

NEUROPROTECCIÓN NO FARMACOLÓGICA



Sociedad Iberoamericana de Enfermedad Cerebro Vascular

FLUJO SANGUÍNEO CEREBRAL

- El tejido cerebral requiere un aporte continuo de sangre que le proporcione oxígeno y glucosa en concentraciones suficientes para satisfacer sus requerimientos metabólicos.
- Flujo sanguíneo cerebral → 50 ml/100g/min.
- El flujo sanguíneo cerebral depende de:
 - presión de perfusión → T.A. - (P.V. + P.I.C.)
 - resistencia vascular → autoregulación



UMBRALES DE ISQUEMIA

INHIBICIÓN DE
SÍNTESIS PROTEICA



ACIDOSIS LÁCTICA



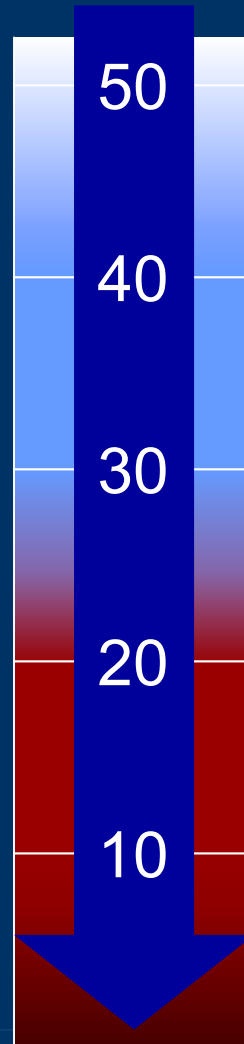
LIBERACIÓN DE
GLUTAMATO



DEPLECIÓN DE ATP



DESPOLARIZACIÓN
ANÓXICA

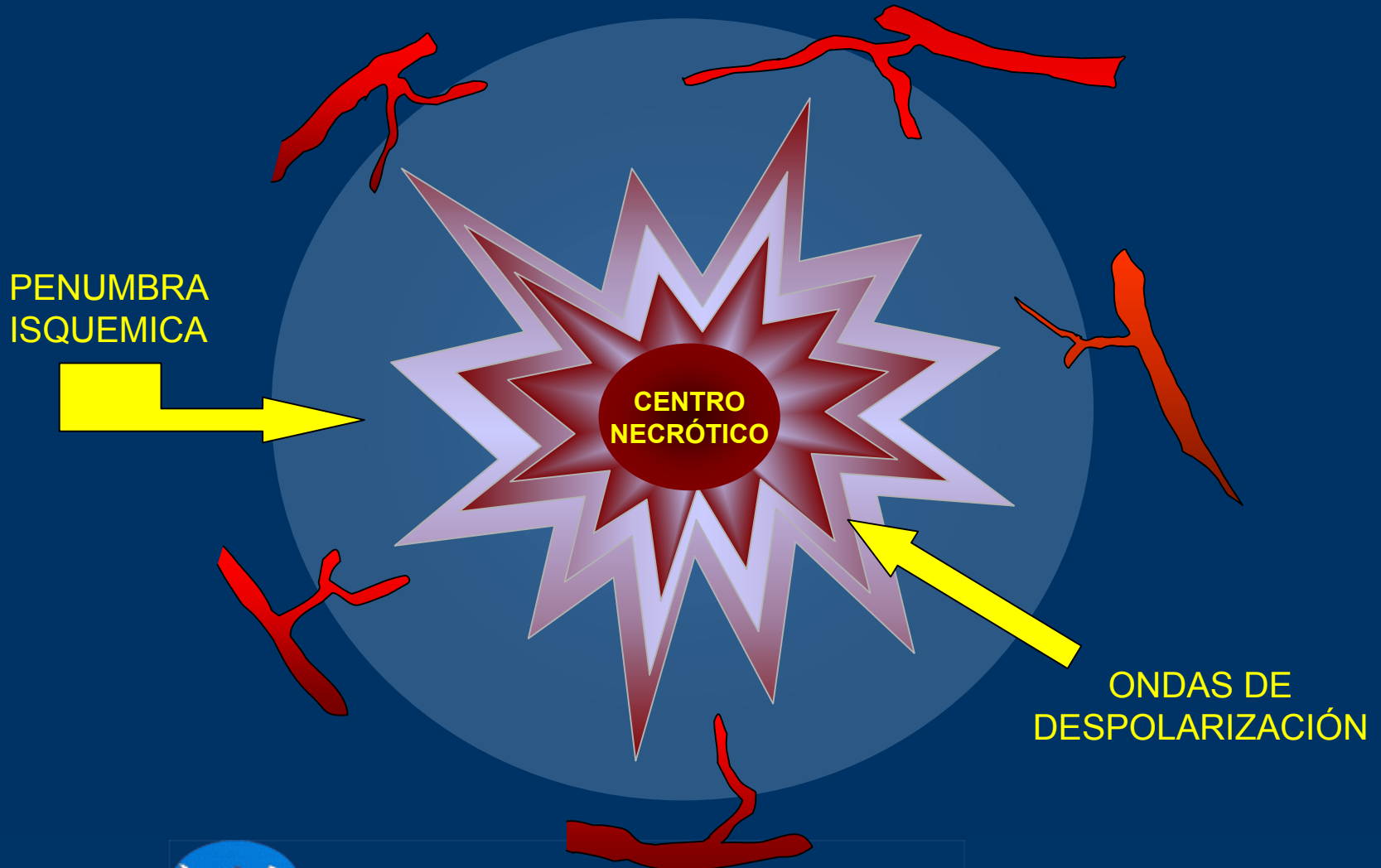


DAÑO CELULAR
FUNCIONAL

DAÑO CELULAR
ESTRUCTURAL



GRADIENTES DE ISQUEMIA



EVOLUCIÓN DE PENUMBRA



-  Zona de depleción de ATP (Centro necrótico)
-  Zona de daño funcional (Penumbra isquémica)



CASCADA ISQUÉMICA



CASCADA ISQUÉMICA



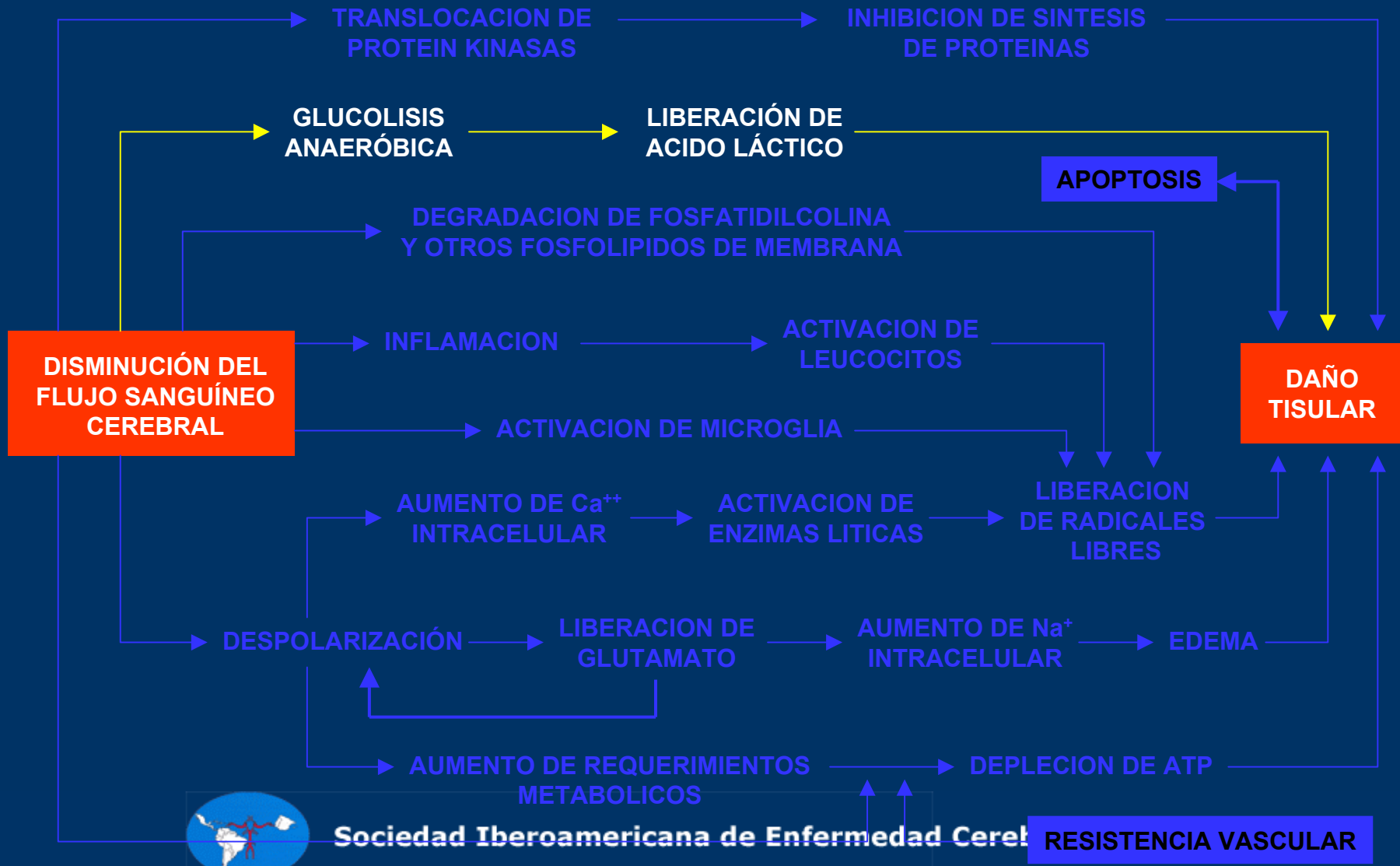
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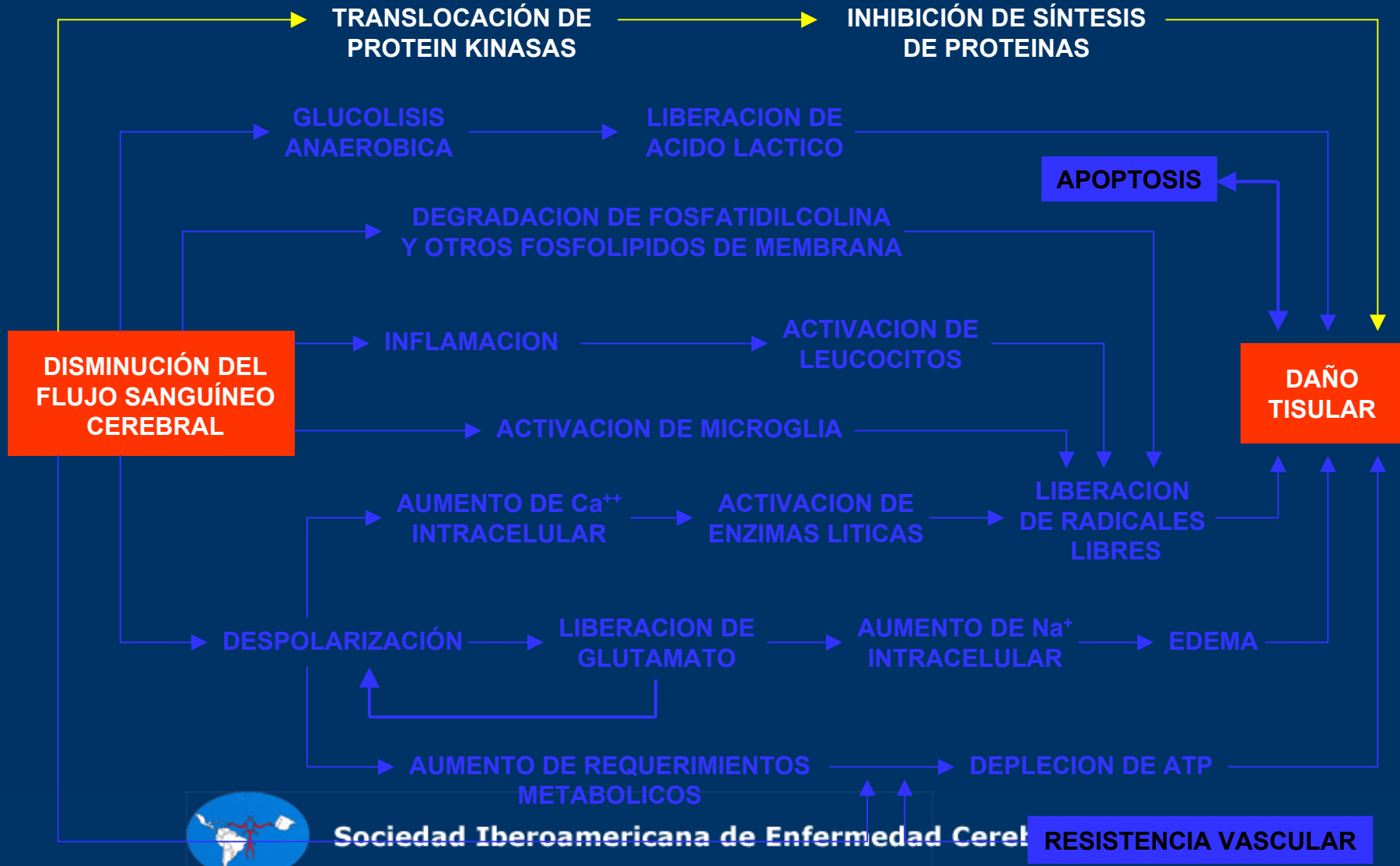
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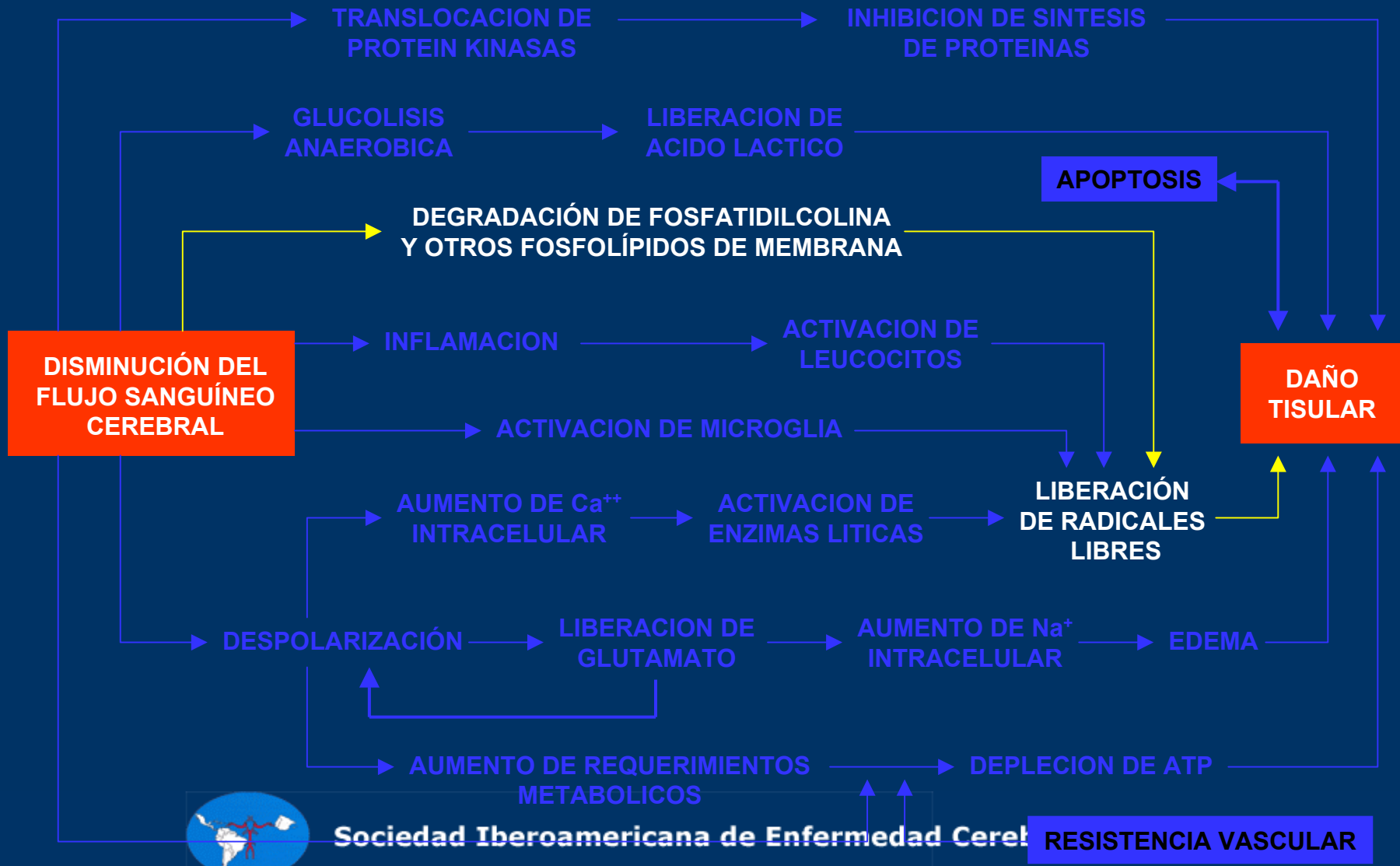
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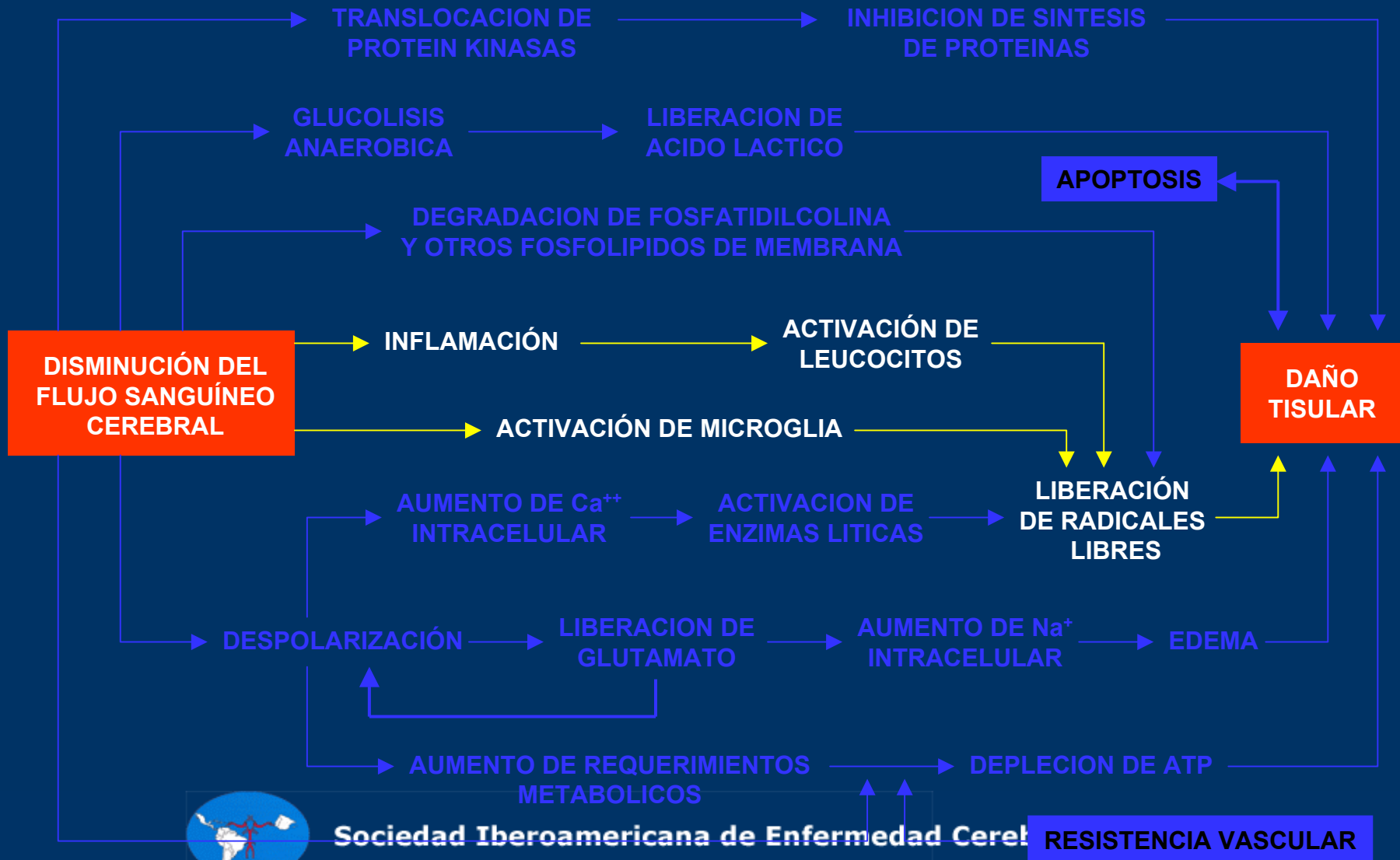
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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE t-PA STROKE STUDY GROUP*

Abstract *Background.* Thrombolytic therapy for acute ischemic stroke has been approached cautiously because there were high rates of intracerebral hemorrhage in early clinical trials. We performed a randomized, double-blind trial of intravenous recombinant tissue plasminogen activator (t-PA) for ischemic stroke after recent pilot studies suggested that t-PA was beneficial when treatment was begun within three hours of the onset of stroke.

Methods. The trial had two parts. Part 1 (in which 291 patients were enrolled) tested whether t-PA had clinical activity, as indicated by an improvement of 4 points over base-line values in the score of the National Institutes of Health stroke scale (NIHSS) or the resolution of the neurologic deficit within 24 hours of the onset of stroke. Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at three months, according to scores on the Barthel index, modified Rankin scale, Glasgow outcome scale, and NIHSS.

Results. In part 1, there was no significant difference between the group given t-PA and that given placebo in

the percentages of patients with neurologic improvement at 24 hours, although a benefit was observed for the t-PA group at three months for all four outcome measures. In part 2, the long-term clinical benefit of t-PA predicted by the results of part 1 was confirmed (global odds ratio for a favorable outcome, 1.7; 95 percent confidence interval, 1.2 to 2.6). As compared with patients given placebo, patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4 percent of patients given t-PA but only 0.6 percent of patients given placebo ($P < 0.001$). Mortality at three months was 17 percent in the t-PA group and 21 percent in the placebo group ($P = 0.30$).

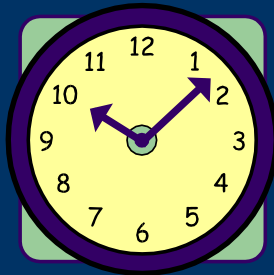
Conclusions. Despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with intravenous t-PA within three hours of the onset of ischemic stroke improved clinical outcome at three months. (N Engl J Med 1995;333:1581-7.)



NEUROPROTECCIÓN

NO FARMACOLÓGICA

- Control de presión arterial.
- Control de viscosidad sanguínea.
- Control de glicemia.
- Control de temperatura.



FARMACOLÓGICA

- Antagonistas de glutamato.
- Antagonistas de canales de Ca^{++} .
- Favorecedores de síntesis de fosfolípidos de membrana.
- Inhibidores de protein kinasas.
- Antioxidantes.
- Estimuladores del metabolismo celular.
- Inhibidores de apoptosis.
- Moduladores de respuesta inflamatoria.



UNIDADES DE ICTUS

Duración y objetivos de la hospitalización en las unidades de ictus

M. Lara, E. Díez-Tejedor, J. Tatay, P. Barreiro

Resumen. *Objetivo.* Dada la importancia epidemiológica de la Enfermedad Cerebrovascular Aguda (ECA) surgió la necesidad de generar unidades específicas para el cuidado de estos pacientes. Revisamos la repercusión de estas unidades en los departamentos de Neurología. *Desarrollo.* En los años 70 se inició en U. de Córdoba Intervención para Ictus, que en los 80 dieron paso a U. de Córdoba No Interventiva e Intermedia (U. Nitec Agudas) que resultaron más eficaces que las oficinas de Rehabilitación. El diseño que planteamos considera Neurología, en el Hospital y el Área de Salud, apreciando que existe un equipo específico para este tipo de enfermos y a pacientes con ECA con un incremento de ingresos del 21%. *Conclusiones.* Las Unidades de Ictus son de gran utilidad en los de secundaria, estancia media y coste, siendo la situación funcional. *Palabras clave:* Enfermedad Cerebrovascular Aguda. Hospital.

Summary. *Objective.* The epidemiological importance of Acute specific units in care for these patients. We review the effect of 1970s Stroke Intervention Care Units were created. In the 1980s the Units (Acute Stroke Units). These Acute Stroke Units are more mortality, morbidity, hospital stay and cost. Care was completely takes into consideration the integration of a Stroke Unit in the No after one year results were compared with those of the previous a 18.5% reduction in total hospital stay and a 23.3% reduction number of complications was reduced by 49.9%. *Conclusions.* They lead to reduced morbidity, sequelae, average hospital improves [REV NEUROLOGIA 1997; 25: 1111-1113].

Key words. Acute Cerebrovascular Disorders. Hospital. Stroke

The Effect of a Stroke Unit: Reductions in Mortality, Discharge Rate to Nursing Home, Length of Hospital Stay, and Cost A Community-Based Study

Henrik S. Jørgensen, MD; Hirofumi Nakayama, MD; Hans O. Raastad, MD; Kim Larsen, MD; Per Høbbe, MD, PhD; Tom Skjold Olsen, MD, PhD

Background and Purpose. Treatment of stroke patients in specialized stroke units has become more frequent, yet the effect of this treatment has not been determined.

Methods. In a community-based, prospective, and consecutive study of 1241 unselected acute stroke patients, we compared outcomes of stroke treatment between two neighboring communities within Greater Copenhagen: the Bispebjerg community, where all acute stroke patients are treated and rehabilitated on a stroke unit, and Fredensborg community, where all acute stroke patients are treated and rehabilitated on general neurological and medical wards. Despite the different organization of stroke treatment, the two communities and the two patient groups were comparable. Specifically, age, sex, marital status, prestroke residence, and stroke severity were not statistically different between patients treated on the stroke unit and those treated on the general neurological and medical wards. Multivariate regression analyses were used to estimate the independent influence of stroke unit treatment on outcome.

Results. Stroke unit treatment significantly reduced in-hospital mortality (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.24 to 0.78, $P < .001$), case-fatality rate (OR, 0.41; CI, 0.28 to 0.71, $P < .001$), 6-month mortality (OR, 0.57; CI, 0.39 to 0.82, $P < .001$), 1-year mortality (OR, 0.59; CI, 0.42 to 0.84, $P < .001$), and discharge rate to a nursing home (OR, 0.65; CI, 0.39 to 0.96, $P < .01$). Discharge rate to the patient's own home was significantly increased (OR, 1.39; CI, 1.20 to 2.20, $P < .001$). The length of hospital stay (including rehabilitation) was reduced significantly by 30% in patients treated on the stroke unit despite their lower mortality ($P < .001$). The savings due to stroke unit treatment were estimated at 1573 bed-days and three places at a nursing home per 100 stroke patients.

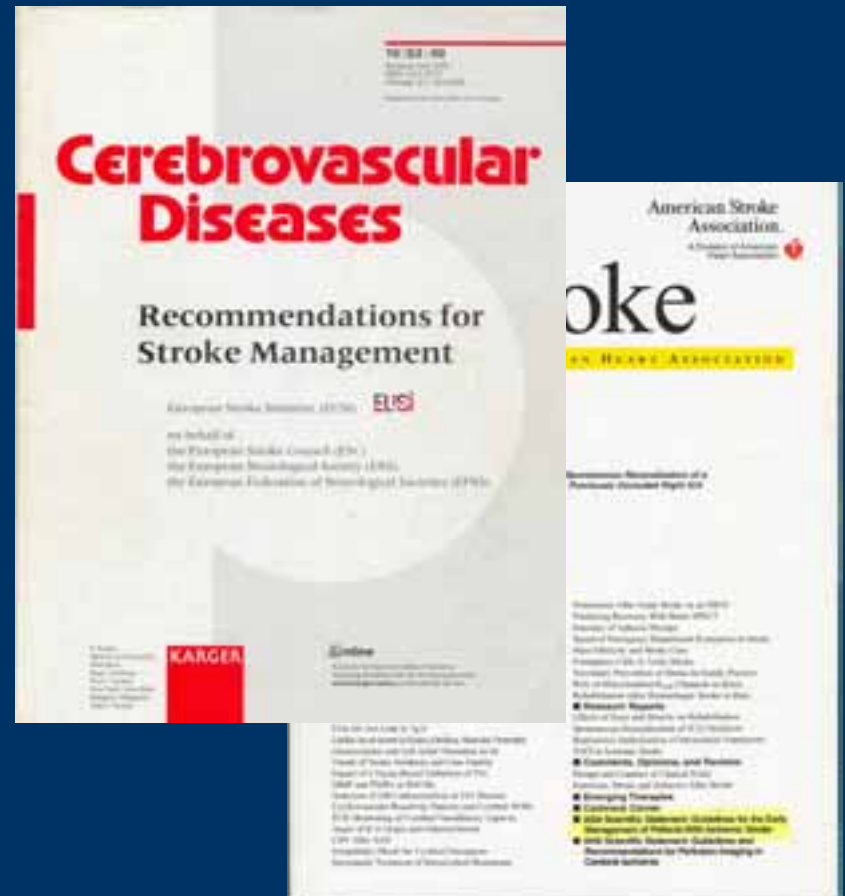
Conclusions. Treatment of unselected acute stroke patients on a stroke unit and saved lives, reduced the length of hospital stay, reduced the frequency of discharge to a nursing home, and potentially reduced cost. (Stroke. 1995;26:1178-1182.)

Key Words: • costs and cost analysis • rehabilitation • outcome • stroke units



UNIDADES DE ICTUS

- Reducción en mortalidad ~20%
- Reducción en número de pacientes dependientes ~30%
- Reducción en tiempo de estancia hospitalaria ~30%
- Reducción en necesidad de cuidado institucional prolongado ~25%



UNIDADES DE ICTUS

- Manejo del ictus agudo por personal entrenado.
- Aplicación de protocolos operacionales estrictos.
- Reducen el riesgo de infecciones nosocomiales.
- Prevención sistemática de complicaciones.
- Favorecen la rehabilitación temprana.



CONTROL DE PRESIÓN ARTERIAL

- Si PS < 200 mmHg, PD < 120 mmHg o PAm < 130 mmHg:
 - No tratamiento
- Si PS 200 – 230 mmHg, PD 120 – 140 mmHg, o PAm > 130 mmHg:
 - Labetalol en bolos i.v. 5 – 20 mg o en infusión continua a dosis de 2 – 8 mg/min (dosis máxima 100 mg/hora)
 - Enalapril en bolos i.v. de 1.25 mg cada 6 horas.
- Si PS > 230 mmHg o PD > 140 mmHg:
 - Nitroprusiato de sodio en infusión a dosis de 0.5 – 10 ug/kg/min



PRESIÓN ARTERIAL Y r-TPA

Management of Blood Pressure after rt-PA in the NINDS Study

If diastolic BP > 140 mm Hg:

Start an intravenous infusion of sodium nitroprusside (0.5 - 1 mcg/kg/min (starting dose) and titrate until diastolic decreases by 20%).

If systolic BP > 230 mm Hg and/or diastolic BP 121-140 mm Hg:

Give labetalol 20 mg intravenously over 1-2 minutes. The dose may be repeated and/or doubled every 10 minutes, up to 150 mg. Alternatively, following the first bolus of labetalol, an intravenous infusion of 2-8 mg/min labetalol may be initiated and continued until the desired BP is reached. If satisfactory response is not obtained, use sodium nitroprusside.

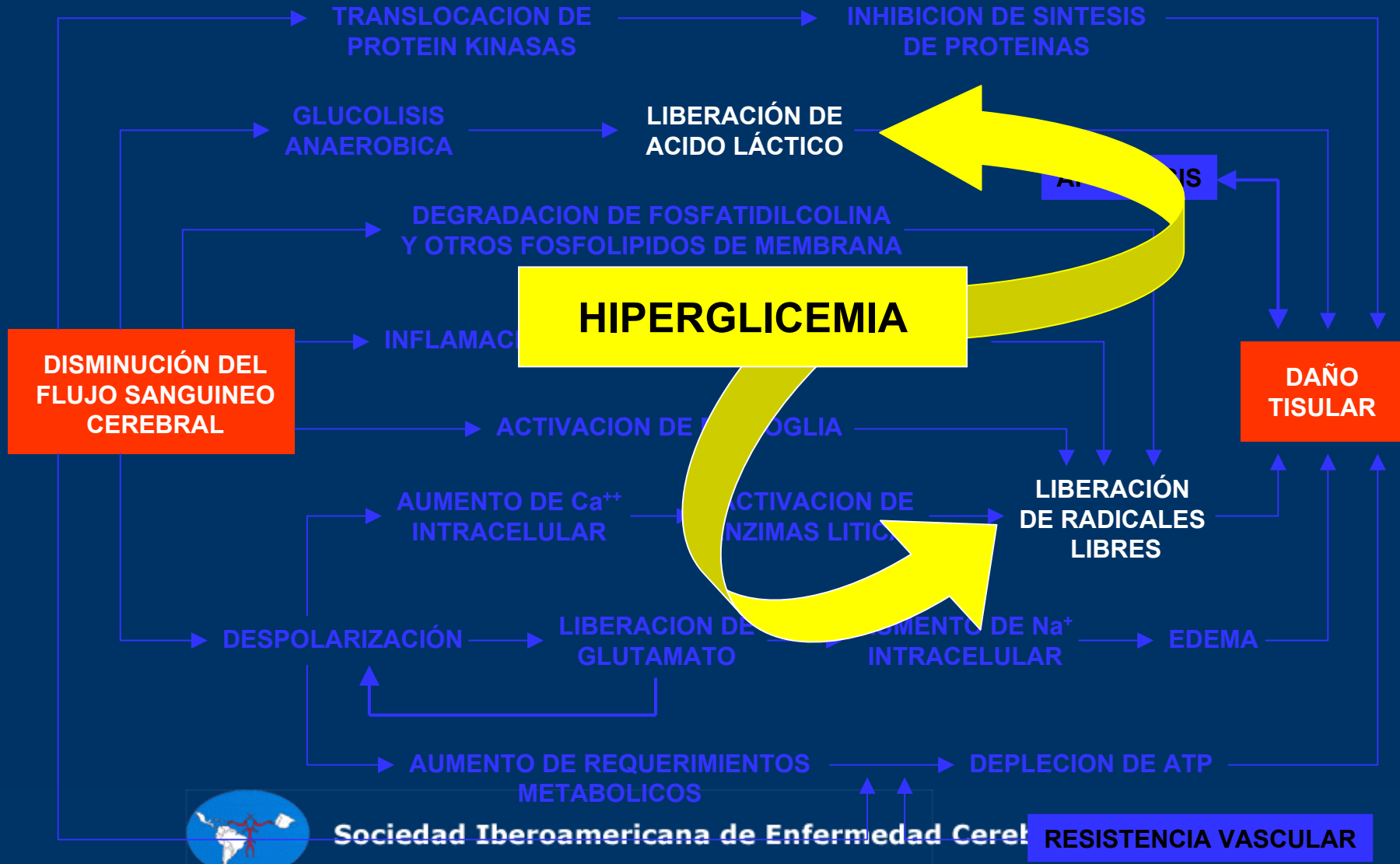
If systolic BP 180-230 mm Hg and/or diastolic BP 105-120 mm Hg on two readings 5 to 10 minutes apart:

Give labetalol 10 mg intravenously over 1-2 minutes. The dose may be repeated or doubled every 10 to 20 minutes, up to 150 mg. Alternatively, following the first bolus of labetalol, an intravenous infusion of the medication can be instituted. The initial infusion rate of labetalol should be 2 mg/min and the dose of medication can be titrated upward as needed to control the blood pressure.

Monitor blood pressure every 15 minutes during the antihypertensive therapy. Observe for hypotension.



GLICEMIA



HIPERGLICEMIA EN ICTUS

- La presencia de hiperglicemia triplica (RR 3.3, CI 2.3 – 4.6) el riesgo de muerte en pacientes no-diabéticos con infarto cerebral, y aumenta el grado de discapacidad en los sobrevivientes.

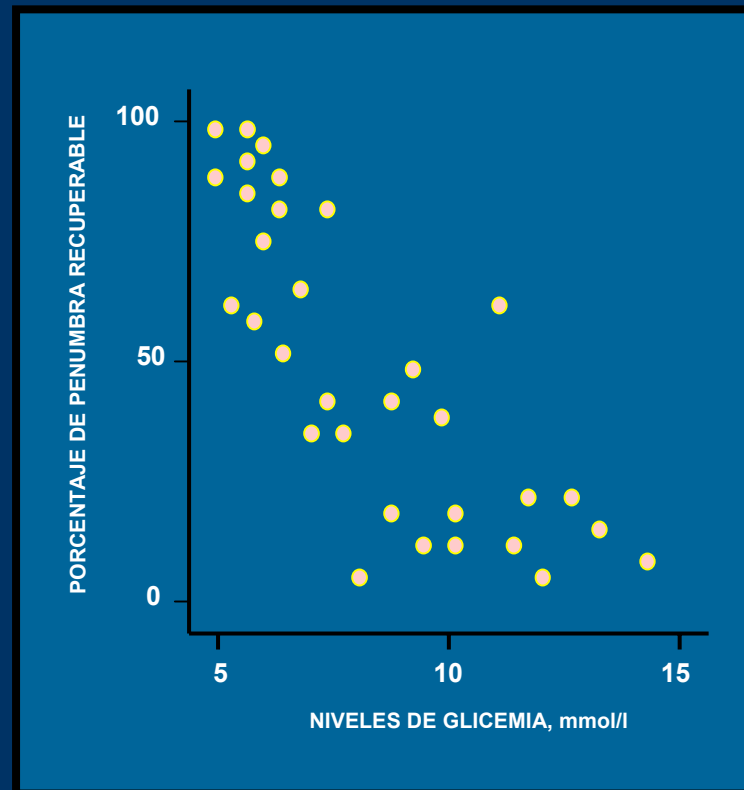
Capes et al. Stroke 2001;32:2426-2432

- La asociación entre hiperglicemia y mal pronóstico no implica necesariamente causalidad. Es probable que la hiperglicemia sea más frecuente en casos más graves ya que estos se asocian con mayor daño cerebral, favoreciendo la liberación de cortisol y epinefrina (hiperglicemia de stress).



CONTROL DE GLICEMIA

- Estudio prospectivo de 69 ptes con ictus isquémico agudo.
- Relación directa entre niveles de glicemia y porcentaje de penumbra isquémica recuperable, valorado con técnicas de difusión-perfusión.
- Relación directa entre niveles de glicemia y producción de lactato, valorado mediante MR espectroscopía.



Parsons y col, Ann Neurol 2002;52:20-28



GLICEMIA y TROMBOLISIS

ESTUDIO	PACIENTES	RESULTADOS	SIGNIFICANCIA
NINDS r-TPA	624 ptes randomizados a r-TPA o placebo	Peor pronóstico y mayor riesgo de hemorragia en ptes con hiperglicemia	$p < 0.02$
PROACT II	110 ptes sometidos a pro-UROK + heparina	Mayor riesgo de hemorragia en ptes con hiperglicemia	$p < 0.02$
Els y colab (2002)	31 ptes sometidos a r-TPA	Peor pronóstico y mayor tamaño de infarto en ptes con hiperglicemia	$p < 0.05$
Alvarez-Sabin y colab (2003)	73 ptes sometidos a r-TPA	Relación entre mal pronóstico, hiperglicemia y <u>reperusión</u>	$p < 0.02$



CONTROL DE GLICEMIA

Glucose Potassium Insulin Infusions in the Treatment of Acute Stroke Patients With Mild to Moderate Hyperglycemia The Glucose Insulin in Stroke Trial (GIST)

Jon F. Scott, BM, BS; Gina M. Robinson, RGN; Joyce M. French, BSc;
Janice E. O'Connell, MB, ChB; K.G.M.M. Alberti, MD; Christopher S. Gray, MD

Background and Purpose—Hyperglycemia following acute stroke is strongly associated with subsequent mortality and impaired neurological recovery, but it is unknown whether maintenance of euglycemia in the acute phase improves prognosis. Furthermore, the safety of such intervention is not established.

Methods—In an explanatory, randomized, controlled trial to test safety, 53 acute (within 24 hours of ictus) stroke patients with mild to moderate hyperglycemia (plasma glucose between 7.0 and 17.0 mmol/L) were randomized to receive either a 24-hour infusion of 0.9% (154 mmol/L) saline or a glucose potassium insulin (GKI) infusion at 100 mL/h. The GKI consisted of 16 U human soluble insulin and 20 mmol potassium chloride in 500 mL 10% glucose. Blood glucose was measured every 2 hours with Boehringer Mannheim Glycaemic test strips, pulse and blood pressure were measured every 4 hours, and plasma glucose samples were taken every 8 hours. Insulin concentration in the GKI was altered according to BM glucose values.

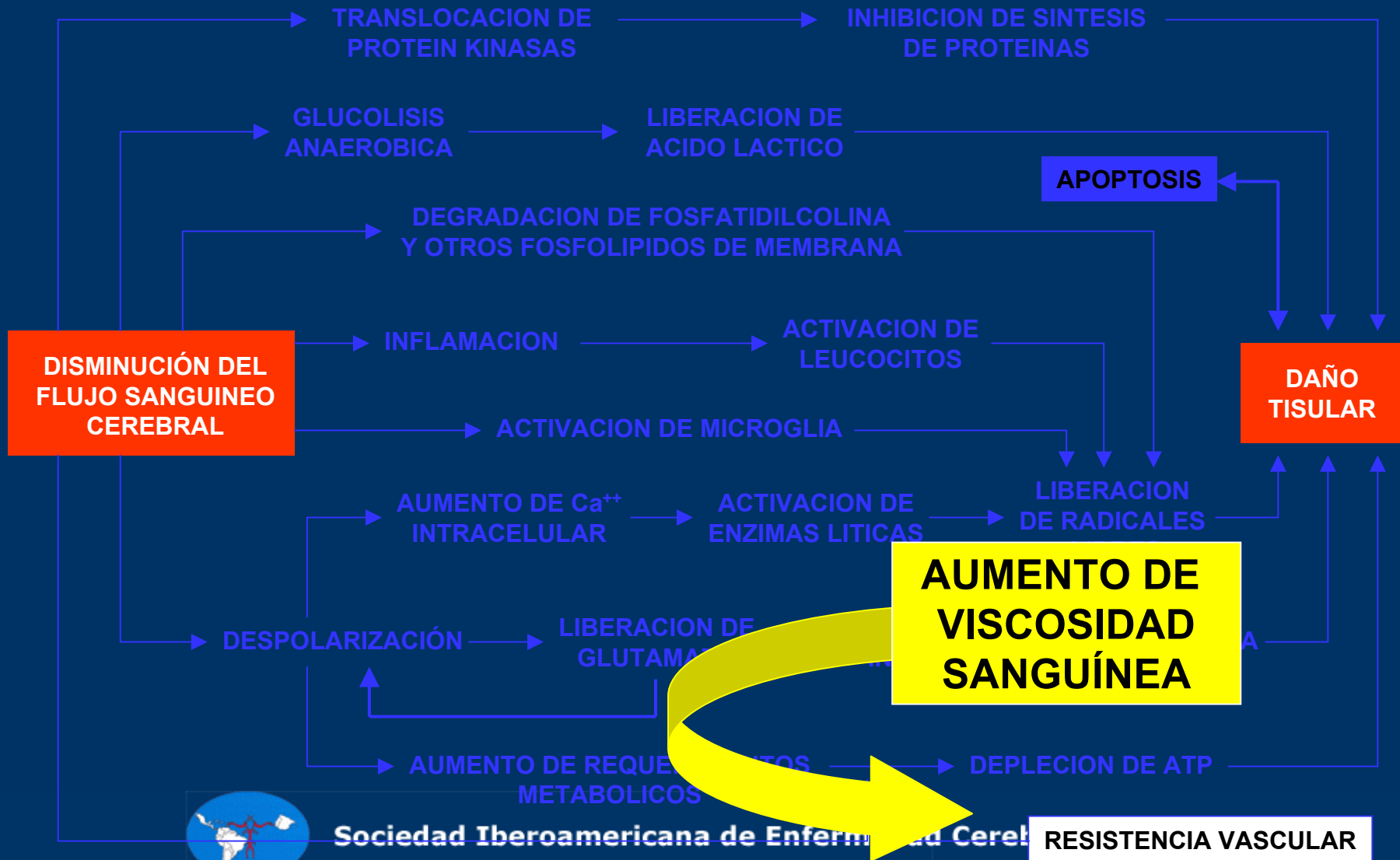
Results—There were no statistically significant differences between the 2 groups at baseline. Twenty-five patients received GKI, 1 of whom required intravenous glucose for symptomatic hypoglycemia. Plasma glucose levels were nonsignificantly lower in the GKI group throughout the infusion period. Four-week mortality in the GKI group was 7 (28%), compared with 8 (32%) in the control group.

Conclusions—GKI infusions can be safely administered to acute stroke patients with mild to moderate hyperglycemia producing a physiological but attenuated glucose response to acute stroke, the effectiveness of which remains to be elucidated. (*Stroke*. 1999;30:793-799.)

Key Words: clinical trials ■ hyperglycemia ■ insulin ■ stroke



VISCOSIDAD DE LA SANGRE



HEMODILUCIÓN

Multicenter Trial of Hemodilution in Acute Ischemic Stroke

I. Results in the Total Patient Population

Scandinavian Stroke Study Group

Hemodilution by the combination of venesection and dextran 40 administration has previously been reported to enhance neurologic recovery in the acute phase of ischemic stroke. To study this therapeutic principle in its "natural habitat," a stratified and randomized multicenter trial involving 15 large and small hospitals was performed. Patients with acute ischemic stroke of <48 hours' duration and with hematocrits of 38–50% on admission were randomized to a hemodilution (183 patients, mean age 72.0 years) or a control group (190 patients, mean age 71.6 years). The two groups did not differ in sex distribution or medical history. Hematocrit, blood pressure, and neurologic score were closely similar at entry. By graded venesection (250–1000 ml) during the first 2 days and dextran 40 infusions (500 ml daily) during 5 days, the mean hematocrit was reduced from 44.2 to 37.1%. Three-month survival expressed as life table product was 0.84 in hemodilution and 0.88 in control patients. In survivors, neurologic score and activities of daily living performance during 3 months of follow-up were not improved by hemodilution. Length of stay in an acute-care hospital and the need for long-term institutional care was not reduced among patients in the hemodilution group. Major cardiovascular events occurred somewhat more often and there was an apparent increase in mortality during the first few days of hemodilution therapy. However, the differences were not significant. We conclude that the present standardized treatment with moderate hemodilution has no overall beneficial effects in general patients with acute ischemic stroke. (*Stroke* 1987;18:691–699)

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HAEMODILUTION IN ACUTE STROKE: RESULTS OF THE ITALIAN HAEMODILUTION TRIAL*

ITALIAN ACUTE STROKE STUDY GROUP

Summary In a multicentre clinical trial 1267 patients with hemispheric stroke of duration 12 h or less and haematocrit of 35% or more were prospectively randomised to either haemodilution (by venesection and replacement of the same volume of dextran 40 in saline solution) or control treatment groups. In the haemodiluted group mean haematocrit declined from 43% to 37% at 48 h and this fall was maintained for seven days. A plain computed tomographic scan was obtained in all but 37 patients. 87% of the strokes were infarcts and 13% were haemorrhages. After six months the numbers of dead or severely disabled patients were equally distributed in the two treatment groups, and this was true also within the ischaemic and haemorrhagic subgroups. Furthermore, haemodilution did not improve outcome either in the group with very recent ischaemic stroke (< 6 h) or in the subgroup with highest haematocrit (>45%). Thus, moderate haemodilution does not improve the outcome in acute stroke patients.

Introduction

EXPERIMENTAL work has shown that a functional neurological deficit can be reversed and the size of a necrotic



HEMODILUCIÓN

- Meta-análisis de 18 estudios controlados de hemodilución en pacientes con ictus de menos de 72 horas de evolución.
- Diseño variable en los estudios:
 - Expansores plasmáticos + sangría..... 8 estudios
 - Expansores plasmáticos solos.....10 estudios
- Expansores plasmáticos utilizados:
 - Dextrano-40.....12 estudios
 - Pentastarch..... 5 estudios
 - Albúmina..... 1 estudio
- Resultados no favorables:
 - Riesgo de muerte en 4 semanas..... OR 1.09 (0.86 – 1.38)
 - Riesgo de muerte en 3 – 6 meses..... OR 1.01 (0.84 – 1.22)
 - Riesgo de muerte o dependencia..... OR 0.98 (0.84 – 1.15)



HIPERTERMIA EN ICTUS

Original Contributions

Timing for Fever-Related Brain Damage in Acute Ischemic Stroke

José Castillo, MD; Antoni Davalos, MD; James Marrugat, MD; Manuel S

Background and Purpose—The association between hyperthermia and early neurological deterioration, and mortality in acute ischemic stroke is well known. However, the timing at which the progression by high temperature has not been firmly established. The aim of this study was to determine the prognostic value of body temperature measured at different times after onset of stroke.

Methods—Axillary temperature was recorded every 2 hours for 72 hours in 360 patients with infarction of <24 hours' duration. A potential infectious focus was examined in all patients with temperature >37.7°C in any of the assessments. Stroke severity was quantified with the Ca

admission. The relationship between the highest temperature recorded in each 6-hour interval and the outcome (Canadian Stroke Scale and Barthel Index) at 3 months or infarct volume was analyzed. The importance of the time at which hyperthermia was first detected was assessed.

Results—During the first 72 hours, 179 patients (50.0%) had hyperthermia, and in 57.0% of these patients, mortality rate at 3 months was 79 in normothermic patients and 15.0% in hyperthermic patients. The correlation coefficients between the first infarct volume, Canadian Stroke Scale and Barthel Index, and each temperature recording decreased progressively over time from symptoms onset within the first 24 hours from stroke onset, but were allowed, was independently related to long-term mortality.

Conclusions—The relationship between brain damage and high temperature occurs. However, only body temperature within the first 24 hours from stroke onset and long-term mortality. *Stroke*. 2006;37:2415-2420.

Key Words: fever • hyperthermia • stroke, ischemic

Influence of Admission Body Temperature on Stroke Mortality

Yang Wang, MD; Lynette L.-Y. Lim, PhD; Christopher Levi, MBBS, FRACP; Richard F. Heller, MD, FRACP, FAFPHM; Jason Fisher, B.Maths

Background and Purpose—The influence of body temperature on stroke outcome remains uncertain. The aim of this study was to investigate the prognostic role of admission body temperature on short-term and long-term mortality in a retrospective cohort study of patients with acute stroke.

Methods—A retrospective cohort of 509 patients with acute stroke, admitted to a tertiary hospital between July 1, 2005, and June 30, 2007, was studied. The relationship between admission body temperature and mortality both at hospital discharge and long-term mortality was assessed.

Results—The mean admission body temperature was 36.7°C (range 35.0–40.0°C). The mean age was 68.5 years (range 18–98 years). The mean duration of illness was 4.5 days (range 0–14 days). The mean length of stay was 10.5 days (range 1–60 days). The mean mortality rate was 15.5% (95% CI, 13.5–17.5%).

Conclusions—Admission body temperature is an independent predictor of short-term and long-term mortality in patients with acute stroke. Hyperthermia was

Effects of Poststroke Pyrexia on Stroke Outcome: A Meta-Analysis of Studies in Patients

Coiter Hajar, MRCP; Shukoor Hajar, MSc; Pankaj Sharma, PhD

Background and Purpose—The effect of pyrexia on cerebral ischemia has been extensively studied in animals. In humans, however, such studies are small and the results conflicting. We undertook a meta-analysis using all such published studies on the effect of hyperthermia on stroke outcome.

Methods—Three databases were searched for all published studies that examined the relationship of raised temperature after stroke onset and eventual outcome. Combined probability values and odds ratios were obtained. A heterogeneity test was performed to ensure that the data were suitable for such an analysis. Morbidity and mortality were used as outcome measures.

Results—Nine studies were identified totaling 1790 patients, providing our study with 99% power to detect a 9% increase in morbidity and 84% power to detect a 1% increase in mortality for the pyrexial group. The combined odds ratio for mortality was 1.18 (95% CI, 0.99 to 1.43). A heterogeneity test was highly nonsignificant ($P=0.05$) for mortality, suggesting that the data were sufficiently similar to be meta-analyzed. Combined probability values were highly significant for both morbidity ($P<0.0001$) and mortality ($P<0.0000001$).

Conclusions—The results from this meta-analysis suggest that pyrexia after stroke onset is associated with a marked increase in morbidity and mortality. Measures should be taken to combat fever in the clinical setting to prevent stroke progression. The possible benefit of therapeutic hypothermia in the management of acute stroke should be further investigated. *Stroke*. 2006;37:412-414.

Key Words: fever • meta-analysis • outcome • stroke



COPENHAGEN STROKE STUDY

- Estudio prospectivo de 390 pacientes con ictus agudo admitidos en las primeras 6 horas del evento.
- Temperatura corporal al ingreso $> 37.4^{\circ}\text{C}$ predijo de manera independiente:
 - Gravedad del evento inicial..... $p < 0.009$
 - Tamaño del infarto..... $p < 0.0001$
 - Mortalidad..... $p < 0.02$
 - Secuelas en sobrevivientes..... $p < 0.003$
- Por cada grado centígrado de aumento de temperatura, el riesgo relativo de mal pronóstico aumentó 2.2 veces.



HIPOTERMIA EN ICTUS

ESTUDIO	TIPO DE ICTUS	PACIENTES	RESULTADOS
Georgiadis y colab (2002)	Infarto masivo ACM	Hipotermia 33oC (n=19) Craniectomía (n=17)	Mayor mortalidad y peor pronóstico en ptes sometidos a hipotermia
Dippel y colab (2001)	Infarto en territorio carotídeo	Acetaminofén 3g/d (n=25) Acetaminofén 6 g/d (n=26) Placebo / no tratam (n=25)	No diferencias en secuelas
Kasner y colab (2002)	Infartos y hemorragias	Acetaminofén 4g/d (n=20) No tratamiento (n=19)	No diferencias en secuelas
Kammersgard y colab (2000)	Infarto cerebral	Hipotermia 35.5oC (n=17) Controles históricos (n=56)	No diferencias en mortalidad o secuelas
Krieger y colab (2001)	Infarto cerebral (post-trombolisis)	Hipotermia 32oC (n=10) No tratamiento (n=9)	No diferencias en mortalidad o secuelas



TEMPERATURA EN ICTUS

- La hipertermia es perjudicial en pacientes con ictus agudo.
- La hipotermia inducida no es un procedimiento de rutina.
- Lo óptimo es inducir hipotermia en las primeras 6-12h del ictus y mantenerla por 24-48h.
- La inducción de hipotermia debe ser con mantas o medios físicos. Los antipiréticos no son eficaces.
- Los pacientes sometidos a hipotermia deben ser monitorizados para evitar complicaciones.
- El recalentamiento debe ser lento para evitar aumento de presión intracraneal.

