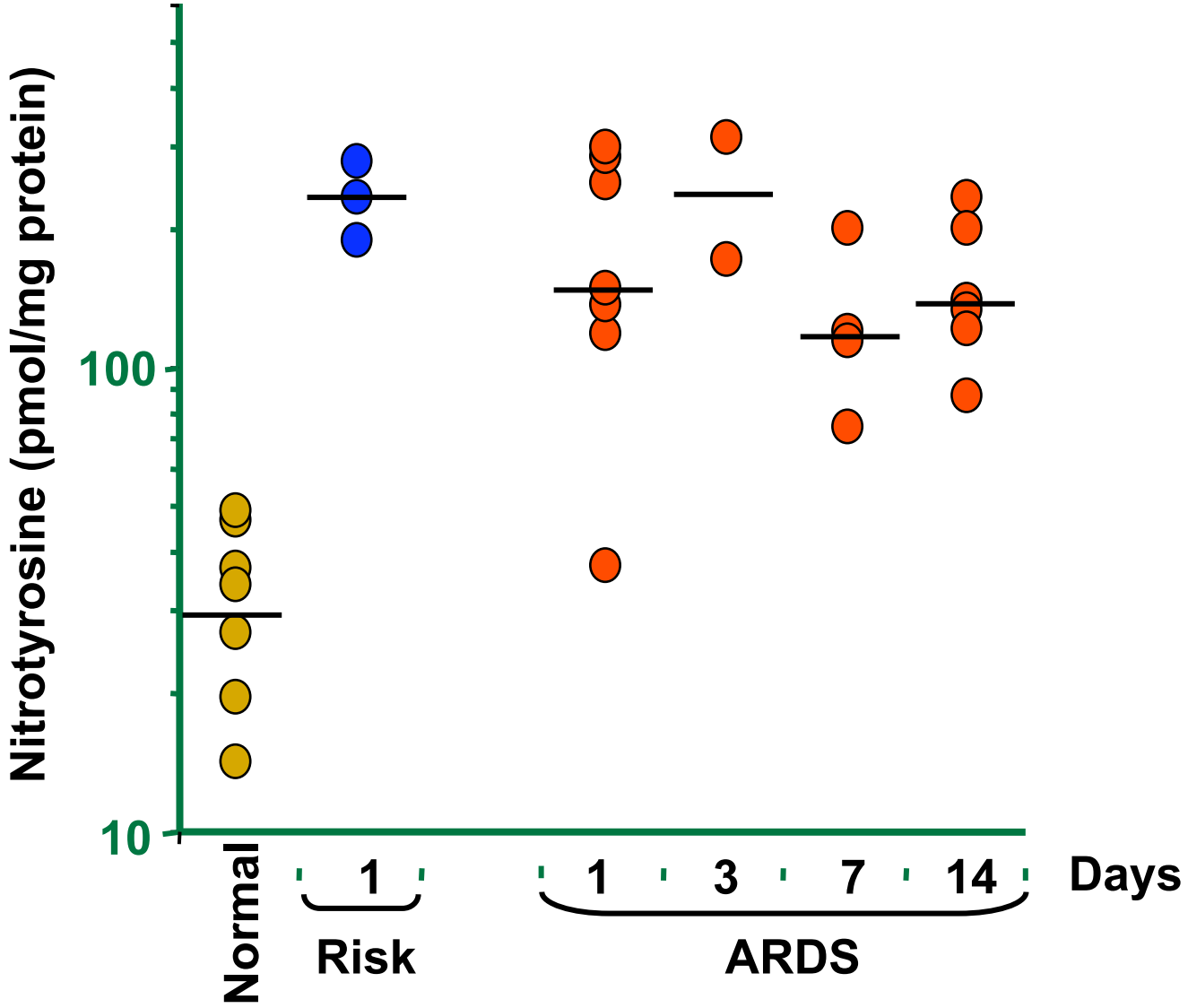
FMD = flow-mediated Dilation
(index of endothelial fct)





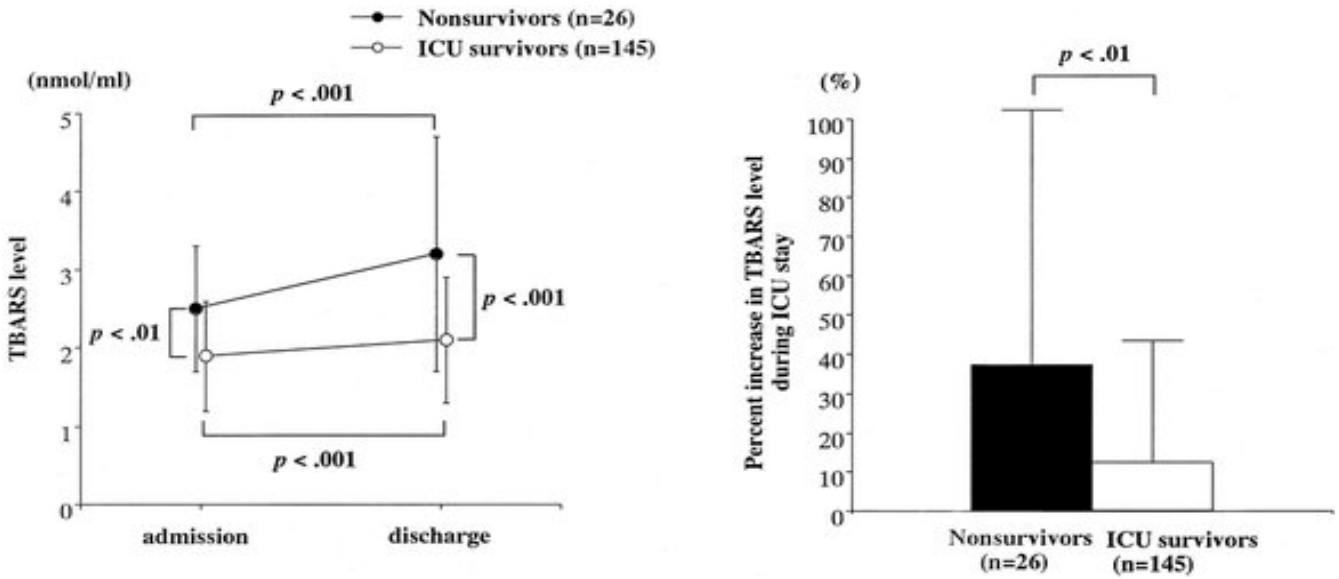


Nitrotyrosine in BAL fluids of ARDS patients



Sittipunt C et al (2001) Am J Respir Crit Care Med 163 : 503

OXIDATIVE / NITROSATIVE STRESS AND MORTALITY



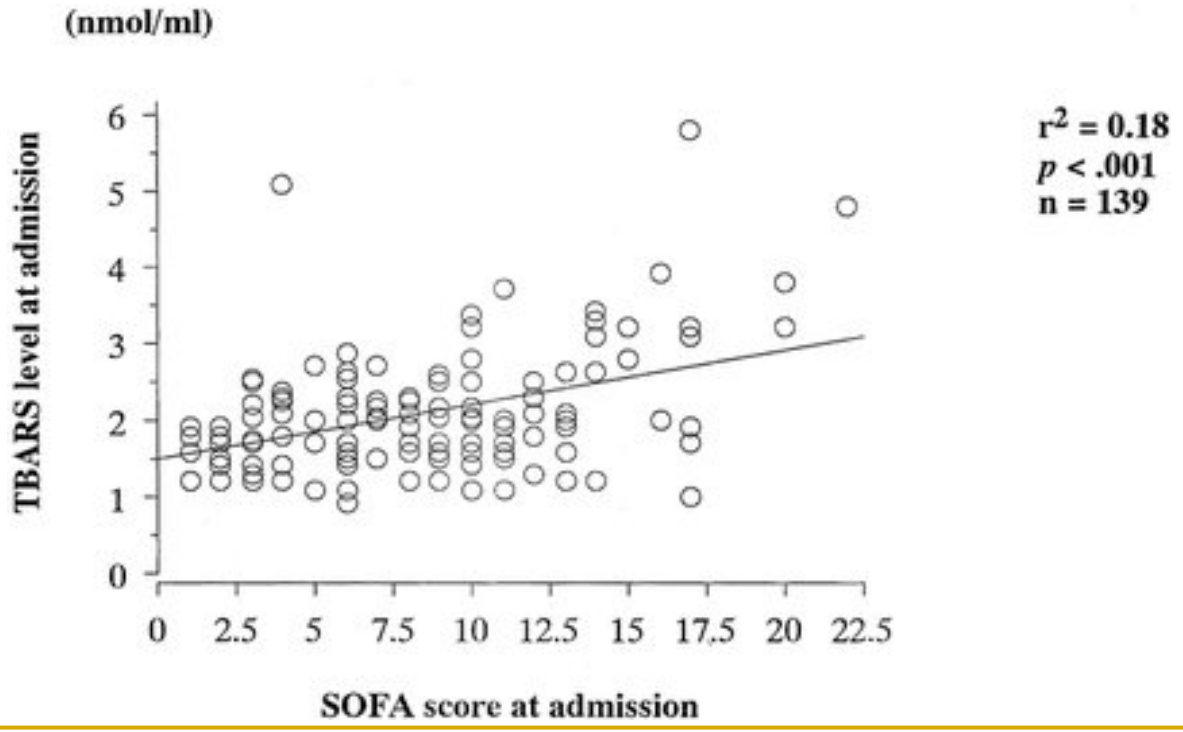
Motoyama et al Crit Care Med 2003;31:1048

Plasma nitrotyrosine concentration relates to prognosis in human septic shock. Ohya et al Shock. 2002 Aug;18(2):116-8

Plasma NT concentrations (means +/- SE) of the non-survivors and survivors were 0.68 +/- 0.13 nmol/mL (n = 7), and 0.21 +/- 0.05 nmol/mL (n = 5). The present results suggest that plasma concentration of NT relates to prognosis in human septic shock

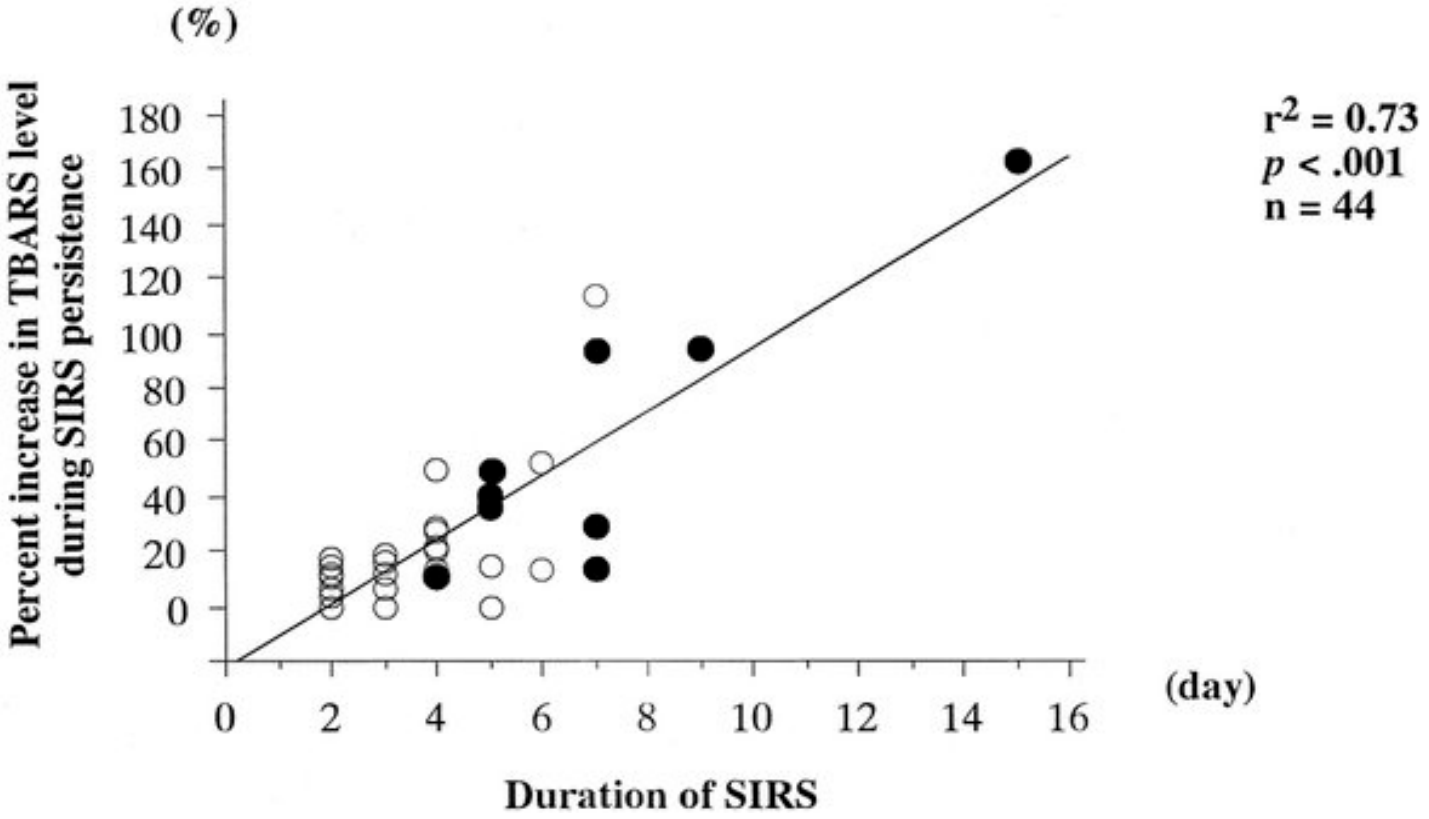
LIPOPEROXIDES ARE PROPORTIONAL TO THE SEVERITY OF ORGAN FAILURE

Motoyama et al Crit Care Med 2003;31:1048



LIPOPEROXIDES INCREASE IS PROPORTIONAL TO THE DURATION OF SIRS

Motoyama et al Crit Care Med 2003;31:1048



An unexplored hypothesis is left and appealing !

- Hypothesis : glucose variability is deleterious
- Supporting data : retrospective cohort study
- Biological plausibility

An unexplored hypothesis is left and appealing !

- Hypothesis : glucose variability is deleterious
- Supporting data : retrospective cohort study
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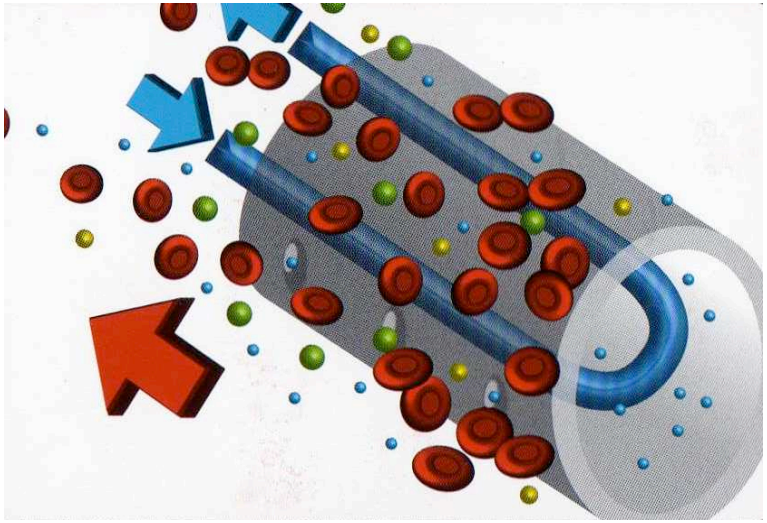
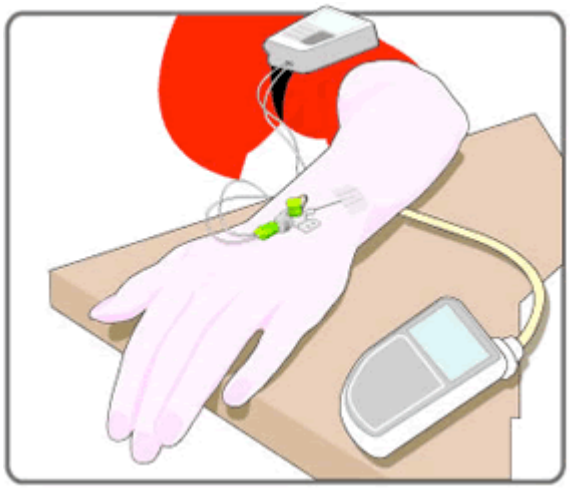
PENDING ISSUES

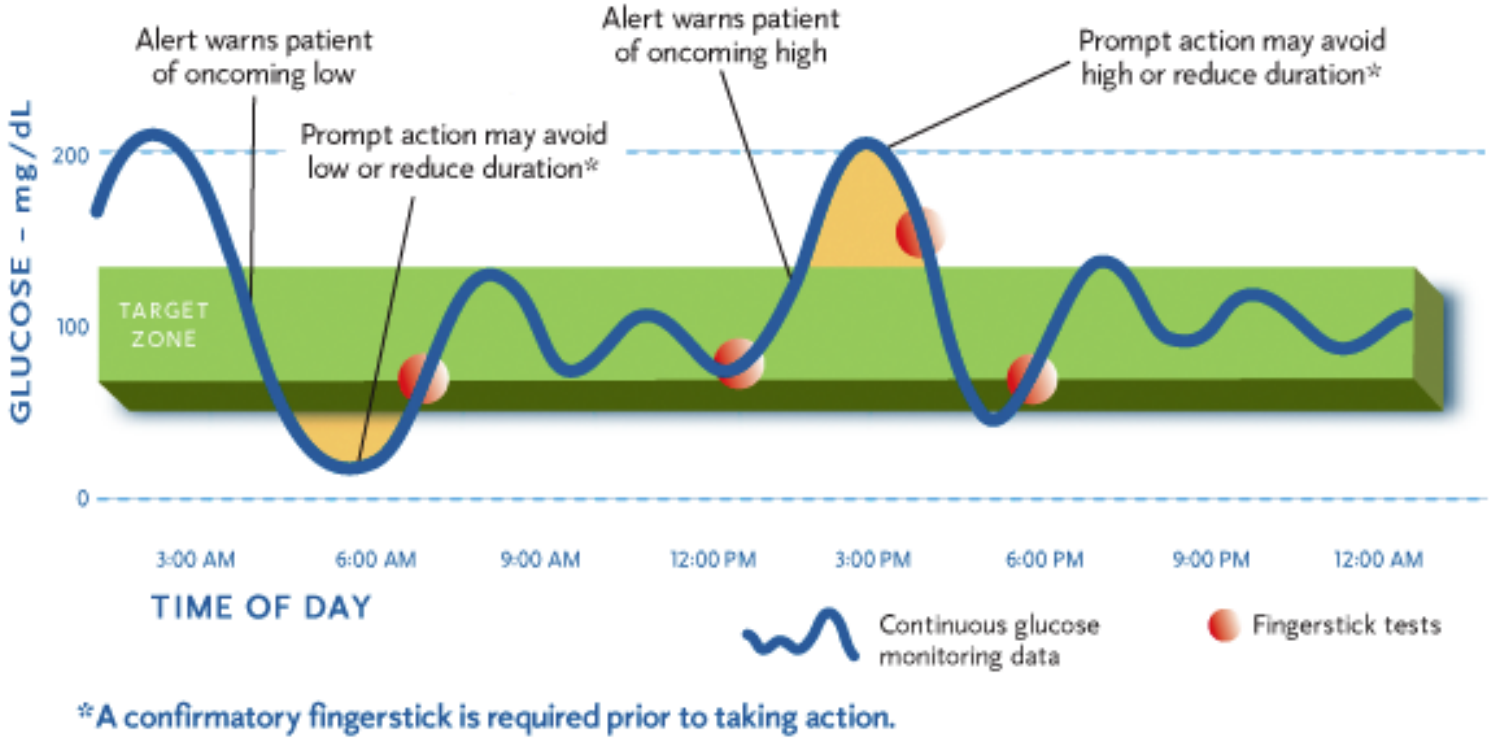
- Clinically useful definition of GV
- Accurate assessment of GV

The answer : Intravascular continuous blood monitoring?





Continuous glucose monitoring vs intermittent checks



*A confirmatory fingerstick is required prior to taking action.


Walt Disney
Dreams Come True


By far the most terrifying film you will ever see.
aninconvenienttruth
A GLOBAL WARNING


STAR WARS
A NEW HOPE