MODIFICATION OF PLATELETS POPULATION DURING THERAPEUTIC PLASMA EXCHANGE STUDIED WITH *IN VIVO* EXPERIMENTS, *IN VITRO* SIMULATIONS AND MATHEMATICAL MODELING

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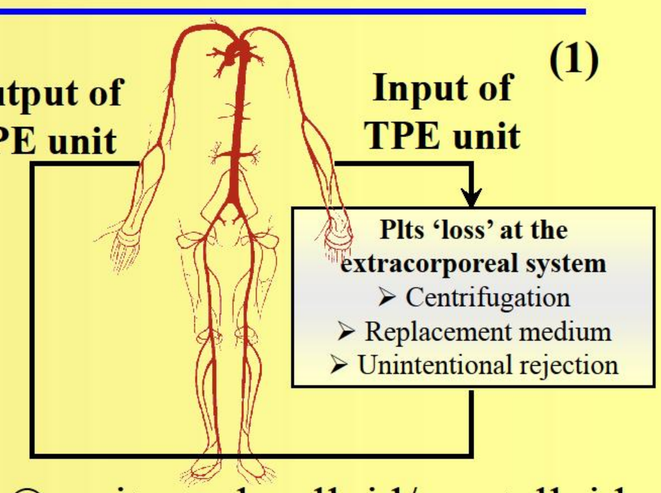
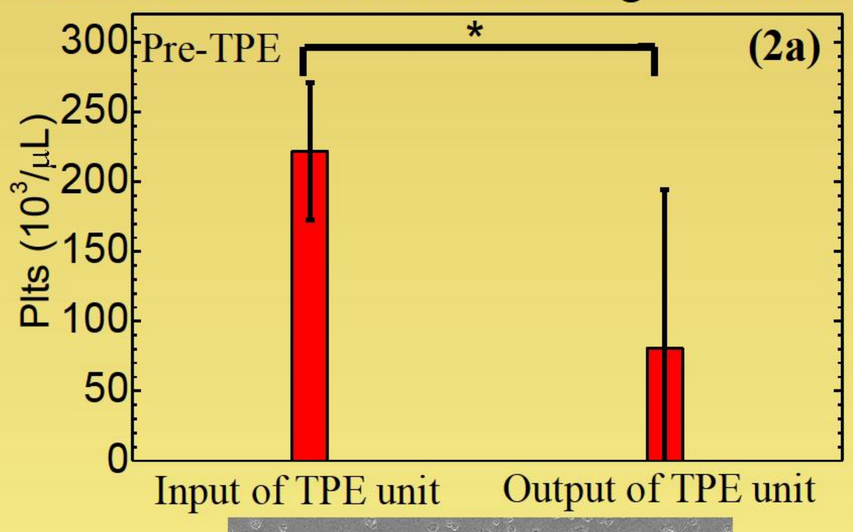
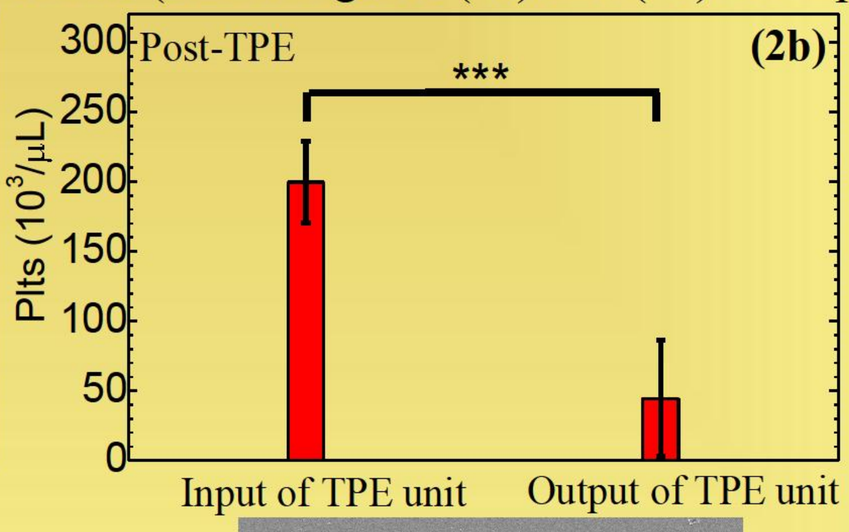
OBJECTIVES: In therapeutic plasma exchange (TPE) (Figure (1)) side effects can be observed on cells of peripheral blood, that originate from: (i) mechanical stress (MS) induced by the centrifugation, (ii) biochemical shock (BS) exerted from the replacement medium and (iii) unintentional rejection together with plasma. Focusing on Platelets (Plts), temporary thrombocytopenia, commonly ascribed exclusively to the third mechanism, is observed in some patients. To explore this issue, we studied intact Plts (iPlts) in both *in vivo* experiments and *in vitro* simulations. Mathematical modeling was also conducted.

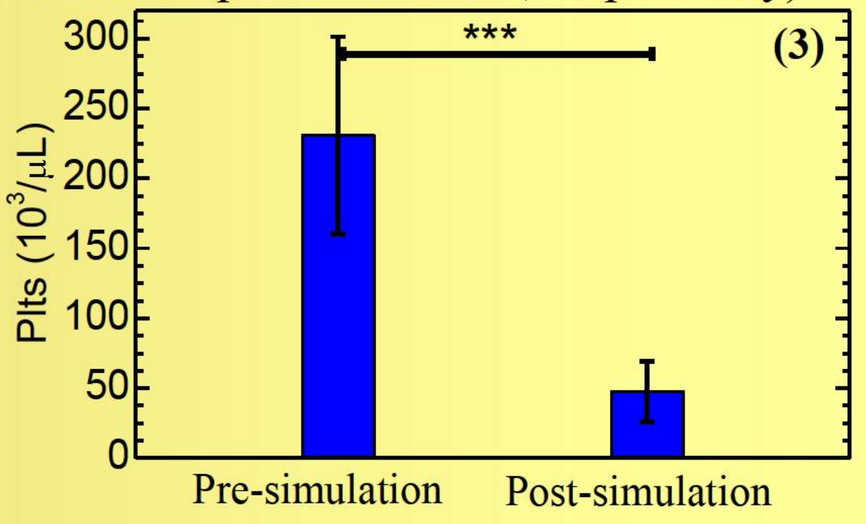


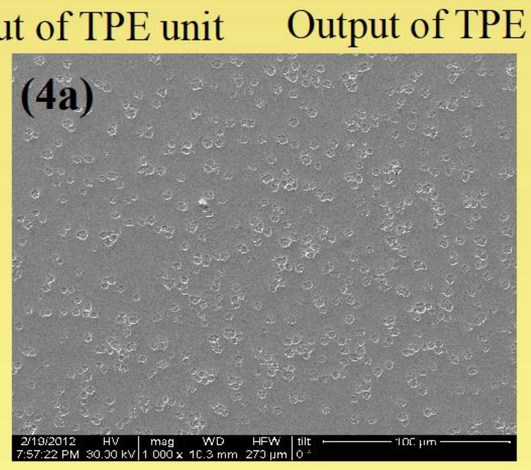
METHODS: *In vivo* experiments: 5 patients were treated with Cobe® Spectra/Spectra Optia® units and colloid/crystalloid media (Human Albumin 5% and Hydroxyethyl Starch 6%). The iPlts were studied comparatively in samples drawn ***simultaneously*** from the *input* and *output* of the TPE unit at both the *beginning* and *end* of the session. *In vitro* experiments: 5 healthy donors provided peripheral blood subjected to simulation of TPE under 3-5 rounds of centrifugation (1200-1600g/2-5min) and washing (human albumin/hydroxyethyl starch=4/1). In both types of experiments quantitative/qualitative information was collected with flow cytometry and two microscopes (Scanning Electron (SEM) and Atomic Force (AFM)).

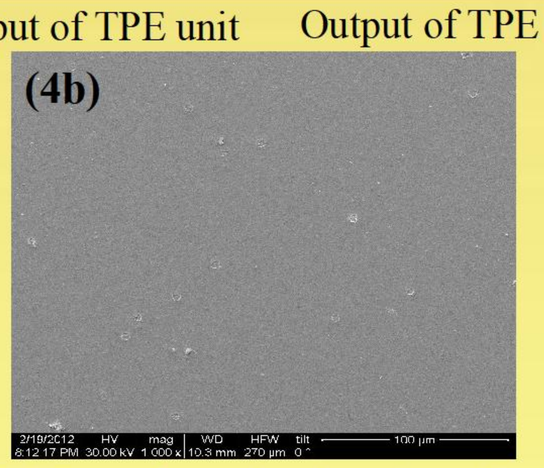
RESULTS: *In vivo* experiments: In all 5 patients, at the beginning of the session the Plts count was normal at the *input* of the TPE unit [Plts-input-beginning]=221.8±49.1 K/μL, but was strongly reduced at its *output* [Plts-output-beginning]=80.6±114.0 K/μL ($p<0.05$) (Figure (2a)). The same was observed until the end of the session with [Plts-input-end]=199.6±29.3 K/μL and [Plts-output-end]=44.8±41.5 K/μL ($p<0.05$) (Figure (2b)). Evidently, the Plts count in the peripheral blood (*input* of the TPE unit) was preserved during the session. *In vitro* experiments: Plts count exhibited statistically significant ($p<0.05$) reduction from [Plts-beginning]=230.8±70.6 K/μL to [Plts-end]=47.4±21.4 K/μL (Figure (3)). In both types of experiments the AFM/SEM data evidenced degranulation of Plts (SEM: Figures (4a) and (4b) for Input and Output of TPE unit, respectively).



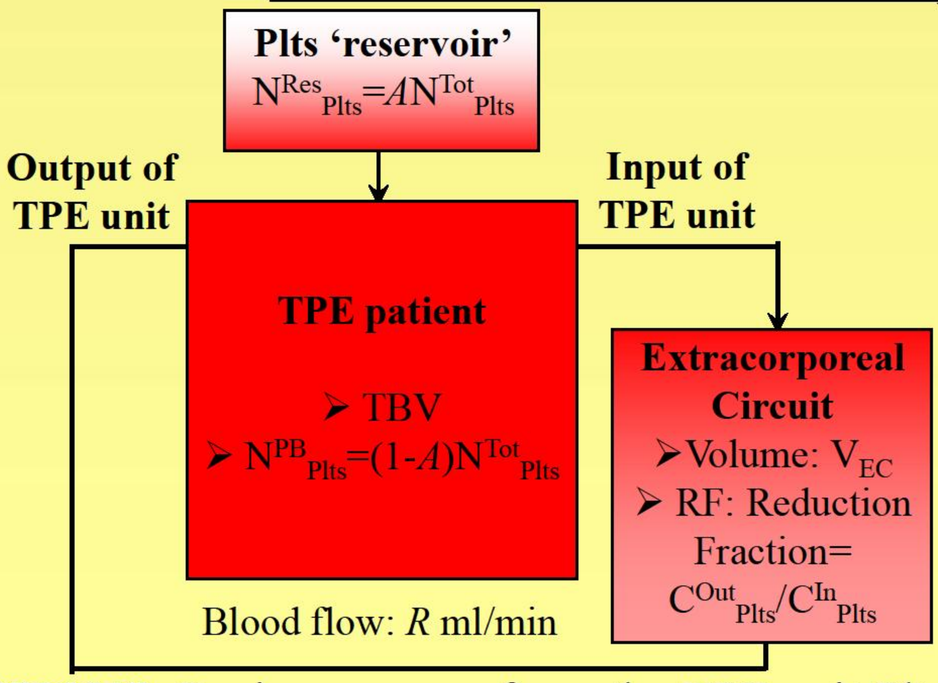








Mathematical model: The TPE patient is simulated as 'one blood-compartment'



❖ **TBV, V_{EC}, C^{VB}_{Plts}, C^{AB}_{Plts} are known**

❖ ***A* is unknown**

- Processed blood is mixed with unprocessed
- TPE refers to J distinct steps, $J=TBV/V_{EC}$ (single passage)
- TBV estimated with formula Nadler/Allen:

$TBV=604+367H^3+32.2W$ for male

$TBV=183+356H^3+33.1W$ for female

- At each step i the total number of Plts that remains in the TPEp is

$TN^i_{Plts}=(TBV-V_{EC})(TN^{i-1}_{Plts}/TBV)+V_{EC}(RF\bullet TN^{i-1}_{Plts}/TBV)$

(given that the replacement medium and removed plasma have the same volume)

CONCLUSIONS: During passage from the TPE unit Plts can be deconstructed by the MS and BS, however with preservation of Plts count in patient peripheral blood. This possibly stems from the release of Plts from storage reservoirs (spleen, endothelium etc). Mathematical modeling of the process evidences that in a typical 1-hour TPE session the storage reservoirs of Plts are drastically depleted. Thus, extra attention should be paid in patients with low baseline of Plts or thrombocytopenia.

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