ГОРОДСКАЯ КЛИНИЧЕСКАЯ БОЛЬНИЦА №52

Российский университет дружбы народов

БЕРЕМЕННОСТЬ, ЭНДОТЕЛИЙ, ГЕМОСТАЗ

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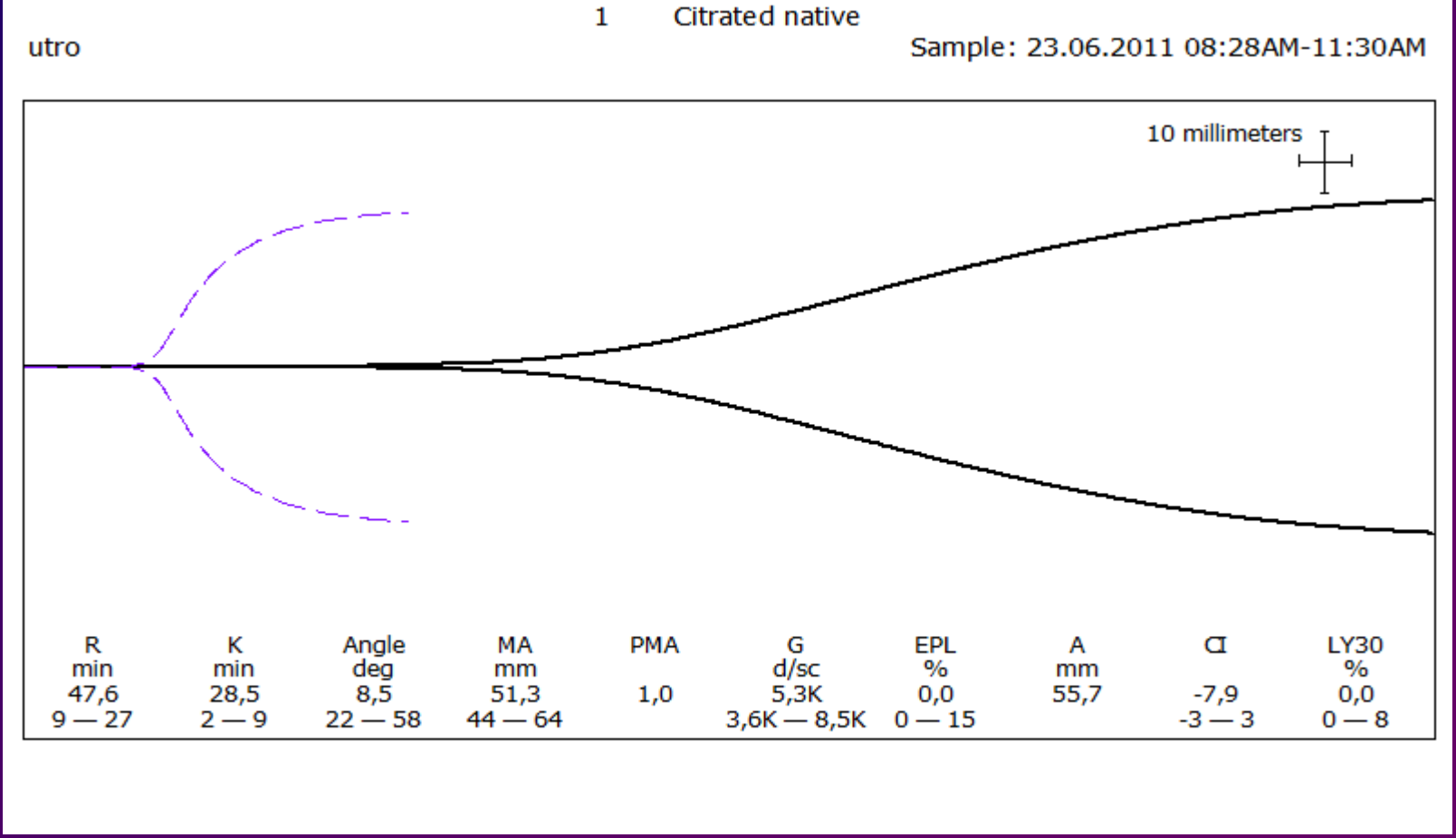
г. Москва

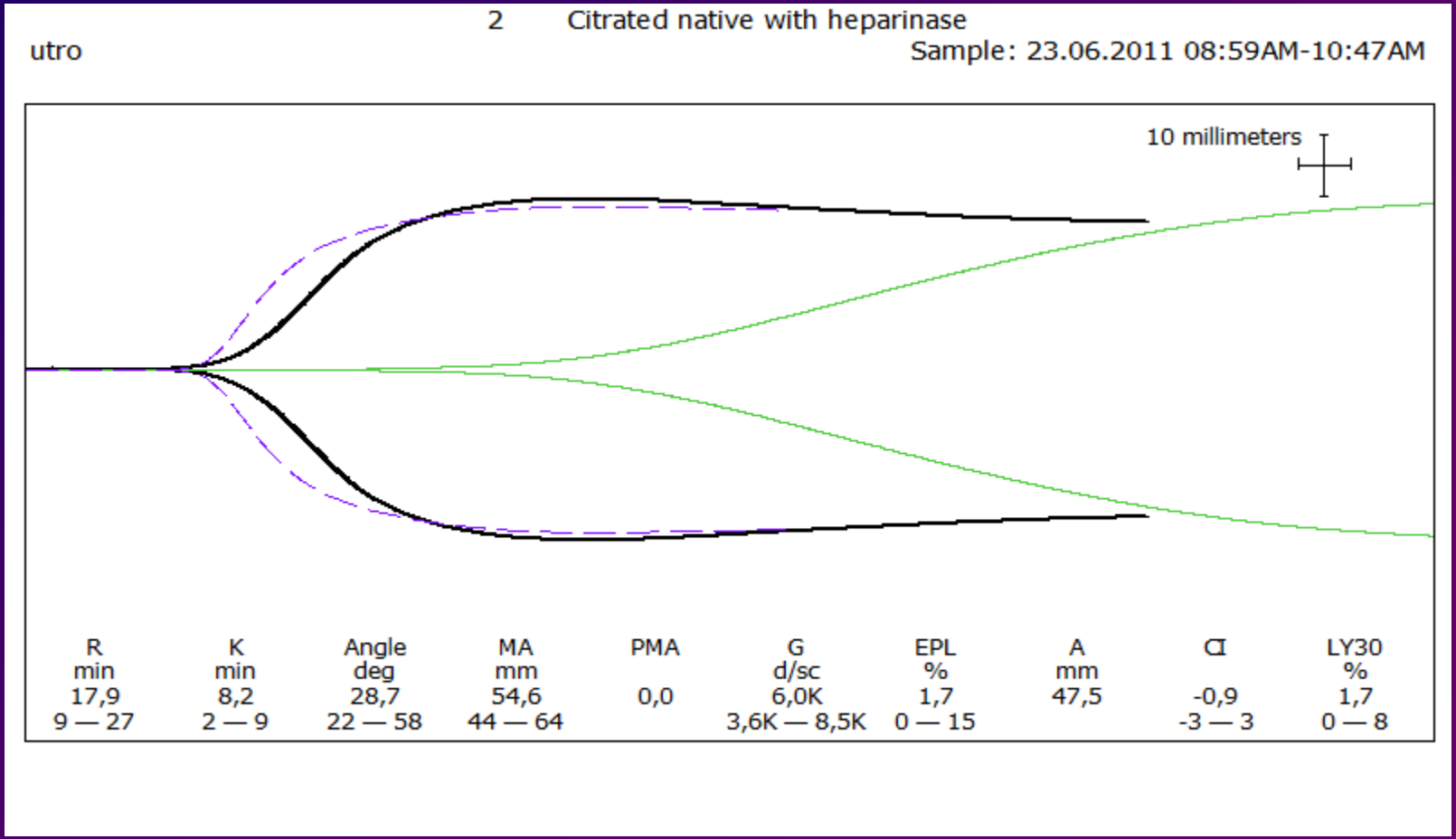
Клинический пример

- П., 32 г.
- Беременность 36 нед
- Гестоз средней тяжести
- Легкое отравление?
- Кесарево сечение
- Массивное кровотечение

Пациентка П., пик кровотечения

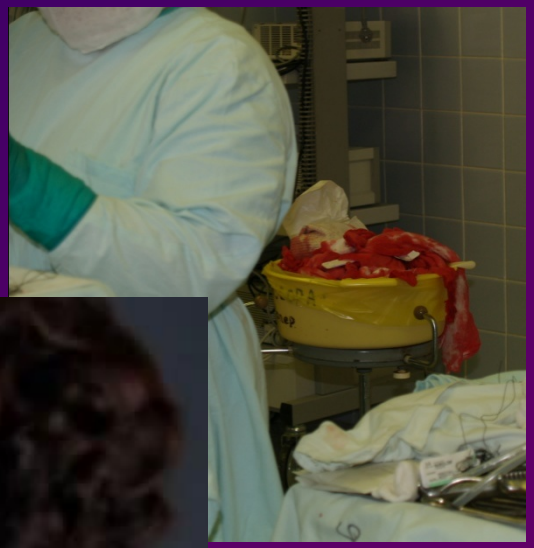


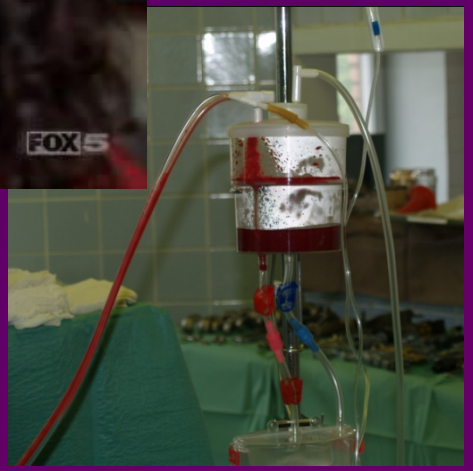
Тест с гепариназой



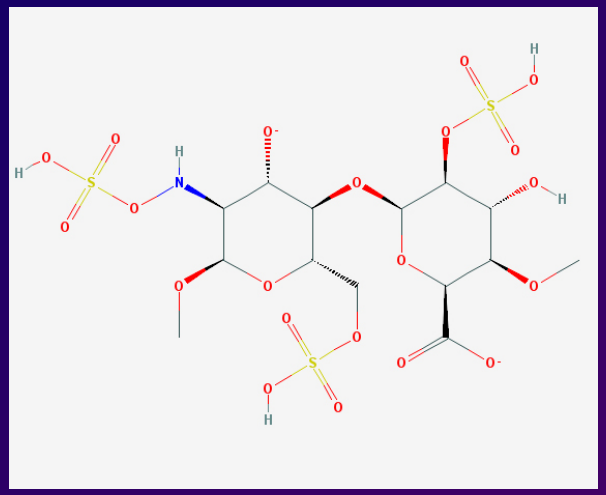
Кровотечение! ГЕПАРИН?!

?!?!?!?!?

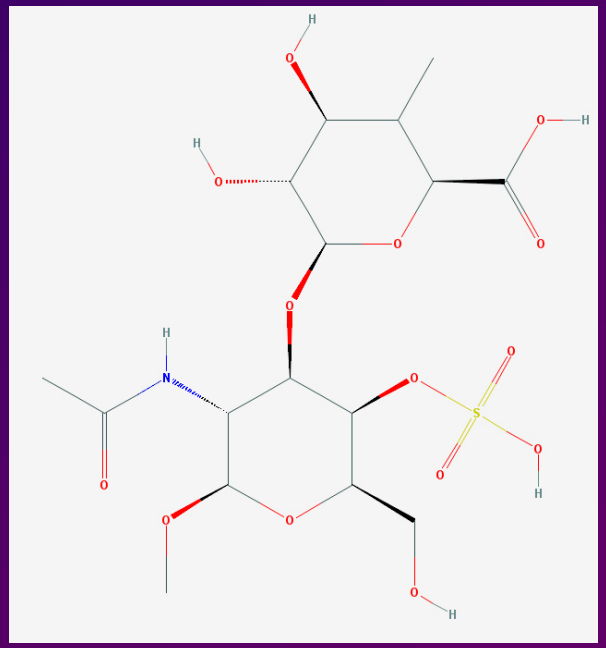




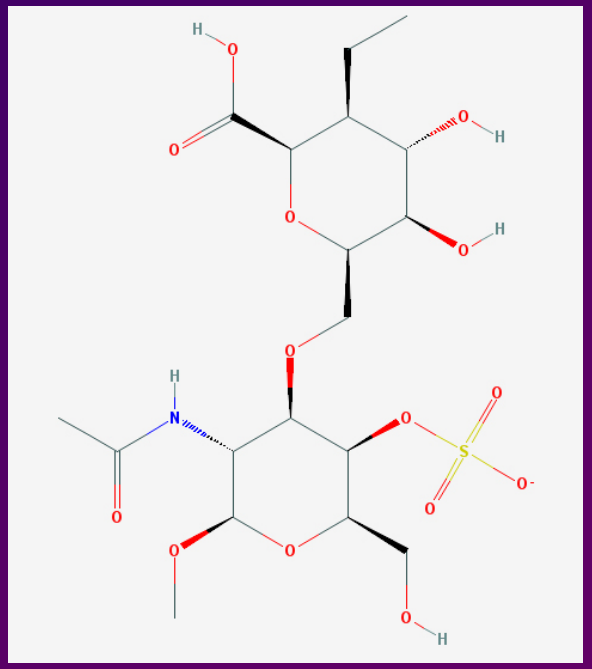
Гликозаминогликаны



Гепаран сульфат

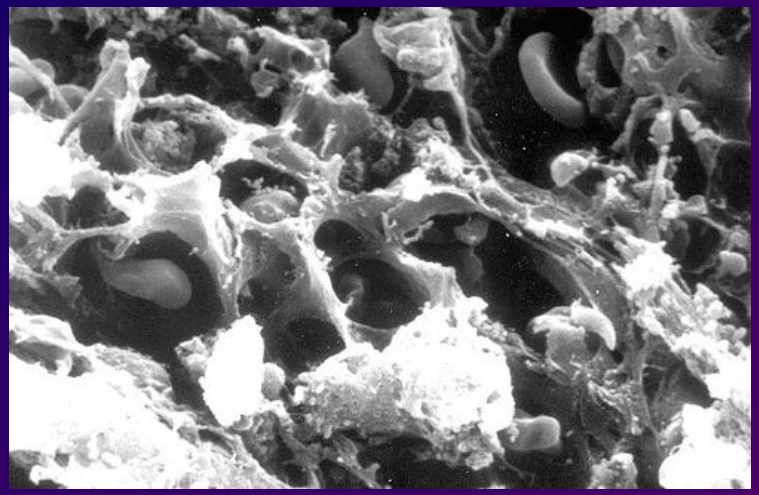


Хондроитин сульфат

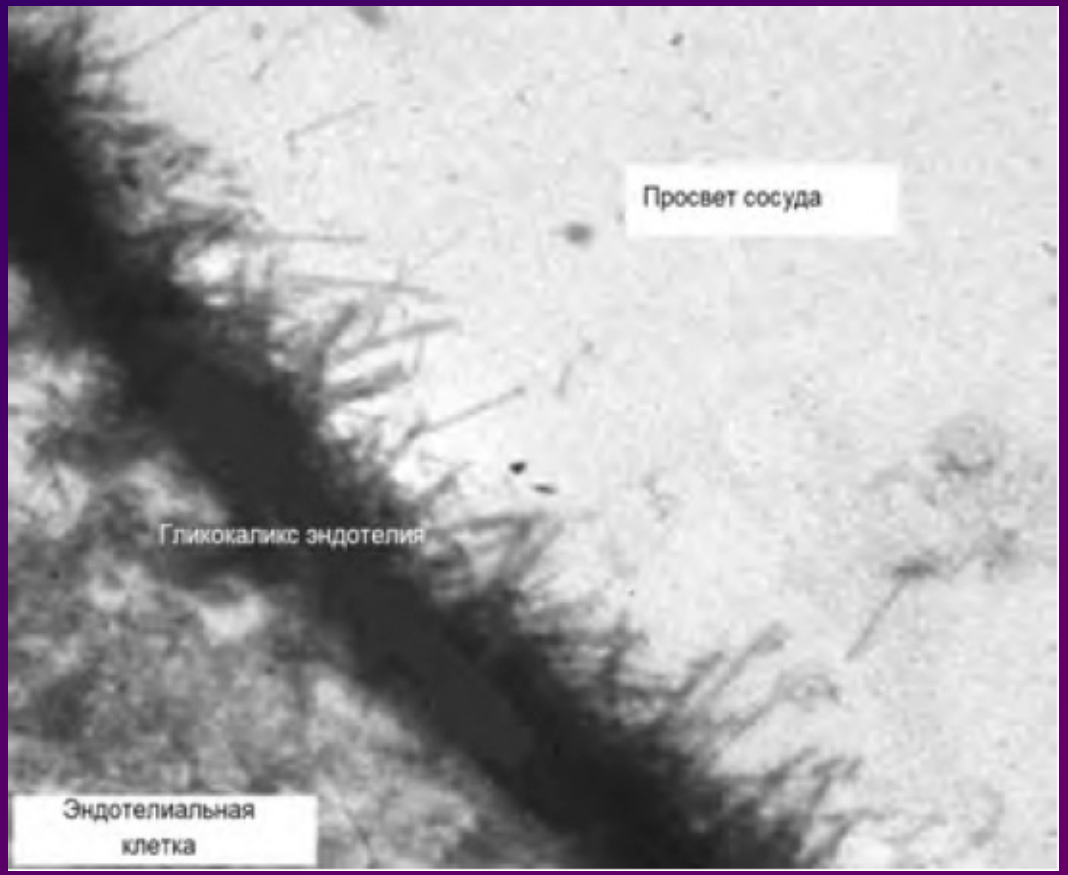


Дерматан сульфат

Гликозаминогликаны: происхождение



Эндотелий сосудов



British Journal of Anaesthesia **108** (3): 384–94 (2012)
Advance Access publication 29 January 2012 · doi:10.1093/bja/aer515

BJA

Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy

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Editor's key points

- The classic Starling principle does not hold for fluid resuscitation in clinical settings.
- The endothelial glycocalyx layer appears to have a major role in fluid exchange.
- A revision of Starling incorporating the glycocalyx model appears to explain better the responses seen clinically.

Summary. I.V. fluid therapy does not result in the extracellular volume distribution expected from Starling's original model of semi-permeable capillaries subject to hydrostatic and oncotic pressure gradients within the extracellular fluid. Fluid therapy to support the circulation relies on applying a physiological paradigm that better explains clinical and research observations. The revised Starling equation based on recent research considers the contributions of the endothelial glycocalyx layer (EGL), the endothelial basement membrane, and the extracellular matrix. The characteristics of capillaries in various tissues are reviewed and some clinical corollaries considered. The oncotic pressure difference across the EGL opposes, but does not reverse, the filtration rate (the 'no absorption' rule) and is an important feature of the revised paradigm and highlights the limitations of attempting to prevent or treat oedema by transfusing colloids. Filtered fluid returns to the circulation as lymph. The EGL excludes larger molecules and occupies a substantial volume of the intravascular space and therefore requires a new interpretation of dilution studies of blood volume and the speculation that protection or restoration of the EGL might be an important therapeutic goal. An explanation for the phenomenon of context sensitivity of fluid volume kinetics is offered, and the proposal that crystalloid resuscitation from low capillary pressures is rational. Any potential advantage of plasma or plasma substitutes over crystalloids for volume expansion only manifests itself at higher capillary pressures.

Keywords: fluid therapy; intensive care

BJA

lyx model
ed paradigm

on SO16 6YD, UK

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fluid exchange.

- A revision of Starling incorporating the glycocalyx model appears to explain better the responses seen clinically.

Keywords: fluid therapy; intensive care

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lyx model

fluid exch

- A revision
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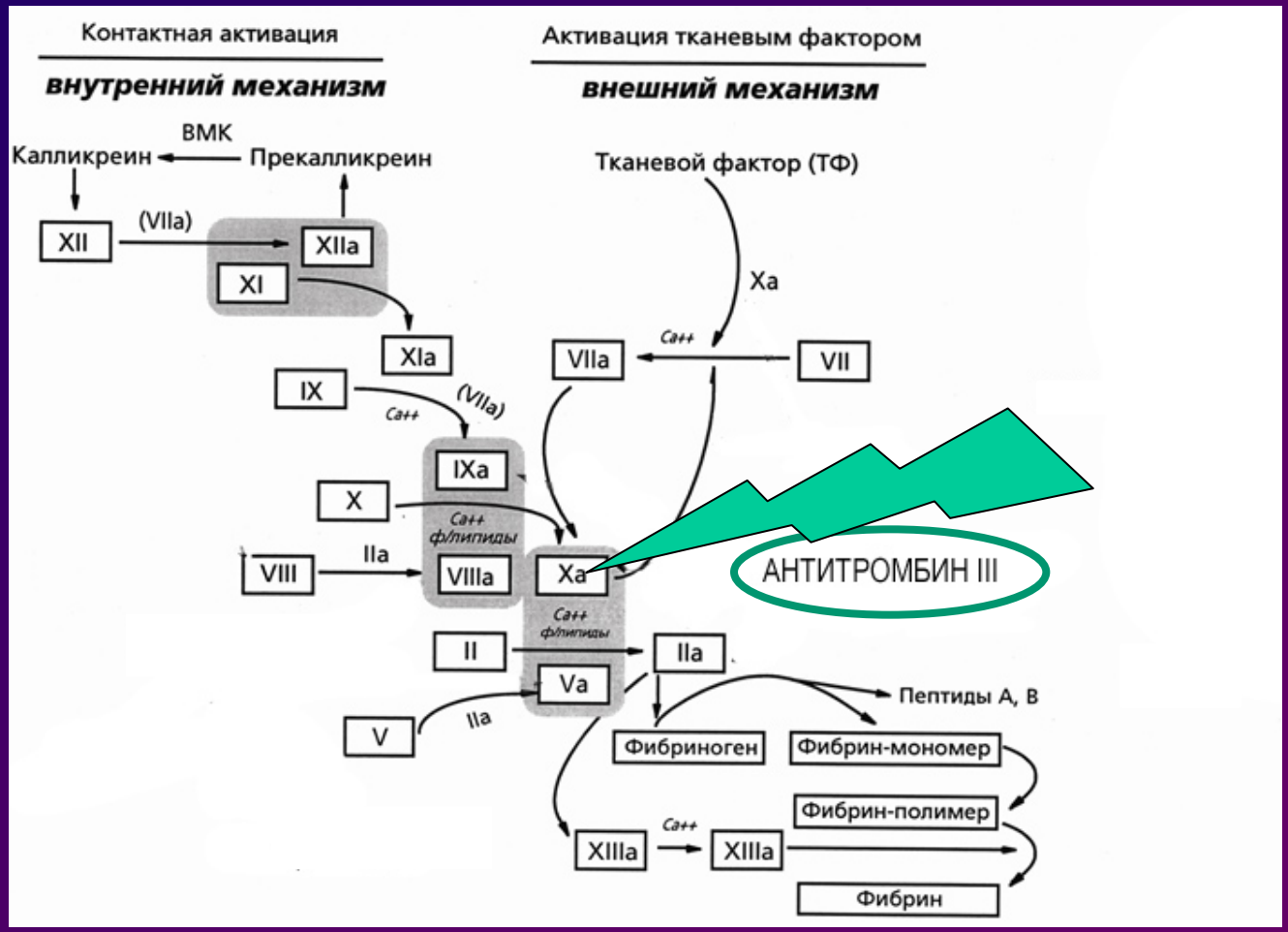
Гликоаминогликаны: локализация действия



- Лабораторные признаки эффекта гепарина, при отсутствии данных за его экзогенное ведение
  - **Гепарино-подобный эффект**

- Кровотечение + лабораторные признаки эффекта гепарина, при отсутствии данных за его экзогенное ведение
  - **Гепарино-подобный синдром**

С.А. Андрейченко и др., 2013

Фоновые состояния:

- Поражения печени

S. Agarwal et al., 2008; M. Senzolo et al., 2009

- Сепсис

M. Senzolo et al., 2009

- Злокачественные новообразования

K.N. Fahl et al., 2009

- Гемобластозы

G.S.Chapman et al., 1985; P. Plamas et al., 2001

L. Torjemale et al., 2009

Эндогенные гепарины при беременности

The defibrination syndrome has become well recognized as an important and treatable cause of acute generalized haemorrhagic states developing in the perinatal period (Schneider, 1951; Soulier, Alagille, and Larrieu, 1956). Simple and rapid laboratory or bed-side tests have been proposed for confirming the diagnosis (Sharp, Howie, Biggs, and Methuen, 1958; Hardisty, 1958; Ingram and Matchett, 1960).

Other types of acute coagulation disorders associated with pregnancy are less common and include unexplained vitamin K deficiency (Larsen, 1960), circulating anticoagulants affecting the early stages of blood coagulation (Hougie, 1955), and increased heparin-like activity of the blood (Ratnoff and Vosburgh, 1952; Jürgens and Stein, 1954; Masure and Schockaert, 1954). Ingram, Norris, and Tanner (1960) have drawn attention to the fact that heparinaemia may cause difficulty in the laboratory diagnosis of acute coagulation disorders. The present case is reported because it endorses this view and emphasizes the importance of distinguishing this state from the more commonly occurring defibrination syndrome. Providing heparinaemia is recognized intravenous protamine sulphate appears to be a simple and effective treatment. Greater awareness of its possible occurrence is therefore desirable.

J. clin. Path. (1963), **16**, 108

A puerperal haemorrhagic state due to a heparin-like anticoagulant

M. L. N. WILLOUGHBY

From the Department of Haematology, Southern General Hospital, Glasgow

Эндогенные гепарины при беременности

Placental dermatan sulfate: isolation, anticoagulant activity, and association with heparin cofactor II

Tusar K. Giri and Douglas M. Tollefsen

Pregnancy is associated with hemostatic challenges that may lead to thrombosis. Heparin cofactor II (HCII) is a glycosaminoglycan-dependent thrombin inhibitor present in both maternal and fetal plasma. HCII activity increases during pregnancy, and HCII levels are significantly decreased in women with severe pre-eclampsia. Dermatan sulfate (DS) specifically activates HCII and is abundant in the placenta, but the locations of DS and HCII in the placenta have not been determined. We present evidence that DS is the major anticoagulant glycosaminoglycan in the human placenta at term. DS isolated from human placenta contains disaccharides implicated in activation of HCII and has anticoagulant activity similar to that of mucosal DS. Immunohistochemical studies revealed that DS is associated with fetal blood vessels and stromal regions of placental villi but is notably absent from the syncytiotrophoblast cells in contact with the maternal circulation. HCII colocalizes with DS in the walls of fetal blood vessels and is also present in syncytiotrophoblast cells. Our data suggest that DS is in a position to activate HCII in the fetal blood vessels or in the stroma of placental villi after injury to the syncytiotrophoblast layer and thereby inhibit fibrin generation in the placenta. (Blood. 2006;107:2753-2758)

In summary, our data suggest that DS is the major anticoagulant GAG in the human placenta at term. In addition, placental DS contains disaccharide subunits known to interact with HCII and stimulates thrombin inhibition by HCII in vitro. Immunohistochemical studies suggest that DS is positioned to activate HCII in the fetal blood vessels or in the stroma of placental villi after injury to the syncytiotrophoblast layer. Thus, HCII may serve to inhibit fibrin generation in the placenta.

Эндогенные гепарины при беременности

- Гепариноподобные вещества одна из причин послеродовых кровотечений

E. Cassele et al., 1998

Original Article

Reproductive Sciences
20(3) 318-325

DOI: 10.1177/1933719112453508
rs.sagepub.com
SAGE

Increased Serum Concentrations of Circulating Glycocalyx Components in HELLP Syndrome Compared to Healthy Pregnancy: An Observational Study

Klaus F. Hofmann-Kiefer, MD[1], J. Knabl, MD[2], N. Martinoff, MD[1], B. Schiessl, MD[2], P. Conzen, MD[1], M. Rehm, MD[1], B. F. Becker, MD[3], and D. Chappell, MD[1]

Abstract

Severe inflammation has been shown to induce a shedding of the endothelial glycocalyx (EGX). Inflammatory cytokines, such as tumor necrosis factor α (TNF-α), impede the thickness of the EGX. While a controlled inflammatory reaction occurs already in normal pregnancy, women with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome had an exaggerated inflammatory response. This study investigates the shedding of the glycocalyx during normal pregnancy and in women with HELLP syndrome. Glycocalyx components (syndecan 1, heparan sulfate, and hyaluronic acid) were measured in serum of healthy women throughout pregnancy (4 time points, n = 26), in women with HELLP syndrome (n = 17) before delivery and in nonpregnant volunteers (n = 10). Serum concentrations of TNF-α and soluble TNF-α receptors (sTNF-Rs) were assessed once in all 3 groups. Syndecan 1 serum concentrations constantly rose throughout normal pregnancy. Immediately before delivery, a 159-fold increase was measured compared to nonpregnant controls ($P < .01$). Even higher amounts were observed in patients with HELLP prior to delivery (median 12 252 ng/mL) compared to healthy women matched by gestational age (median 5943 ng/mL; $P < .01$). Relevantly, increased serum levels of heparan sulfate, hyaluronic acid, and sTNF-Rs were only detected in patients with HELLP ($P < .01$). These findings suggest that considerable amounts of syndecan 1 are released into maternal blood during uncomplicated pregnancy. The HELLP syndrome is associated with an even more pronounced shedding of glycocalyx components. The maternal vasculature as well as the placenta has to be discussed as a possible origin of circulating glycocalyx components.

Инфузионно-трансфузионная терапия и гликокаликс

- Объемная перегрузка (BNP) – повреждение

M. Rehm et al. 2004, 2010
M.S. Strunden et al., 2012

Кристаллоидные растворы гликокаликс

- Избыток кристаллоидов (отек) – повреждение
- Гиперхлоремия – повреждение

  Сбалансированные растворы (ионостерил, плазмалит и др.) – профилактика повреждения (не протекция!)
- Гипергликемия - повреждение

M. Rehm et al. 2004, 2010
M. Jacob et al., 2013

Трансфузионная терапия и гликокаликс

- Эндогенные эритроциты и тромбоциты - протекция
- Трансфузия ?

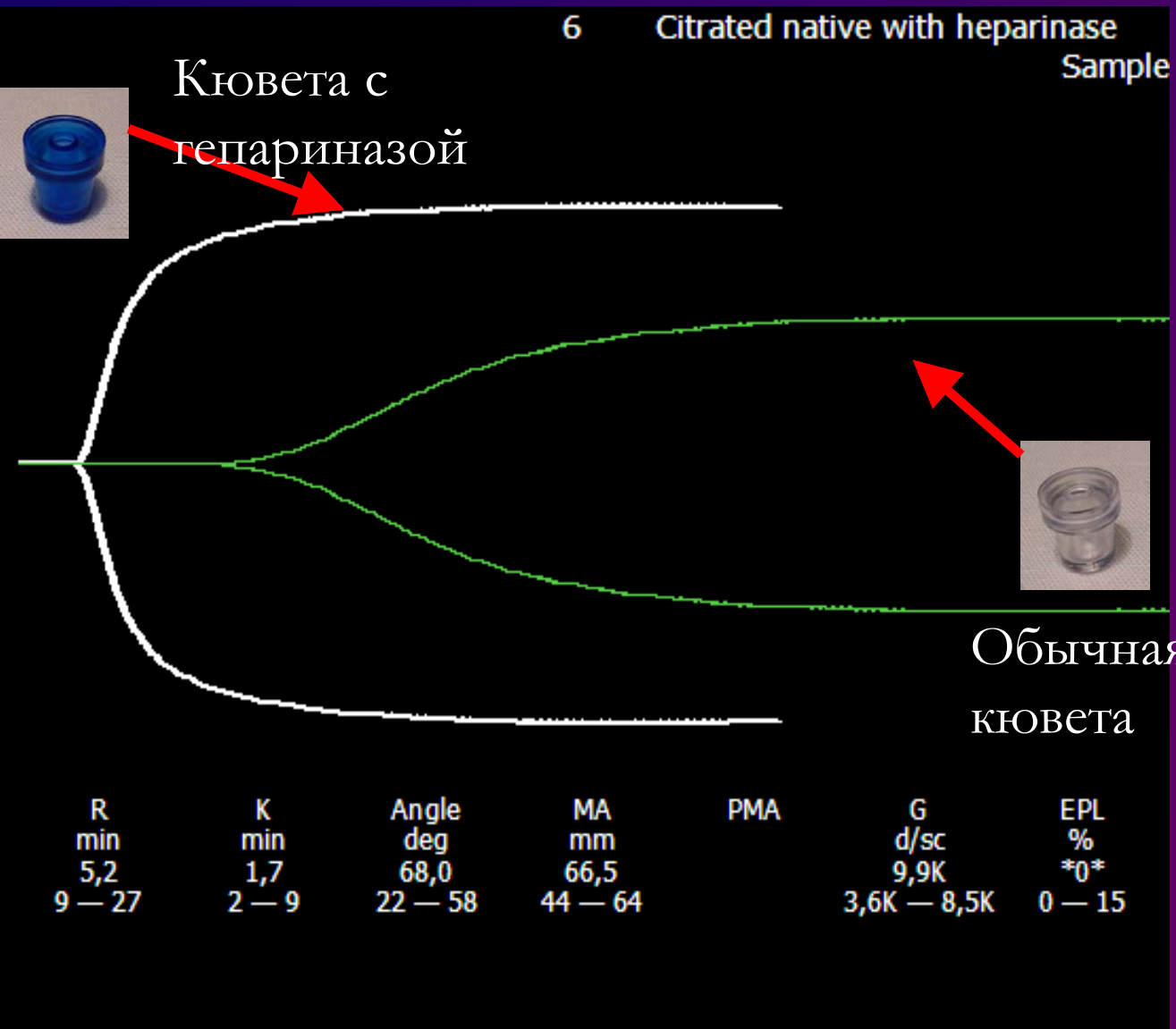
M.S. Strunden et al., 2012
A.M. Larsen et al., 2013
H. Oberleithner, 2013

Трансфузионная терапия и гликокаликс

- СЗП – протекция !
- Антитромбин III – протекция !!!

R.A. Kozar et al. 2011
D. Chappell et al., 2009, 2014

Тест с гепариназой



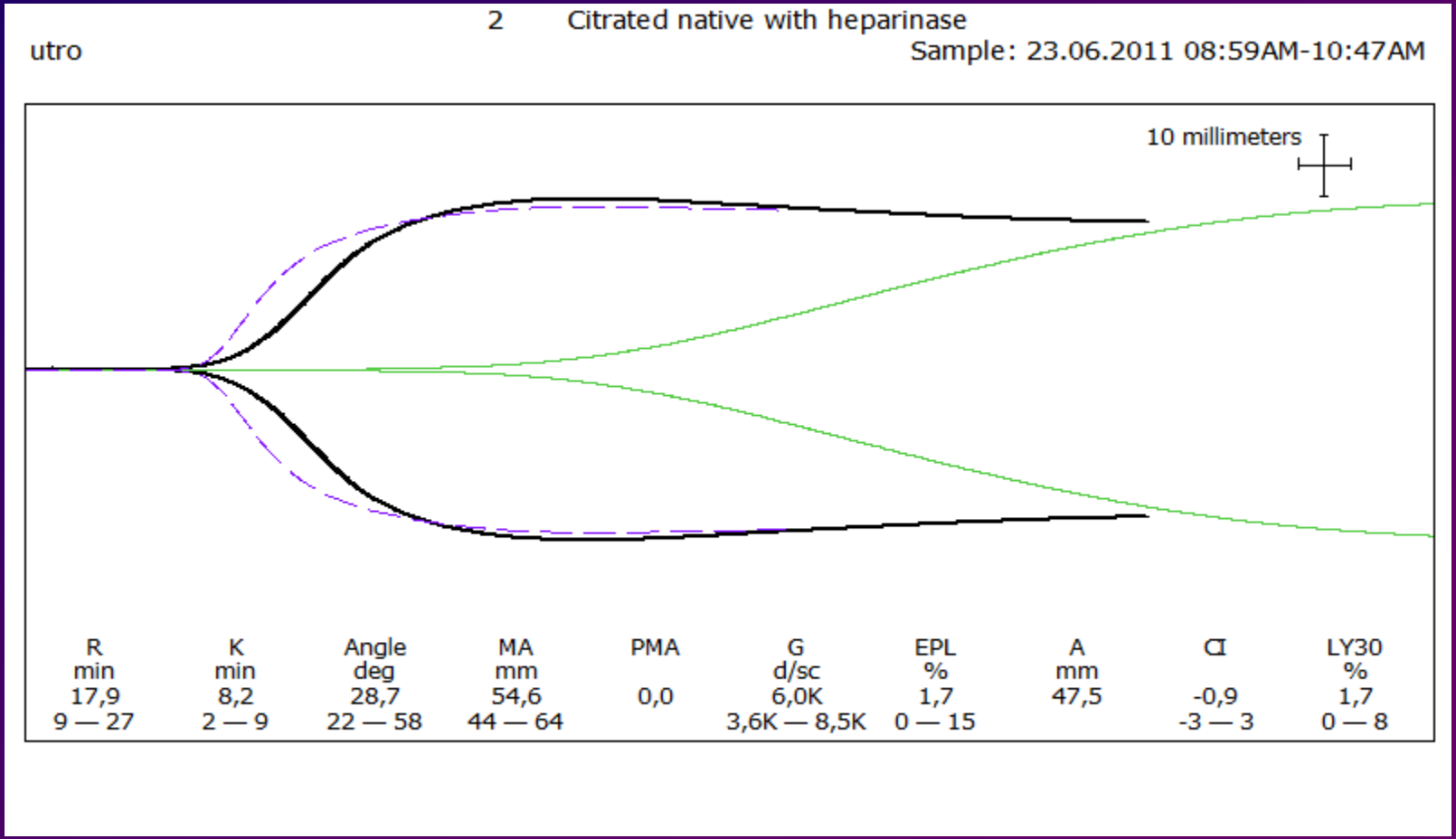
Коэффициент коррекции в тесте с гепариназой

$$\frac{(r + k) \text{ нативной пробы} - (r + k) \text{ гепариназной пробы}}{(r + k) \text{ нативной пробы}} \times 100\%$$

- > 50% - достоверный ГПС
- > 80% - тяжелый ГПС

M. Senzolo et al.,2008

Тест с гепариназой



Коэффициент коррекции – 65%

Лечение ГПС: протамина сульфат

- Эффективность in vitro

Y. Kang, 1997

- Клиническая эффективность не продемонстрирована

M. Senzolo, 2009

Лечение ГПС: гепариназа

- Использование препарата гепариназы I (Нейтралаза) ?

J. Zimmermann, 1996

- Гепариназа РАЗРУШАЕТ ГЛИКОКАЛИКС

D. Chappell et al., 2008

Лечение ГПС: СЗП

- Эффективно

M. Senzolo et al., 2009

- Не эффективно

U. Thalheimer et al., 2005

Лечение ГПС: рекомбинантный VIIa

- Альтернативная терапия при неэффективности других подходов

Shami V.M. et al., 2003

ЭНДОГЕННЫЙ ГЕПАРИНОПОДОБНЫЙ СИНДРОМ: АНАЛИЗ КЛИНИЧЕСКИХ НАБЛЮДЕНИЙ

БУЛАНОВ АНДРЕЙ ЮЛЬЕВИЧ [1], **ЯЦКОВ К. В.**, **ШУЛУТКО Е. М.**, **ГЛУХОВА Т. Е.**, **АНДРЕЙЧЕНКО С. А.**

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Первый МГМУ им. И. М. Сеченова

Тип: статья в журнале - научная статья Язык: русский

Номер: 3 Год: 2012 Страницы: 51-54

Цит. в РИНЦ®: 0

УДК: 616.151.514-092:612.014.1:547.963.1

ЖУРНАЛ:

АНЕСТЕЗИОЛОГИЯ И РЕАНИМАТОЛОГИЯ
Издательство: Издательство "Медицина" (Москва)
ISSN: 0201-7563

ГПС: важный вопрос

- Дифференциальная диагностика с экзогенным гепарином?

  - Рутинных тестов не описано

Диагностика ГПС

ИФА

Microcirculation imaging

Диагностика ГПС: клинический алгоритм

- Эффект гепарина в ТЭГ с гепариназой
- Отсутствие факта введения гепарина
- Отсутствие эффекта от протамина сульфата

ГПС: другие аспекты

- Частота встречаемости

  Данных не приводится

- Корреляция между тяжестью ГПС и геморрагическим синдромом

  Не выявлено

!!!

ГПС

≠

ДВС

Спасибо за внимание!