

A Totally Recombinant Factor XIII- Supplemented Fibrin Sealant

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Disclosure/Conflicts:
None

Introduction

- Available fibrin sealants are plasma-derived (pd-FS)
- pd-FS contain fibrinogen + thrombin
- pd-FS does not much Factor XIII
- Some limitations of pd-FS: abundance & cost

Human Recombinant Fibrin Sealant (r-FS)

- rHu-Fibrinogen secreted in milk of transgenic cows
- rHu-thrombin available commercially (Recothrom®)
- rHu-Factor XIII made in yeast (*Pichia pastoris*)
- Factor concentration in r-FS optimized with TEG

TEG: effect of Factor XIII

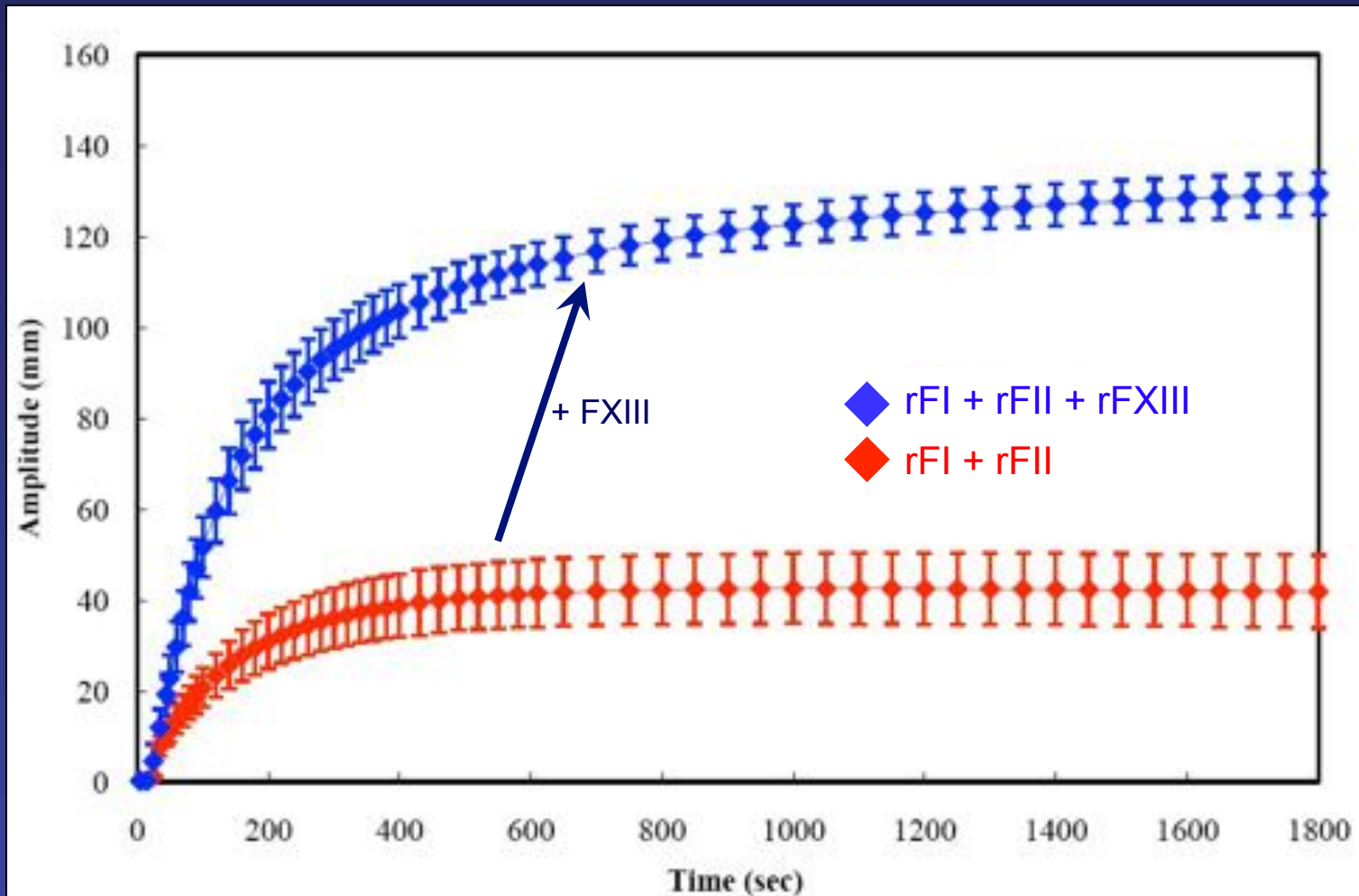
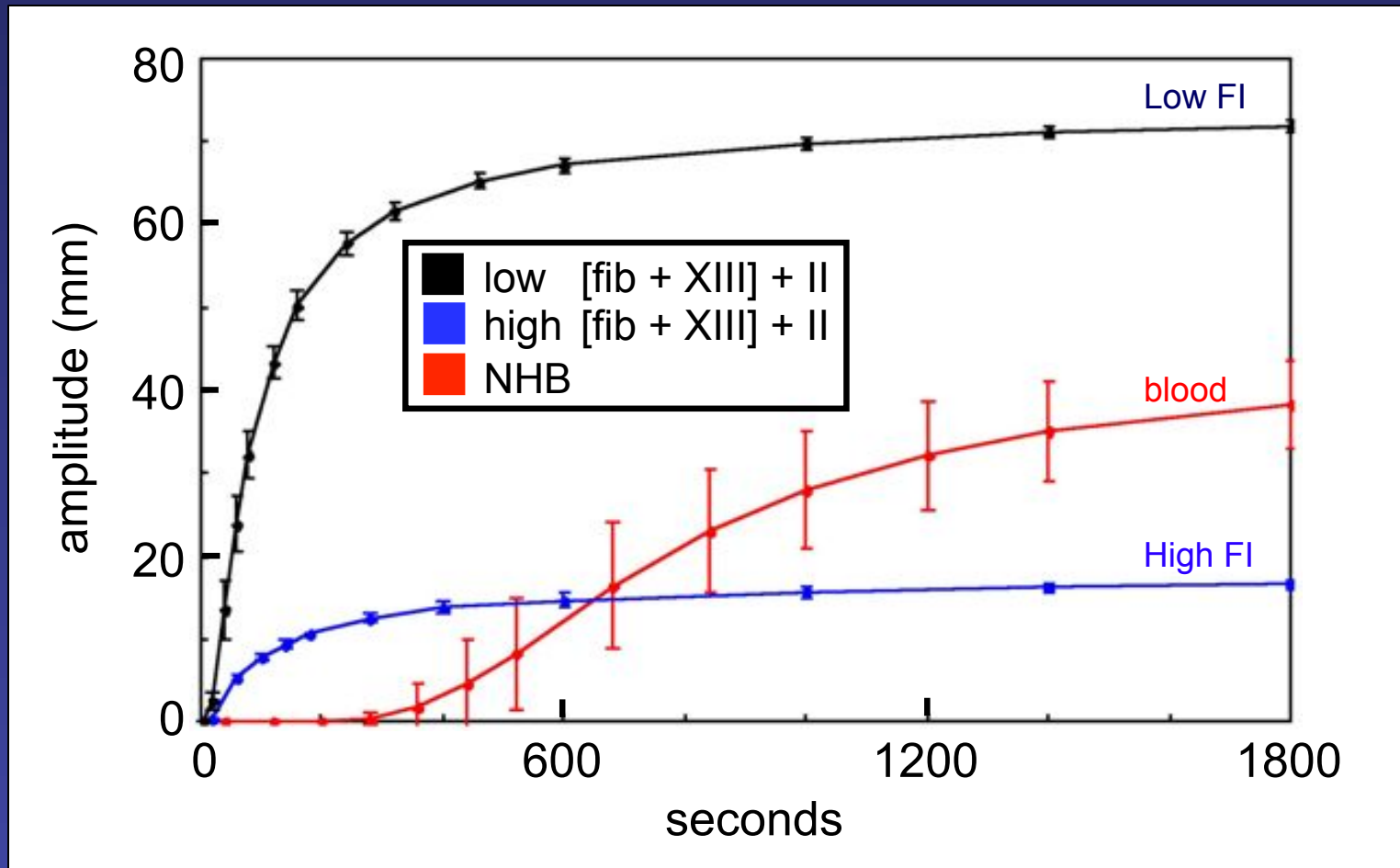


Figure 3.11. Analysis of the effect of rFXIIIa on clot strength by thromboelastography. TEG monitored the change in clot strength over time of recombinant fibrinogen (8.56 mg/ml) activated by recombinant thrombin (52.8 U/ml) with (blue) and without (red) rFXIII (0.35 mg/ml). Data are expressed as mean +/- standard deviation.

TEG: r-FS vs. normal human blood (NHB)



TEG: r-FS vs. pd-FS (Tisseel)

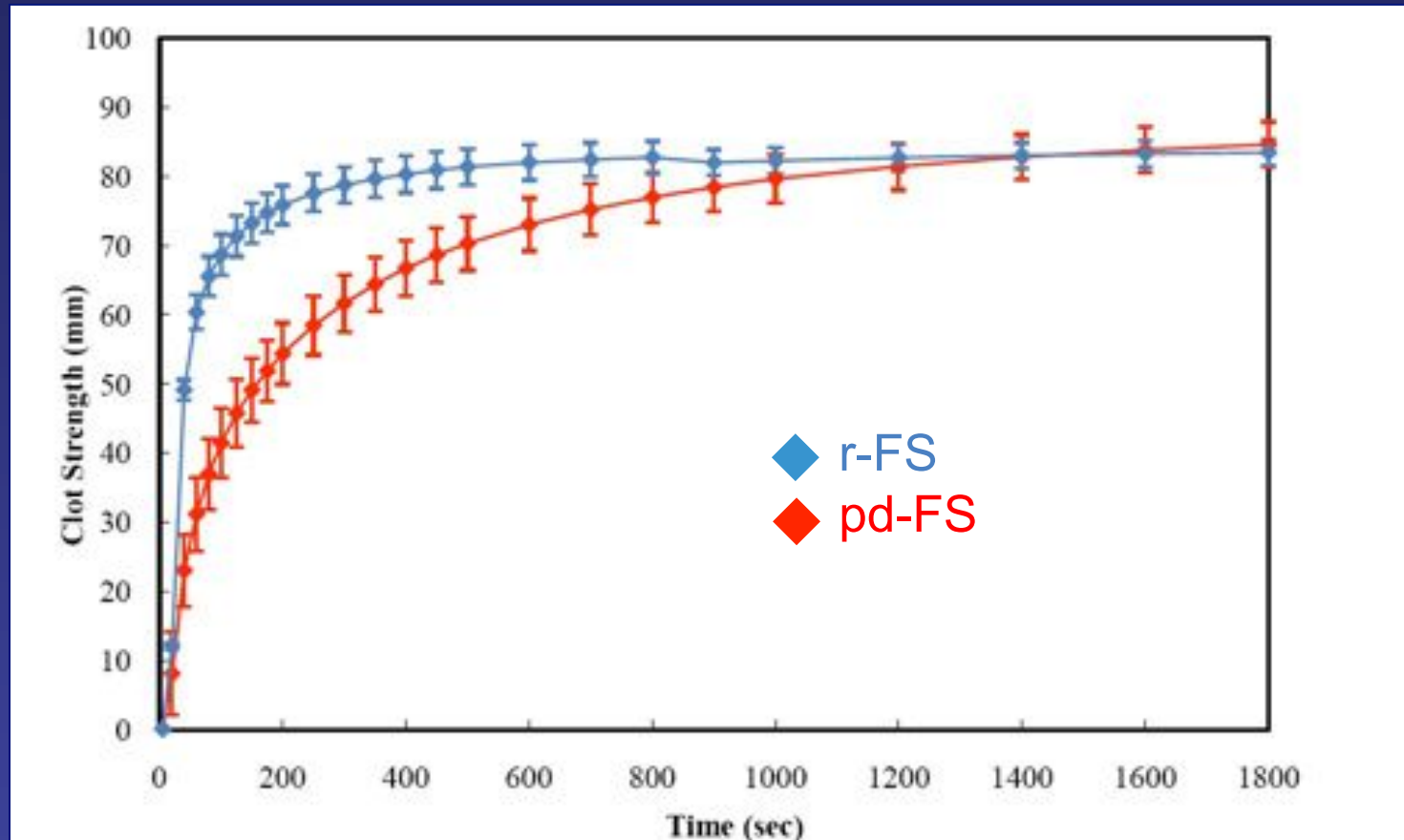


Figure 4.10. Thromboelastographic properties of the optimized tri-component rLFS and a pdLFS (Tisseel®). Clots consisting of 15 mg/ml rFII, 0.59 mg/ml (4,095 U/ml) rFXIIIa and 0.33 mg/ml (176.7 U/ml) rFIIa (FXIIIa/FI = 0.16, FIIa/FI = 0.18) (blue) have faster clot kinetics and equivalent maximal clot strengths as a pdLFS (Tisseel®) as prepared by its manufacturer's instructions (red). Tisseel contains 33.5 to 53 mg/ml pdFI and 200 to 312.5 U/ml pdFIIa. Data were expressed as mean +/- standard deviation.

Hepatic wedge excision model (domestic swine)



marking of excisions



post-procedure (ex vivo)

- Constant base dimension (1 cm)
- Incremental increase in depth dimension (0.5 to 3.0 cm)
- Six wedge excisions per series
- Two series per swine (i.e., two lobar edges)
- N = 6 swine per group (r-FS vs. pd-FS)

Fibrin sealant delivery



Tisseel® Duploject® syringe
(Baxter Biosurgery)

Fibrin sealant delivery

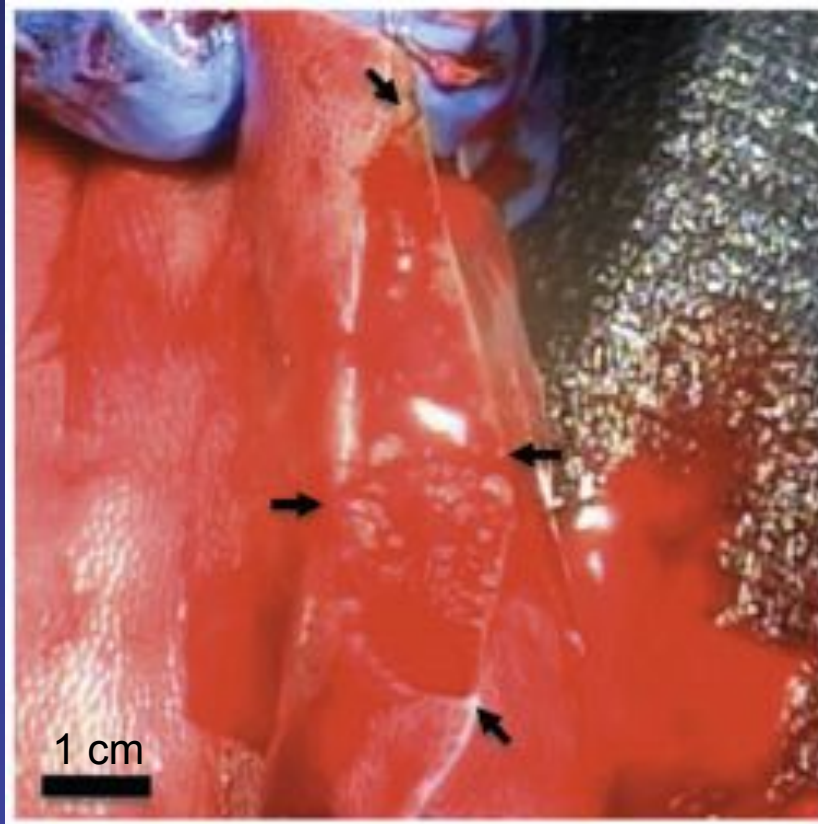


Tisseel® Duploject® syringe
(Baxter Biosurgery)

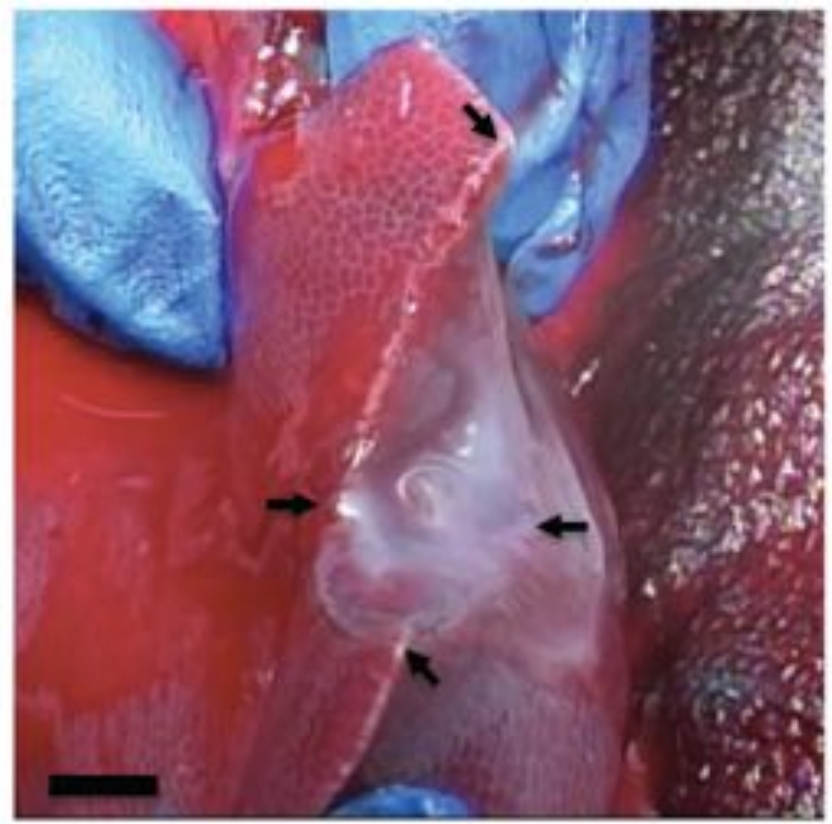


System without a common
mixing channel

Hepatic wedge excision model



pretreatment

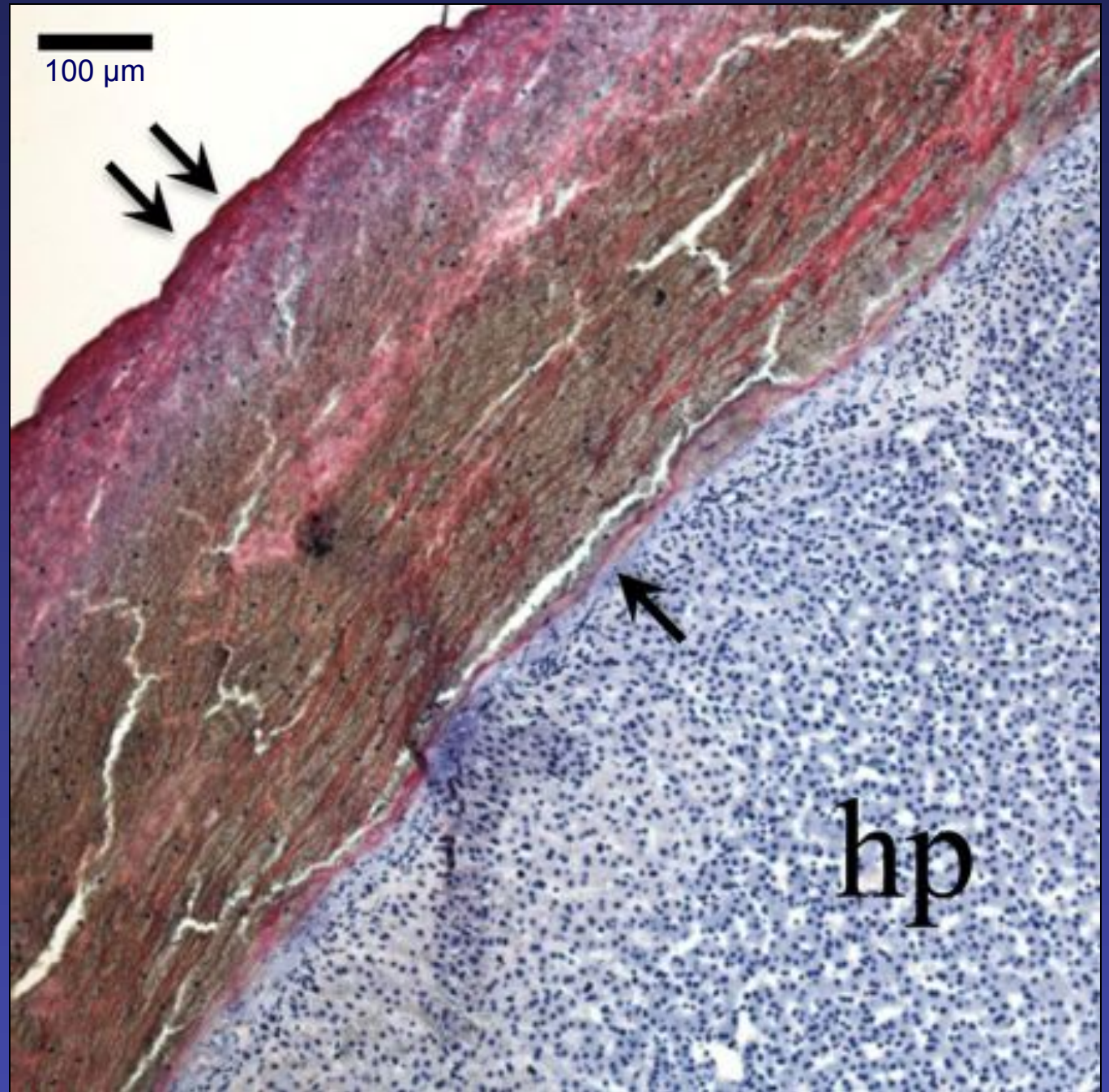


post-treatment

IHC

red:
human FI

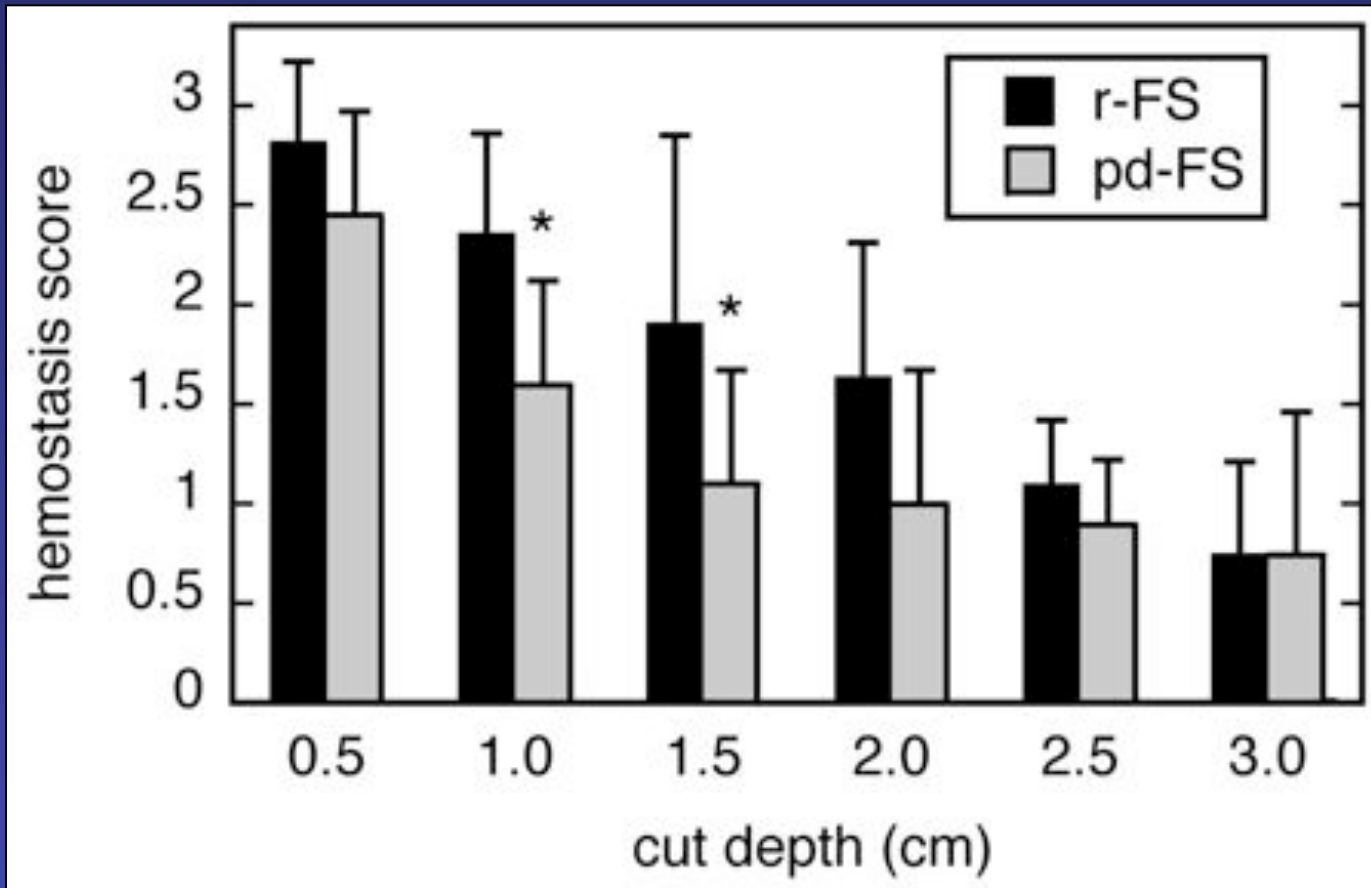
brown:
porcine FI



Results

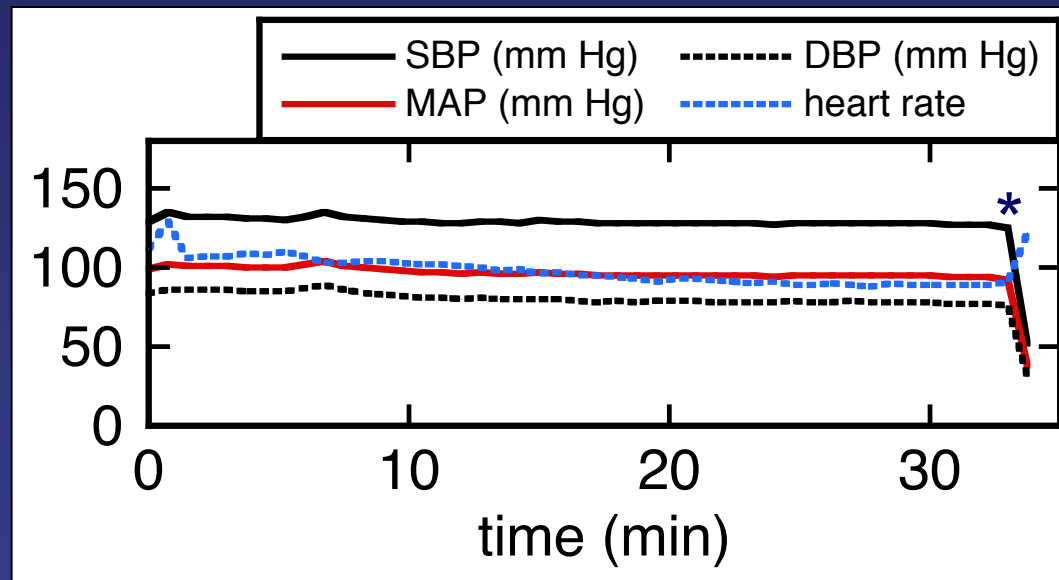
Hemostasis Score definitions:

- 0 = failure/minimal effect
- 1 = steady bleeding
- 2 = oozing
- 3 = hemostatic



Each bar = mean \pm sd of 10-12 excisions

Vital signs during a typical testing period



*Euthanasia

Serum TEG data also was unchanged before, during, and after procedure (DNS)

Aerosol delivery of r-FS



Aerosol delivery of r-FS



[Go to video: "Aerosol Delivery of r-FS"](#)

Conclusions

- r-FS had equivalent or better hemostatic efficacy compared to pd-FS, despite the [FII] in r-FS being about one-third of that in the pd-FS.
- The r-FS performance may be due to the TEG-optimized proportions of FII, FIII, and FXIII.

Future

- r-FS production is scalable
- 100 transgenic cows = ~1 metric ton of FI per year
- Cost vs. pd-FS could be much less
- Production of other human recombinant proteins?