The role of C-terminal-pro-endothelin-1 in predicting ischemic stroke outcome

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Introduction

- Endothelin-1 (ET-1) is a vasoactive peptide with vasoconstrictor properties, the C-terminal-pro-ET-1 constitutes a stable fragment of the ET-1-precursor (2).
- Endothelins have shown to be of prognostic value in cardiovascular diseases (3) and play a role in ischemic stroke pathophysiology.
- However, concerning their prognostic value in clinical settings only controversial data in mainly small studies exist.
- We aimed at evaluating the incremental prognostic value of endothelin-1 in a well-described cohort of acute stroke patients.

Methods

- In this prospective cohort-study we prospectively measured endothelin-1 levels of 359 ischemic stroke patients within 72 hours of symptom onset.
- Outcome measures were functional outcome (defined as a modified Rankin Scale of ≤ 2 for good and ≥ 3 for unfavourable outcome) and mortality assessed after 90 days.
- We calculated logistic regression and cox proportional hazards models, respectively, to estimate the association of endothelin-1 with our outcome measures after adjusting for demographic and medical risk factors.
- To assess the discriminatory accuracy and the incremental value of endothelin-1 beyond known risk factors, we calculated and compared the area under the receiver operating characteristics (AUC) curve.
- To further estimate the additive benefit of ET-1 to the traditional outcome predictors, we calculated the net reclassification improvement (NRI).

Results

In the univariate analysis endothelin-1 was associated with unfavourable outcome with an OR of 1.32 [95% CI, 1.16 – 1.51] and with mortality with a HR of 1.45 [95% CI, 1.29 – 1.63]. After adjusting, endothelin-1 remained in the multivariate analysis an independent predictor for mortality with an adjusted HR of 1.58 [95% CI, 1.34 – 1.85], but not for functional outcome. Adding endothelin-1 to the cox-regression model for mortality, the discriminatory accuracy improved from 0.89 [95% CI, 0.84 – 0.94] to 0.92 [95% CI, 0.88 – 0.96] $p < 0.001$. The addition of ET-1 to the multivariate model for mortality led to a continuous NRI of 0.76 [95% CI, 0.32 – 1.15].

Table 1. Univariate logistic regression for 90 day functional outcome			
Predictors	Functional Outcome		
	OR	95% CI	p
ET day 0 (*)	1.09	1.00 – 1.19	0.04
ET day 1 (*)	1.32	1.16–1.51	<0.0001
ET day 3 (*)	1.29	1.11–1.51	0.001
ET day 5 (*)	1.18	1.03–1.34	0.02
CRP (increase per unit)	1.01	1.00 – 1.02	0.02
Glucose (increase per unit)	1.07	0.97 – 1.18	0.15
Age (increase per unit)	1.06	1.04 – 1.08	<0.0001
Temperature (increase per unit)	0.87	0.61 – 1.24	0.44
Systolic blood pressure (increase per unit)	0.99	0.99 – 1.01	0.45
Female sex	1.79	1.17 – 2.74	0.01
NIHSS (increase per unit)	1.16	1.12 – 1.21	<0.0001
Risk factors			
Hypertension	1.62	0.97 – 2.70	0.06
Atrial fibrillation	1.91	1.14 – 3.12	0.01
Current smoking	0.69	0.44 – 1.08	0.11
Diabetes mellitus	1.17	0.69 – 1.97	0.57
Coronary heart disease	1.33	0.82 – 2.14	0.25
Dyslipidemia	0.78	0.48 – 1.27	0.31
Previous cerebrovascular event	1.20	0.74 – 1.95	0.46
Modified Charlson Index (IQR)	1.34	1.15 – 1.56	<0.0001
Stroke syndrome and causative factors			
TACS	4.44	2.15 – 9.12	<0.0001
PACS	1.09	0.72 – 1.66	0.69
LACS	0.75	0.44 – 1.27	0.27
POCS	0.49	0.29 – 0.83	<0.01
Large-vessel disease	0.97	0.56 – 1.68	0.92
Cardioembolic	1.05	0.68 – 1.61	0.84
Small-vessel disease	0.57	0.31 – 1.05	0.06
Multiple causes/other	0.61	0.21 – 1.80	0.36
Undetermined	1.54	0.96 – 2.5	0.08

(*) After extracting the square root; OR= odds ratio; CI= confidence interval; ET= Endothelin-1; CRP= C-reactive protein; NIHSS= National Institutes of Health Stroke Scale; TACS= total anterior circulation syndrome; PACS= partial anterior circulation syndrome; LACS= lacunar circulation syndrome; POCS= posterior circulation syndrome.

Table 2. Multivariate logistic regression for 90 day functional outcome			
Predictors	Functional Outcome		
	OR	95% CI	p
ET day 1 (*)	1.11	0.94–1.29	0.22
Age (increase per unit)	1.06	1.03–1.09	<0.0001
Female sex	1.27	0.70–2.29	0.43
NIHSS (increase per unit)	1.18	1.12–1.25	<0.0001
Modified Charlson Index (IQR)	1.37	1.12–1.67	0.002
TACS	1.95	0.62–6.09	0.25

(*) After extracting the square root; ET= Endothelin-1; OR= odds ratio; CI= confidence interval; NIHSS= National Institutes of Health Stroke Scale; IQR= interquartile range; TACS= total anterior circulation syndrome. The multivariate logistic regression model included all parameters from univariate analysis with a statistical significance level $p \leq 0.001$.

Table 3. Univariate cox proportional hazards model for 90 day survival			
Predictors	Mortality		
	HR	95% CI	p
ET day 0 (*)	1.26	1.13–1.40	<0.0001
ET day 1 (*)	1.45	1.29–1.63	<0.0001
ET day 3 (*)	1.47	1.27–1.72	<0.0001
ET day 5 (*)	1.67	1.42–1.97	<0.0001
CRP (increase per unit)	1.01	1.00–1.01	0.003
Glucose (increase per unit)	1.02	0.91–1.15	0.69
Age (increase per unit)	1.09	1.05–1.22	<0.0001
Temperature (increase per unit)	0.89	0.53–1.49	0.67
Systolic blood pressure (increase per unit)	0.99	0.98–1.00	0.14
Female sex	1.32	0.73–2.39	0.35
NIHSS (increase per unit)	1.14	1.11–1.17	<0.0001
Risk factors			
Hypertension	1.71	0.76–3.83	0.19
Atrial fibrillation	2.88	1.58–5.25	0.001
Current smoking	0.62	0.31–1.22	0.164
Diabetes mellitus	1.04	0.49–2.16	0.918
Coronary heart disease	1.97	1.07–3.62	0.03
Dyslipidemia	0.95	0.48–1.88	0.98
Previous cerebrovascular event	0.68	0.31–1.46	0.32
Modified Charlson Index (IQR)	1.14	0.96–1.35	0.13
Stroke syndrome and causative factors			
TACS	5.46	2.95–10.10	<0.0001
PACS	0.83	0.46–1.51	0.54
LACS	0.37	0.13–1.04	0.06
POCS	0.51	0.22–1.21	0.13
Large-vessel disease	0.56	0.22–1.43	0.23
Cardioembolic	1.49	0.82–2.69	0.19
Small-vessel disease	0.12	0.02–0.89	0.04
Multiple causes/other	0.46	0.06–3.33	0.44
Undetermined	1.92	1.05–3.52	0.04

(*) After extracting the square root; ET= Endothelin-1; HR= hazard ratio; CI= confidence interval; IQR= interquartile range; CRP= C-reactive protein; NIHSS= National Institutes of Health Stroke Scale; TACS= total anterior circulation syndrome; PACS= partial anterior circulation syndrome; LACS= lacunar circulation syndrome; POCS= posterior circulation syndrome.

Table 4. Multivariate cox proportional hazards model for 90 day survival			
Predictors	Mortality		
	HR	95% CI	p
ET day 1 (*)	1.58	1.34–1.85	<0.0001
Age (increase per unit)	1.06	1.02–1.09	0.001
NIHSS (increase per unit)	1.11	1.07–1.15	<0.0001
TACS	2.85	1.19–6.76	0.02
Atrial fibrillation	0.45	0.19–1.01	0.05

(*) After extracting the square root; ET= Endothelin-1; HR= hazard ratio; CI= confidence interval; NIHSS= National Institutes of Health Stroke Scale; TACS= total anterior circulation syndrome. The multivariate cox proportional hazards model included all parameters from univariate analysis with a statistical significance level $p \leq 0.001$.

Figure 1: Comparison of AUCs: Model with and without ET-1 and 90 day mortality

Conclusion

Endothelin-1 is an independent predictor of mortality in ischemic stroke adding incremental prognostic value beyond traditional demographic and vascular risk factors. These results need further validation in independent larger cohorts.

References:
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