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

Borné, Yan; Gränsbo, Klas; Nilsson, Jan; Melander, Olle; Orho-Melander, Marju; Smith, J Gustav; Engström, Gunnar

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2017.11.058

2018

Document Version:
Peer reviewed version (aka post-print)

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

Yan Borné [a] PhD, Klas Gränsbo [a] MD, PhD, Jan Nilsson [a] MD, PhD, Olle Melander [a] MD, PhD, Marju Orho-Melander [a] MD, PhD, J. Gustav Smith [a,b] MD, PhD, Gunnar Engström [a] MD, PhD

[a] Department of Clinical Sciences in Malmö, Lund University, Malmö, SE-205 02 Malmö, Sweden

[b] Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, SE-221 85 Lund, Sweden

Total word count:

Funding: This work was supported by the Swedish Heart and Lung Foundation, the Swedish Research Council, the European Research Council, the Crafoord Foundation, governmental funding of clinical research within the Swedish National Health Service, and Skåne University Hospital.

Disclosures: All authors have nothing to disclose.

Acknowledgements: The biomarker facility of SciLifeLab is acknowledged for analysis of VEGF-D.

Address for correspondence: Yan Borné, Department of Clinical Sciences in Malmö, Lund University, Malmö, CRC, Jan Waldenströms gata 35, SE-205 02 Malmö, Sweden. Telephone: 004640391327, Email: yan.borne@med.lu.se

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

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

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

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

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

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

Different cut-offs for VEGF-D were explored. The HR was 1.49 (CI:1.10-2.01)(p=0.010) comparing Q4 vs Q1-3, and 1.79 (CI:1.20-2.67)(p=0.004) comparing those above and below the 90^{th} percentile.

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

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

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

References

Dashkevich A, Hagl C, Beyersdorf F Nykanen AI, Lemstrom KB. VEGF Pathways in the Lymphatics of Healthy and Diseased Heart. Microcirculation 2016;23:5-14.

Simons M, Gordon E, Claesson-Welsh L. Mechanisms and regulation of endothelial VEGF receptor signalling. Nature Rev Mol Cell Biol 2016;17:611-25.

Wiklund K, Gränsbo K, Lund N et al. Inflammatory biomarkers predicting prognosis in patients with acute dyspnea. Am J Emerg Med 2016;34:370-4.

Smith JG, Newton-Cheh C, Almgren P, et al. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. J Am Coll Cardiol. 2010;56:1712-9.

Zhao T, Zhao W, Meng W et al. Vascular endothelial growth factor-D mediates fibrogenic response in myofibroblasts. Mol Cell Biochem 2016;413:127-35.

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

Acute dyspnea patients cohort (n=430)						
	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
the MDC-CC cohort (n=4265)						
	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

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

HR 1: Hazards ratio adjusted for age and sex.

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

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