Cardiotrophin-1 is differentially induced in the myocardium of infants with congenital cardiac defects depending on hypoxemia

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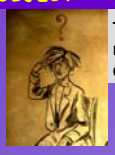
BACKGROUND

CT-1 is up regulated by hypoxemia and hemodynamic overload and induces cardiac hypertrophy via the janus kinase / signal transducer and activator of transcription pathway.

SUBJECT



To test if cardiotrophin (CT)-1 is differentially induced in the myocardium of infants with congenital cardiac defects depending on hypoxemia.

METHODS

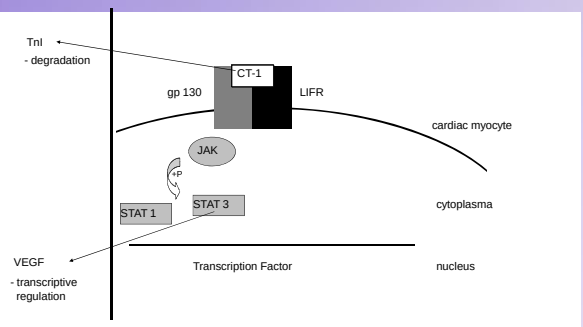
- Infants with Tetralogy of Fallot (TOF) or with large ventricular septal defect (VSD) undergoing corrective surgery were investigated.
- Expression of CT-1 was assessed at mRNA- and protein level in the right atrial and -ventricular myocardium.
- We measured the activation of the signal transducer and activator of transcription (STAT)-3 and vascular endothelial growth factor (VEGF)165.
- Degradation of cardiac troponin (cTn)-I served as a marker of myocardial damage.

Patients clinical data

	TOF group (n = 8)	VSD group (n = 8)	p-Value
Gender (female / male)	2 / 6	5 / 3	NS
Age at operation (months)	3.8 ± 3.0	5.8 ± 4.3	NS
Weight (g)	7.5 ± 3.4	6,1 ± 2.7	NS
Preoperative SaO_2 (%)	87.4 ± 3.6	97.7 ± 1.0	0.001

Data are presented as the mean value ± SD. SaO_2 : transcutaneous arterial oxygen saturation; TOF: Tetralogy of Fallot; VSD: ventricular septal defect; NS: not significant.

Schematic structure of CT-1 and activated pathways

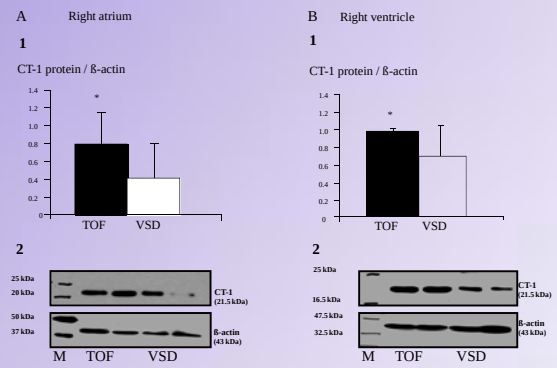


The CT-1 receptor is composedas a heterodimer by the leukemia inhibitory factor receptor (LIFR) and glycoprotein 130 (gp130). Intracellular, CT-1 activates the JAK/STAT pathway which causes thyrosine phosphorylation of the STAT3 factor. JAK = Janus Kinase, STAT = Signal Transducer and Activator of Transcription. TnI = Troponin I, VEGF = Vascular Endothelial Growth Factor.

RESULTS

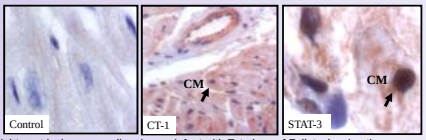
- CT-1 was detected in all patients.
- Infants with TOF showed significantly higher protein levels of CT-1 than those with VSD.
- In all patients, levels of CT-1 negatively correlated with arterial oxygen saturation.
- Patients with TOF showed higher levels of phospho-STAT-3 and VEGF165 and higher levels of cTn-I.

Myocardial expression of CT-1.



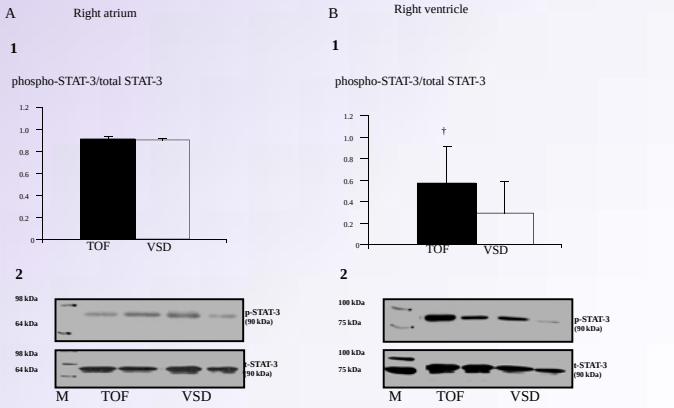
1) Levels of cardiotrophin (CT)-1 measured by Western blotting in the right atrium (A) and right ventricle (B) of infants with Tetralogy of Fallot (TOF; n = 7) or with ventricular septal defect (VSD; n = 8). Results are expressed as the mean value ± SD. * $p < 0.05$ between groups.
2) Gels obtained after Western blotting of one representative experiment showing a higher synthesis of CT-1 in children with TOF. M = marker.

Presence of CT-1 and STAT-3.



Immunocytochemistry of the right ventricular myocardium in one infant with Tetralogy of Fallot, showing the presence of cardiotrophin-1 (CT-1) in the cardiomyocytes (CM,) and of signal transducer and activator of transcription (STAT)-3 in the nuclei of cardiomyocytes (CM). Control: negative control (no primary antibody). Original magnification x 400 (CT-1) and x 1000 (control and STAT-3).

Expression of STAT-3.



1) Levels of phospho-signal transducer and activator of transcription (STAT)-3 measured by Western blotting in the right atrium (A) and right ventricle (B) of infants with Tetralogy of Fallot (TOF; n = 7) or with ventricular septal defect (VSD; n = 8). Results of phospho-STAT-3 are normalized for the bands of total STAT-3 and are expressed as the mean value ± SD. †: $p < 0.1$ between groups.
2) Gels obtained after Western blotting of one representative experiment showing a higher activation of STAT-3 in children with TOF. M = marker.

CONCLUSION

CT-1 is differentially expressed in the myocardium of infants with heart defects:

- Higher CT-1 expression in patients with TOF is associated with activation of the Jak/STAT pathway and higher cTn-I degradation.
- CT-1 might mediate myocardial hypertrophy and myocardial dysfunction in infants with congenital cardiac defects, particularly in those with hypoxemia.