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Serum levels of growth differentiation factor 15 are associated with outcomes in patients with a Fontan circulation

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Introduction: Growth differentiation factor 15 (GDF-15) is involved in noncardiac and cardiac stress pathways. Elevated levels are associated with mortality in acquired heart disease. The aim of this study was to investigate GDF-15 in Fontan patients.

Methods: In this prospective study, Fontan patients were followed at the University Medical Center Groningen from 2012 to 2018. Serial serum GDF-15 measurement and clinical assessment was done both at baseline and after two years. The association between GDF-15 and clinical outcome, including Fontan-related hospitalization and all-cause mortality, was investigated.

Results: Eighty-one patients were included, of which 51 patients had a 2-year follow-up. Median age at baseline was 21 years (IQR 14.5-27.5) (table 1). Median GDF-15 levels at baseline were 552 pg/mL (IQR 453-729). Patients in NYHA class III (n=10) had higher GDF-15 levels than patients in NYHA class I or II (n=71) (1086 pg/mL (IQR 659-1239) versus 539 pg/mL (IQR 443-670), P=0.001). GDF-15 correlated positively with age and time since Fontan completion, Fontan type, ɣGT and beta blocker use and negatively with exercise capacity. There was no significant relationship with sex, ventricular ejection fraction or morphology. During a median follow-up of 58 months (IQR 39–66), the clinical outcome occurred in 33 patients (41%): 30 Fontan-related hospitalizations and 3 deaths. Patients with an elevated baseline GDF-15 (n=20, defined as upper quartile) had a higher risk of hospitalization or death (HR 3.8, 95% CI 1.9-7.5, P<0.001). This relationship persisted after individual and multivariate adjustment for independently predictive covariates (HR 3.0, 95% CI 1.5-6.2, P=0.004). Median GDF-15 did not increase significantly after 2 years in patients with serial GDF-15 measurements (570 pg/mL (IQR 450-740) versus 595 pg/mL (IQR 483-872), P=0.146). Patients with a GDF-15 increase >70 pg/mL (n=13, defined as the upper quartile of interval change between baseline and the second visit) had a higher, yet not statistically significant, risk of hospitalization or death (HR 2.3, 95% CI 0.9-5.8, P=0.071).

Conclusions: In Fontan patients, elevated serum levels of GDF-15 are associated with worse functional status and increased risk of Fontan-related hospitalization or death. The additional value of serial GDF-15 measurements requires further investigation.

Table 1- Baseline characteristics (n=81)

Age (years)	21.0 (14.5-27.5)
Females	41 (51)
Left ventricular morphology	68 (84)
Time since Fontan (years)	15.4 (9.0-22.5)
Type Fontan	
Atriopulmonary connection	16 (20)
Lateral tunnel	44 (54)
Extracardiac tunnel	21 (26)
NYHA class	
I/II	71 (88)
III	10 (12)
Ejection fraction (%)	58.0 (50.4-62.3)
ß-blocker users	20 (25)
ɣGT (U/L)	59.2 (39.4-102.5)
Peak VO_2 (ml/min/kg)	23.9 (19.5-32.7)

All values are expressed as median (interquartile range) or frequency (percentage)