Department of Thoracic and Cardiovascular Surgery

Are Elevated Serum Hemolysis Markers a Harbinger of Thromboembolic Events in HeartMate II Patients?

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PURPOSE

Haemolysis during left ventricular assist device support is associated with thrombosis. In this retrospective study, we analysed whether low-level haemolysis (LLH) as defined by simultaneously elevated lactate dehydrogenase (LDH) and free haemoglobin (fHb) levels had an impact on thromboembolic and bleeding events and on von Willebrand factor levels in HeartMate II patients.

METHODS

After exclusion of patients with LDH >700 U/l and fHb >40 mg/dl at hospital discharge, 79 HeartMate II patients were included. LDH and fHb levels were measured at discharge and in 3 months interval. von Willebrand factor activity and antigen activity were measured 3 months postoperatively. Outcomes regarding ischaemic stroke (IS), pump thrombosis (PT) and gastrointestinal bleeding were recorded. Patients with LLH (400 < LDH <700 U/l and 30 < fHb <40 mg/dl) at discharge (pre-Hemolyzers) were compared with the rest of the cohort (non-Hemolyzers). Competing risk analysis and Cox regression were applied for the comparison between groups.

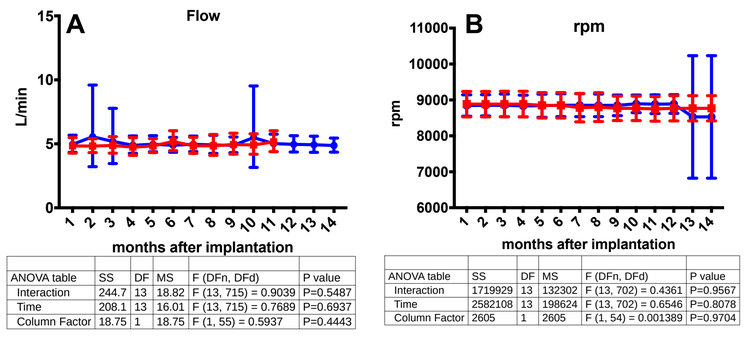
Table 1.Patient characteristics, preoperative laboratory and perioperative data.

	Pre-hemolyzers (n = 16)	non-hemolyzers (n = 63)	p - values
Age years	61.1±9.2	64.1±7.8	0.324
Female n (%)	3 (18.8)	9 (14.3)	0.701
BMI Kg/m^2	27.2±4.2	26.9±4.3	0.803
ICM n (%)	11 (68.7)	42 (66.42)	1.000
IDDM n (%)	0	7 (11.1)	0.333
PAD n (%)	6 (37.5)	15 (23.8)	0.343
HT	9 (56.3)	51 (81.0)	0.052
CVA n (%)	3 (18.7)	4 (6.3)	0.652
PHT	8 (50.0)	35 (55.6)	0.451
EF %	20.8±8.5	18.5±5.8	0.341
Prior PCI	4 (25.0)	16 (25.4)	0.624
Prior surgery n (%)	5 (31.5)	7 (11.1)	0.059
Preop Inotropic	5 (31.3)	10 (15.9)	0.148
Preop ECMO n (%)	3 (18.7)	4 (6.3)	0.143
Preop IABP n (%)	2 (12.5)	4 (6.3)	0.350
Preop Ventilation n (%)	3 (18.7)	7 (11.1)	0.325
DT n (%)	10 (62.5)	42 (66.7)	0.484
INTERMACS:			
I	4 (25)	6 (9.5)	0.110
II	2 (12.5)	9 (14.3)	0.608
III	1 (6.3)	6 (9.5)	0.565
IV	9 (56.2)	42 (66.7)	0.309
Preop-Laboratory:			
Creatinine mg/dL	1.1±.36	1.2±0.5	0.228
NT-proBNP	3562 (2307.2, 7352)	3200 (2028.2, 5998.7)	0.745
LDH	261 (211, 423)	219 (184, 285)	0.059
Hb	11.9±2.4	12.6±2.3	0.274
Platelet counts	197.5 (160.5, 253.2)	216 (182.7, 274.7)	0.072
AST	47 (33.2, 98)	28.5 (21.2, 38.7)	0.001
ALT	56.5 (29.2, 93)	29 (20, 51.2)	0.007
INR	1.1±0.24	1.2±0.33	0.424
Peri-Op Data:			
HMII alone	12 (75)	31 (38.1)	0.056
HMII+CABG	3 (18.7)	25 (39.7)	0.150
HMII+TVR	1 (6.3)	6 (9.5)	0.099
HMII+CABG+ Valve	0	1 (1.5)	0.797
CPB time in min.	114 (102, 151.5)	123 (92, 152)	0.630
Device parameter at discharge:			
Flow L/min	4.9±0.62	5.0±0.67	0.648
rpm	8844±296	8882±356	0.883
Pulsatility index	5.4±1.10	5.5±1.54	0.962
Power Watt	5.4±0.94	5.1±0.97	0.439

RESULTS

In all, 20% of the patients were identified as pre-Hemolyzers. Of these, 5 patients had PT and 3 patients had IS compared with 2 PT and 2 IS in the non-Hemolyzers group (P = 0.003 and P = 0.053, respectively). Fifty percent of the pre-Hemolyzers suffered gastrointestinal bleeding compared with 42% of the non-Hemolyzers (P = 0.399). The cumulative risk of thromboembolic events (IS or PT) in the pre-Hemolyzers group was significantly higher compared with the non-Hemolyzers group (hazard ratio 11.8, 95% confidence interval 3.7–37.7; P = 0.005). LLH did not have an impact on von Willebrand factor and the incidence of gastrointestinal bleeding.

Figure 1. Time course of the HeartMate II device parameters.



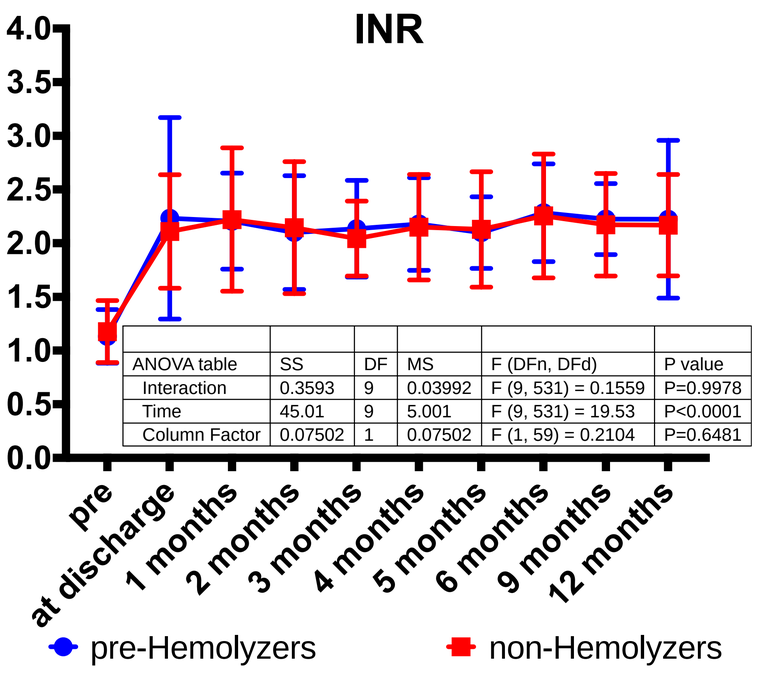
ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Interaction	244.7	13	18.82	F (13, 715) = 0.9039	P=0.5487
Time	208.1	13	16.01	F (13, 715) = 0.7689	P=0.6937
Column Factor	18.75	1	18.75	F (1, 55) = 0.5937	P=0.4443

ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Interaction	1719929	13	132302	F (13, 702) = 0.4361	P=0.9567
Time	2582108	13	198624	F (13, 702) = 0.6546	P=0.8078
Column Factor	2605	1	2605	F (1, 54) = 0.001389	P=0.9704

ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Interaction	15.95	13	1.227	F (13, 741) = 0.9278	P=0.5233
Time	19.07	13	1.467	F (13, 741) = 1.109	P=0.3474
Column Factor	34.23	1	34.23	F (1, 57) = 3.48	P=0.0673

ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Interaction	416.8	13	32.06	F (13, 611) = 1.424	P=0.1431
Time	311.3	13	23.95	F (13, 611) = 1.063	P=0.3887
Column Factor	6.071	1	6.071	F (1, 47) = 0.1955	P=0.6604

Figure 2. Time course of INR range.

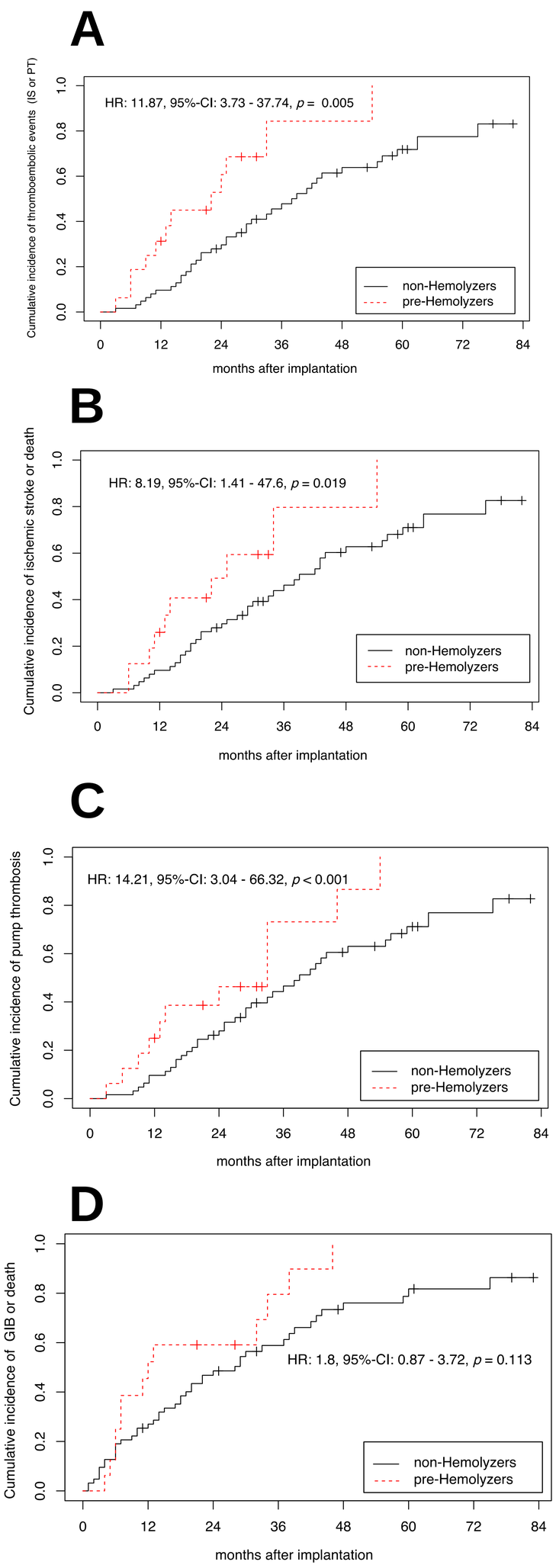


ANOVA table	SS	DF	MS	F (DFn, DFd)	P value
Interaction	0.3593	9	0.03992	F (9, 531) = 0.1559	P=0.9978
Time	45.01	9	5.001	F (9, 531) = 19.53	P<0.0001
Column Factor	0.07502	1	0.07502	F (1, 59) = 0.2104	P=0.6481

Figure 3. Echocardiographic findings of the aortic valve during HMII support

	pre-hemolyzers (n = 16)	non-hemolyzers (n = 63)	p - values
Aortic valve opening at discharge			
regular	4 (25)	11 (17.4)	0.722
intermittent	3 (18.7)	18 (28.6)	0.537
closed	9 (56.3)	34 (53.7)	1.000
Mild AVR	2 (12.5)	10 (15.8)	0.543
Moderate AVR	0	1 (1.5)	0.797
Severe AVR	0	0	-
Aortic valve opening 3 months after implantation			
regular	3 (18.7)	11 (17.4)	0.577
intermittent	2 (12.5)	19 (30.1)	0.131
closed	11 (68.7)	33 (52.3)	0.189
Mild AVR	4 (25)	9 (14.3)	0.247
Moderate AVR	0	2 (3.2)	0.633
Severe AVR	0	0	-
Aortic valve opening 6 months after implantation			
regular	5 (31.2)	16 (25.4)	0.426
intermittent	4 (25)	21 (33.3)	0.567
closed	7 (43.7)	26 (41.3)	1.000
Mild AVR	3 (18.7)	9 (14.3)	0.700
Moderate AVR	1 (6.2)	2 (3.2)	0.999
Severe AVR	0	0	-

Fig 4. Estimates of cumulative incidence for adverse events using death as competing risk event. (A) Cumulative incidence of thromboembolic events (IS or PT), (B) cumulative incidence of ischaemic stroke, (C) cumulative incidence of PT and (D) cumulative incidence of GIB.



CONCLUSION

LLH, as assessed by elevated fHB and LDH values at discharge during HMII support, is associated with an increased risk for thromboembolic events. HMII patients with LLH require intensive follow-up and optimized anticoagulation regimen. Future evaluations should focus on mechanisms of a haemolysis induced prothrombotic state during LVAD support as well as better strategies for the early detection and management of haemolysis and thromboembolic events.