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## Vascular Endothelial Growth Factor D, Pulmonary Congestion, and Incidence of Heart Failure

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1                   **Vascular endothelial growth factor D, pulmonary congestion**  
2                   **and incidence of heart failure**

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1 Heart failure (HF) is characterized by myocardial dysfunction resulting in increased venous  
2 and capillary pressure, and extra-vascular fluid accumulation when the transport capacity of  
3 the lymphatic system is insufficient. Vascular endothelial growth factor D (VEGF-D)  
4 activates the VEGFR-2 and VEGFR-3 receptors and is a key regulator of lymphatic growth  
5 (Dashkevich2016; Simmons2016). We hypothesized that VEGF-D could be associated with  
6 HF. This hypothesis was explored in (I) a cohort of patients admitted to hospital for acute  
7 dyspnea and (II) the population-based cohort Malmö Diet and Cancer (MDC-CC), which was  
8 followed prospectively over 20 years for incidence of hospitalizations due to HF.

9 VEGF-D was analyzed in (I) 430 patients admitted to the emergency unit at Skåne University  
10 Hospital, Malmö, Sweden, during 2013-2014 for symptoms of acute dyspnea (mean age 67.8  
11 years, 46.5% men) (Wiklund2016). Blood samples were collected after informed consent  
12 immediately at presentation. Presence of HF was based on the diagnosis at discharge from  
13 hospital. (II) VEGF-D was analyzed in 4265 subjects (46-68 years, 61% women) from MDC-  
14 CC, without a history of HF and myocardial infarction (MI) at the baseline examination in  
15 1991-1994. Details of MDC-CC and the endpoint registration have been reported previously  
16 (Smith2010). All participants provided informed consent. Both studies were approved by the  
17 regional ethics committee. VEGF-D was measured using the Olink CVD panel (Olink  
18 Bioscience, Uppsala, Sweden) based on the Proximity Extension Assay technology. The  
19 output unit is presented as arbitrary units (AU).

20 Both cohorts were divided into sex-specific quartiles of VEGF-D (Q1-Q4). Logistic  
21 regression was used to analyze the association between VEGF-D and HF in the dyspnea  
22 patients. In MDC-CC, Cox proportional hazards regression was used to examine the  
23 association between VEGF-D (Q1-Q4) and incidence of HF hospitalizations. The Spearman  
24 correlation between VEGF-D and NT-proBNP was 0.54 in the dyspnea cohort ( $p < 0.001$ ) and  
25 0.10 in MDC-CC ( $p < 0.001$ ).

1 (I) Among 430 patients with acute dyspnea, 152 (35%) were discharged with a diagnosis of  
2 HF. OR for HF (Q4 vs Q1) was 4.00 (CI:1.73-9.23, p for trend=0.003, adjusted for age, sex  
3 and NT-proBNP) (Table). Mean VEGF-D in patients with and without HF was  $7.32\pm 0.53$  and  
4  $6.80\pm 0.65$  AU, respectively ( $p<0.001$ ). VEGF-D was higher in HF patients with pulmonary  
5 congestion (n=50) on X-ray compared to other HF patients:  $7.59\pm 0.38$  vs  $7.19\pm 0.55$  AU  
6 ( $p<0.001$ ).

7 (II) In MDC-CC, 202 subjects were hospitalized due to HF during a mean follow-up of 19.9  
8 years. Incidence of HF was significantly associated with VEGF-D, even after adjustment for  
9 multiple risk factors (Table). C-statistics increased from 0.7327 to 0.7407 when VEGF-D  
10 was added to a model including age and sex; 0.7606 for model including age, sex and NT-  
11 proBNP, and 0.7646 if both VEGF-D and NT-proBNP were included.

12 A significant interaction between VEGF-D and sex was observed, and the HR (Q4 vs Q1) was  
13 significant for women (HR:2.0, CI:1.1-3.7) but not for men (HR:1.0, CI:0.6-1.7).

14 Different cut-offs for VEGF-D were explored. The HR was 1.49 (CI:1.10-2.01)( $p=0.010$ )  
15 comparing Q4 vs Q1-3, and 1.79 (CI:1.20-2.67)( $p=0.004$ ) comparing those above and below  
16 the 90<sup>th</sup> percentile.

17 Our results from patients with acute dyspnea indicate that biomarkers of lymphatic growth  
18 could be used to identify subjects with HF from other causes of dyspnea, and potentially  
19 enhance rapid diagnostic accuracy in addition to natriuretic peptides. The prospective results  
20 from the MDC cohort indicate that VEGF-D could also be an early predictor of future HF,  
21 which could represent early adaptation to increasing demands of the lymphatic system.

22 Besides the role of VEGF-D in the lymphatic system, it is also possible that VEGF-D could  
23 be linked to HF through other mechanisms, such as coronary atherosclerosis, cardiac  
24 remodeling, or pulmonary vascular remodeling. An experimental in vitro study demonstrated  
25 that VEGF-D serves as a stimulator of myofibroblast growth and collagen synthesis

1 (Zhao2016), and it could also be hypothesized that raised VEGF-D may reflect an adaptation  
2 to increased cardiac strain in the subclinical phase of HF. This view is supported by the  
3 significant correlations between VEGF-D and NT-proBNP. The results need to be replicated  
4 in further studies. However, we conclude that high VEGF-D is a potential new biomarker of  
5 pulmonary congestion and HF in both dyspnea patients and the general population.

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1 Table. Incidence of HF hospitalizations in relation to quartiles of VEGF-D in the MDC-CC  
 2 cohort.

<b>Acute dyspnea patients cohort (n=430)</b>						
	Q1	Q2	Q3	Q4	P	P per 1SD
ALL, n	106	107	108	109		
VEGF-D (AU)	6.16±0.41	6.76±0.11	7.21±0.13	7.81±0.28		
Age (years)	61.46 ±18.97	66.34 ± 19.64	1.91 ± 18.09	79.21 ± 12.61		
HF (n)	12	29	41	70		
OR 1	1.00	2.44 (1.12-5.33)	3.29 (1.54-7.04)	7.83 (3.67-16.73)	<0.001	<0.001
OR 2	1.00	2.44 (1.02-5.81)	2.23 (0.96-5.14)	4.00 (1.73-9.23)	0.003	0.010
<b>the MDC-CC cohort (n=4265)</b>						
	Q1	Q2	Q3	Q4	P	P per 1SD
ALL, n	1066	1066	1067	1066		
VEGF-D (AU)	6.09±0.31	6.54±0.12	6.85±0.12	7.30±0.24		
Age (years)	57.49 ±6.03	57.32 ± 5.89	57.28 ± 5.98	57.34 ± 5.92		
HF, n (n/1000)*	46(1.82)	40(1.88)	52(2.42)	64(3.11)		
HR 1	1.00	0.86(0.63-1.47)	1.18(0.79-1.75)	1.61(1.10-2.36)	0.008	0.028
HR 2	1.00	0.84(0.55-1.30)	1.19(0.79-1.80)	1.50(1.01-2.23)	0.012	0.043

3 OR 1: odds ratio adjusted for age and sex. OR 2: adjusted for age, sex, NT-proBNP.

4 HR 1: Hazards ratio adjusted for age and sex.

5 HR 2: adjusted for age, sex, waist circumference, smoking, alcohol consumption, diabetes,  
 6 systolic blood pressure, anti-hypertensive drug, LDL, HDL, Lipid-lowering drug, CRP and  
 7 NT-proBNP.

8 \*number of cases (incidence per 1000 person years).