Tumor necrosis factor alpha- an underestimated risk predictor in patients undergoing transcatheter aortic valve replacement (TAVR)?

Moritz Mirna[1], Mario Holnthoner[1], Albert Topf[1], Peter Jirak[1], Dzeneta Fejzic[1], Vera Paar[1], Jörg Kellermair[2], Hermann Blessberger[2], Christian Reiter[2], Jürgen Kammler[2,3], Lukas J. Motloch[1], Christian Jung[4], Daniel Kretzschmar[5], Marcus Franz[5], Brunilda Alushi[6], Alexander Lauten[6], Uta C. Hoppe[1], Clemens Steinwender[2,3], Michael Lichtenauer[1]

1 Department of Internal Medicine II, Division of Cardiology, Paracelsus Medical University of Salzburg, Austria; 2 Department of Cardiology, Kepler University Hospital, Medical Faculty, Johannes Kepler University Linz, Linz, Austria; 3 Paracelsus Medical University of Salzburg, Austria; 4 Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Duesseldorf, Germany; 5 Universitätsherzzentrum Thüringen, Clinic of Internal Medicine I, Department of Cardiology, Friedrich Schiller University Jena, Germany; 6 Department of General and Interventional Cardiology and Rhythmology, Helios Clinic Erfurt, Germany.

Background

Although systemic inflammation has been identified as a major cardiovascular risk factor, it is currently not adequately portrayed in scores for pre-interventional risk assessment in patients undergoing transcatheter aortic valve replacement (TAVR). The aim of this study was to investigate the predictive ability of tumor necrosis factor alpha (TNF-α) in TAVR.

Methods

A total of 431 patients undergoing transfemoral TAVR were enrolled in this study. Blood samples were drawn pre-interventionally, after 24 hours, after 4, 5 and 7 days and after 1, 3 and 6 months post TAVR. Biomarker concentrations were analyzed by ELISA.

Results

TAVR resulted in a 1.6-fold increase of the concentrations of TNF-α after 5 days (mean 26.8 ±115.0 pg/ml vs. 42.0 ±151.3 pg/ml, p= 0.269, **see Figure 1** and **Table 1**). In univariate Cox proportional hazards analysis, plasma concentrations of TNF-α after 24h and after 5 days were associated with mortality after 12 months (after 24h: HR 1.002 (1.000-1.004), p= 0.028; after 5d: HR 1.003 (1.001-1.005), p= 0.013, **see Table 2**). This association remained significant even after correction for confounders in a multivariate Cox regression analysis. Additionally, cut-offs were calculated. Patients above the cut-off for TNF-α after 5d had a significantly worse 12-month mortality than patients below the cut-off (18.8% vs. 2.8%, p= 0.046).

Conclusion

Plasma levels of TNF-α after 24h and 5 days were independently associated with 12-month mortality in patients undergoing TAVR. Thus, TNF-α could represent a novel inflammatory biomarker for enhanced peri-interventional risk stratification in these patients.

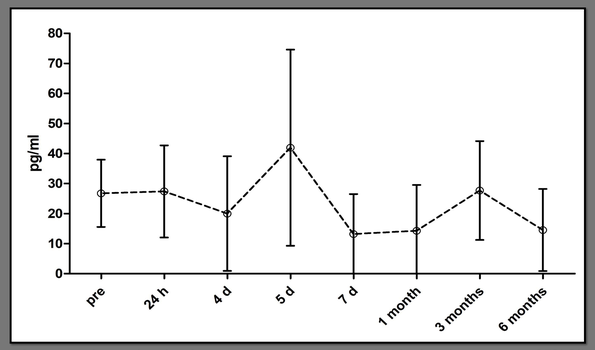

Figure 1: Plasma levels of TNF-α throughout the study (depicted are mean +95%CI).

	pre, (n= 408)		24 h, (n= 201)		4 days, (n= 73)		5 days, (n= 85)		7 days, (n= 66)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
TNF-α (pg/ml)	26.8	115.0	27.4	110.3	20.0	81.7	42.0	151.3	13.2	54.2
	1 month, (n= 66)		3 months (n= 151)		6 months (n= 65)					
	mean	SD	mean	SD	mean	SD				
TNF-α (pg/ml)	14.3	62.1	27.7	102.2	14.5	55.2				

Table 1: Plasma concentrations of TNF-α throughout the study.

	Univariate HR			Multivariate HR		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	0.980	0.943-1.018	0.980			
BMI (kg/m²)	0.971	0.914-1.032	0.345			
Gender	1.386	0.673-2.853	0.376			
Diabetes mellitus	1.867	1.111-3.138	0.018	2.462	0.552-10.988	0.238
Peripheral artery disease	1.865	1.005-3.463	0.048	0.000	0.000-0.001	0.987
Coronary artery disease	0.872	0.503-1.513	0.626			
NYHA stage, pre.	1.106	0.725-1.689	0.640			
EF (%), pre.	0.976	0.955-0.998	0.030	0.961	0.916-1.008	0.102
CRP (mg/dl), pre.	1.080	1.022-1.140	0.006	0.056	0.001-2.804	0.149
BNP (ng/l), pre.	1.000	1.000-1.000	0.745			
Creatinine (µmol/l), pre.	1.005	1.002-1.007	0.001	1.004	0.971-1.038	0.823
eGFR (ml/min/1.73m²), pre.	0.987	0.974-1.001	0.063			
Hemoglobin (mmol/l), pre.	0.855	0.672-1.089	0.205			
Mean pressure gradient (mmHg), pre.	0.991	0.971-1.011	0.363			
TNF-α, pre. (pg/ml)	1.001	1.000-1.003	0.109			
TNF-α, after 24 h (pg/ml)	1.002	1.000-1.004	0.028	1.004	1.001-1.006	0.007
TNF-α, after 4 days (pg/ml)	0.931	0.733-1.183	0.559			
TNF-α, after 5 days (pg/ml)	1.003	1.001-1.005	0.013	1.004	1.001-1.008	0.012
TNF-α, after 7 days (pg/ml)	0.756	0.399-1.433	0.392			
TNF-α, after 1 month (pg/ml)	0.578	0.180-1.856	0.357			
TNF-α, after 3 month (pg/ml)	0.787	0.436-1.422	0.428			
TNF-α, after 6 months (pg/ml)	0.982	0.898-1.073	0.688			

Table 2: Univariate and multivariate Cox proportional hazard analysis (VIF: diabetes: 1.031, EF: 1.007, PAD: 1.033, CRP: 1.015, creatinine: 1.043).

Contact: Dr. Moritz Mirna, Department of Internal Medicine II, Paracelsus Medical University Salzburg, Landeskrankenhaus Salzburg, m.mirna@salk.at