CLINICAL RELEVANCE OF FREE WATER TRANSPORT AND EFFLUENT BIOMARKERS IN THE DETECTION OF ENCAPSULATING PERITONEAL SCLEROSIS

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INTRODUCTION

Currently no diagnostic tool or methodology is available for the early detection of encapsulating peritoneal sclerosis (EPS). Over the past years a number of effluent markers have been related to the development of EPS. To date only cancer antigen 125 (CA125) and interleukin-6 (IL-6) indicated clinical validity. More recently plasminogen activator inhibitor-1 (PAI-1) as a marker for peritoneal fibrosis has been studied. Hence, in this study optimal effluent biomarker combinations are gauged in conjunction with FWT to investigate their clinical significance in PD treatment and the diagnosis of EPS.

AIM

The objective of this study was to investigate and construct a panel of effluent biomarkers in conjunction with free water transport (FWT) to monitor peritoneal dialysis (PD) treatment and aid early identification of EPS.

STUDY DESIGN AND METHODS

Study design
- Longitudinal nested case-control study
  - Inclusion period: July 1995 - July 2012
  - Restriction: PD duration of at least 57 months
- EPS diagnosis confirmed and reviewed by two experienced nephrologists and a radiologist

Data collection and biochemical assay
- Patient characteristics
- Repeated measurements from peritoneal function test (SPA)
- Quantity of FWT assessed by means of sodium (Na^+) kinetics after one hour of a standardized 3.86% dwell
- Levels of effluent CA125, IL-6, PAI-1 and VEGF measured by means of ELISA

CALCULATIONS AND STATISTICS

Calculations:
- **Appearance rate (AR):**

$$AR = \frac{[Protein] \times Volume\ effluent}{Dwell\ time}$$

Statistics:
- **Univariate comparison** between patients who develop EPS and controls
- **Time-specific ROC analysis**
  - Assessment discriminative capacity of effluent biomarkers and free water transport years prior to EPS diagnosis
  - Estimates of sensitivity and specificity based on Youden Index
  - Threshold values based on pre-defined minimally acceptable true positive rates of 75%

PATIENTS

Table 1. Patient characteristics

Factors	EPS (n=11)	Controls (n=34)
Gender (% male)	64	61
Age at start PD (years)	35 (21 - 73)	52 (32 - 87)*
Primary Kidney Disease (%)		
- Diabetic Nephropathy	0	24
- Multisystem disease	9	6
- Other	91	70
PD regimen (%)		
- APD	18	13
- CAPD	36	55
- APD / CAPD	36	32
Nr. of peritonitis episodes	4 (0 - 15)	3 (0 - 11)
PD duration (months)	104 (57 - 149)	72 (57 - 112)*
Net UF at 240 minutes (mL)	121 (-113 - 308)	494 (73 - 920)**
FWT at 60 minutes (mL)	21 (-41 - 72)	151 (21 - 371)**

Data are presented as median and ranges.
FWT: free water transport, UF: ultrafiltration.
* $p \leq 0.03$, ** $p \leq 0.002$

RESULTS

Table 2. Time specific ROC analysis

	Area under the ROC curve		
Lag time[a] (years)	1	2	3
FWT_{0-60} (mL)	0.94***	0.87***	0.92***
CA125 AR (U/min)	0.63	0.47	0.70
IL-6 AR (pg/min)	0.62	0.65	0.67
PAI-1 AR (ng/min)	0.77**	0.72*	0.71
VEGF AR (pg/min)	0.68	0.59	0.63

[a] Time from dialysate sampling to EPS diagnosis.
* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$.

Figure 1. Diagnostic accuracy measures are depicted for quantity of FWT_{0-60}, CA125 AR, IL-6 AR, PAI-1 AR and VEGF AR
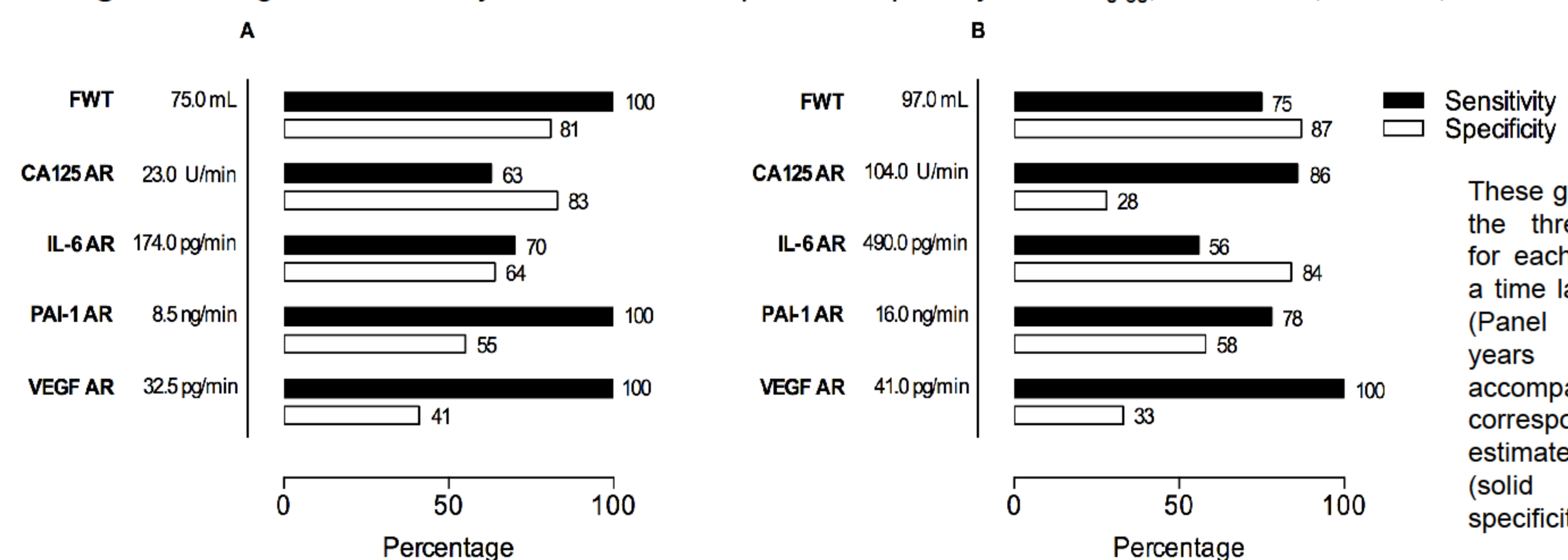
These graphs illustrate the threshold values for each parameter at a time lag of one year (Panel A) and two years (Panel B) accompanied by their corresponding estimates of sensitivity (solid bars) and specificity (open bars).

Table 3. Diagnostic accuracy measures for quantity of free water transport combined with effluent biomarkers at one year prior to EPS diagnosis.

Lag time[a] (years)			Sensitivity (%)	Specificity (%)
FWT_{0-60} <75.0 mL	& PAI-1 AR	>8.5 ng/min	100	94
FWT_{0-60} <75.0 mL	& IL-6 AR	>174.0 pg/min	70	94
FWT_{0-60} <75.0 mL	& CA125 AR	<23.0 U/min	63	94

CONCLUSIONS

Measurement of effluent biomarkers complementary to peritoneal function test provides an all-round insight into the state of the peritoneal membrane. Our data indicate that an effluent biomarker panel including the quantity of FWT may aid in the early detection of EPS where high estimates of specificity are required to avoid unnecessary discontinuation of PD treatment.

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M) Dialysis. M2) Peritoneal dialysis.
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