

Biochemical markers and Doppler changes in fetal growth restriction

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Biomarkers of cardiac dysfunction

Natriuretic peptides

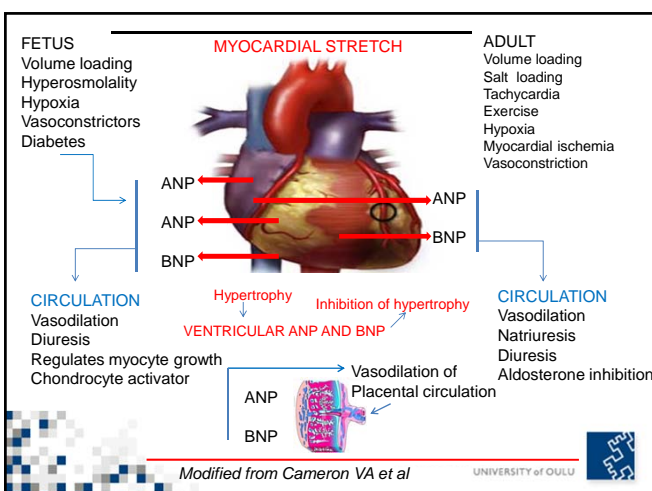
Atrial natriuretic peptide (ANP)

B-type natriuretic peptide (BNP)

Cardiac troponin-T (cTnT)

Erythropoietin (EPO)

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Dual natriuretic peptide response to volume load in the fetal circulation

T. Walther^{a,*}, H. Stepan^b, R. Faber^b

	ANP (pg/ml)	BNP (pg/ml)
Maternal (n=9)	17.3±2.4	26.8±3.9
Fetal controls (n=9)	31.6±7.7§	56.6±11.9§
Rh before transfusion (n=9)	80.8±16.6*	64.8±6.6
Rh after transfusion (n=9)	100.8±24.2	112.9±14.1#

^a ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide. Values are mean±S.E.M.

[§] P<0.05 fetal controls versus maternal.

^{*} P<0.05 fetal controls versus before transfusion.

[#] P<0.05 before versus after transfusion.

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N-terminal peptides of ANP and BNP

NT-proANP , NT-proBNP

Released in equimolar amounts with BNP and ANP

Half-life longer than those of BNP and ANP

Used to characterize endogenous secretion of BNP and ANP

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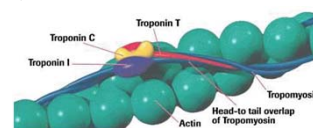
Cardiac Troponin-T (cTnT)

Thin filament protein taking part to muscle contraction

Cardiospecific, not present after nonmyocardial damage

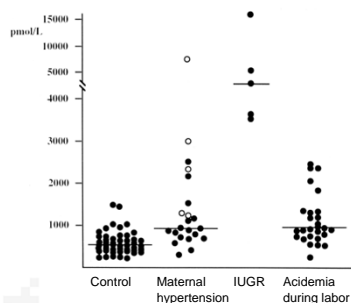
Peaks 12-48 hours after injury

Concentration in direct proportion to the extent of myocardial injury



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NT-proANP, IUGR and fetal acidemia during labor



Makikallio et al, Obstet Gynecol 2000

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NT-proANP and cTnT Fetal growth restriction

Group 1 (12 fetuses) 'Normal Cardiac Function'

- NT-proANP < 1145 pmol/L
- cTnT < 0.10 ng/mL

Group 2 (25 fetuses) 'Cardiac Dysfunction'

- NT-proANP > 1145 pmol/L
- cTnT < 0.10 ng/mL

Group 3 (11 fetuses) 'Myocardial Injury'

- NT-proANP > 1145 pmol/L
- cTnT > 0.10 ng/mL

Makikallio et al, Circulation 2002

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NT-proANP and cTnT

Cardiac output

	Normal	cTnT normal NT-proANP ↑	cTnT ↑
CCO, mL/min per kg	523 (72)	548 (121)	499 (189)
RVCO, mL/min per kg	299 (40)	327 (90)	272 (129)
LVC0, mL/min per kg	223 (51)	221 (42)	226 (77)
RVCO%	57.2 (5.2)	59.1 (4.5)	53.3 (13.1)*
LVC0%	42.8 (5.2)	40.9 (4.5)	46.7 (13.0)*

All values given are mean (SD).

*P<0.05 vs group 2.

Makikallio et al, Circulation 2002

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NT-proANP and cTnT

Afterload

	Normal	cTnT normal NT-proANP ↑	cTnT ↑
CG/TC, %	57.0 (4.4)	57.5 (3.3)	61.3 (6.1)*
RVFS, %	22.6 (7.6)	26.2 (5.0)	13.2 (11.4)†
LVFS, %	29.0 (7.3)	32.8 (6.7)	26.2 (12.0)
TR, %	25.0	12.0	54.5†

All values given are mean (SD).

*P<0.05 vs groups 1 and 2.

†P<0.05 vs group 2.

Makikallio et al, Circulation 2002

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NT-proANP and cTnT

Venous circulation

	Normal	cTnT normal NT-proANP ↑	cTnT ↑
PIV of IVC	2.32 (1.60-4.36)	2.33 (1.02-5.66)	4.95 (2.46-6.45)
PIV of LHV	2.50 (1.06-7.28)	3.86 (1.76-9.37)	5.84 (3.29-46.59)*
PIV of DV	0.59 (0.34-1.14)	0.55 (0.26-1.24)	1.17 (0.57-3.81)†
IA UV pulsations, %	16.7	16.0	81.8*

IA UV indicates intra-abdominal umbilical vein. All values given are median (range).

*P<0.01 vs groups 1 and 2.

†P<0.001 vs groups 1 and 2.

Makikallio et al, Circulation 2002

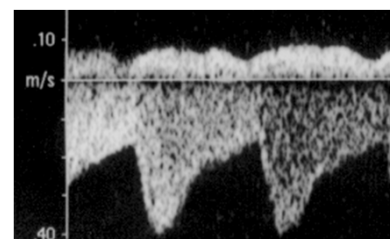
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Umbilical vein

Abnormal

- end diastolic pulsations



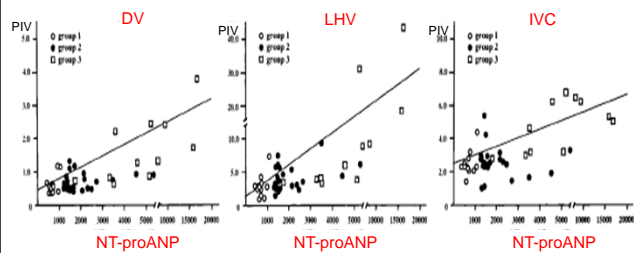
Makikallio et al, Circulation 2002

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Systemic venous pulsatility

NT-proANP

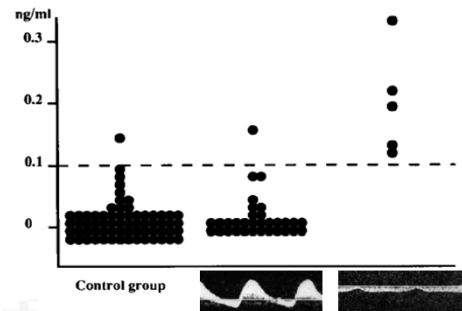


Makikallio et al, Circulation 2002

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Umbilical vein

cTnT



Makikallio et al, Am J Obstet Gynecol 2000

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NT-proBNP

Fetal growth restriction

Study group (n=42)

IUGR (Abnormal UA velocimetry)
Doppler examination < 7 days prior to delivery
Umbilical artery blood sample at delivery

Control group (n=49)

Uncomplicated pregnancy and labor
95th percentile value of NT-proBNP determined

Girsen et al, Ultrasound Obstet Gynecol 2007

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Material

Study groups

Group 1 (n=13)

Normal UA velocimetry
Birth weight < 10th percentile

Group 2 (n=15)

Abnormal UA
Normal DV

Group 3 (n=14)

Abnormal UA and DV

Girsen et al, Ultrasound Obstet Gynecol 2007

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Results

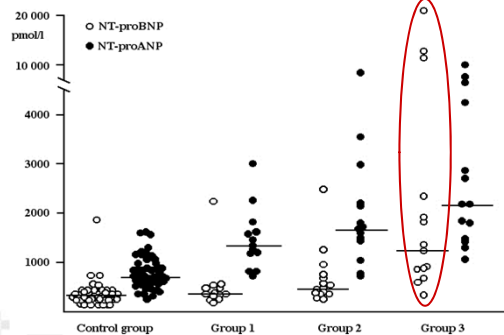
	Group 1 mean (SD)	Group 2 mean (SD)	Group 3 mean (SD)
GA at delivery (w)	37.9 (1.7)	34.6 (3.6)*	32.8 (4.2)*
Birth weight (g)	2525 (274)	1778 (632)*	1432 (661)*
5 min Apgar score	9 (7-10)	8 (5-10)	8 (1-9)*
UA pH	7.26 (0.05)	7.28 (0.05)	7.24 (0.04)

* p<0.05 vs Group 1

Girsen et al, Ultrasound Obstet Gynecol 2007

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Umbilical artery ANP and BNP



Girsen et al, Ultrasound Obstet Gynecol 2007

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Results

	Controls	Group 1	Group 2	Group 3
NT-proBNP (pmol/L)	311 (156-1870)	334 (156-2251)	453 (263-2498)	1263* (380-21 000)
NT-proBNP > 518 pmol/L		4/13	7/15	13/14

Girsen et al, Ultrasound Obstet Gynecol 2007

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Conclusions

ANP

Maternal hypertensive disorder and fetal acidemia during labor stimulate fetal atrial natriuretic peptide production.

In IUGR, pulsatility in human fetal systemic veins correlate significantly with the cardiac secretion of ANP

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Conclusions

BNP

In IUGR, increased cardiac afterload and pulsatility in ductus venosus correlate with increased BNP secretion.

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Conclusions

cTnT

Fetuses with myocardial damage demonstrate increased systemic venous pressure, a change in the distribution of cardiac output toward the left ventricle, and a rise in right ventricular afterload.

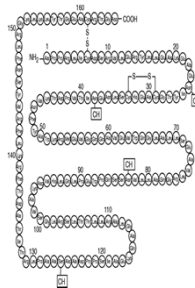
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Erythropoietin (EPO)

Neuroprotective, tissue protective
(*Sasaki et al 2003*)

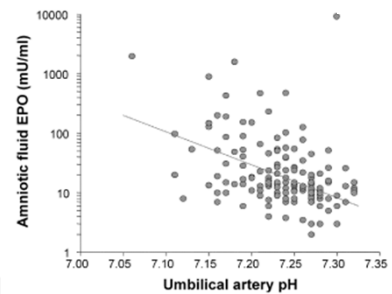
Hypoxemia is the main stimulus for EPO synthesis
(*Fisher et al 1984*)

Plasma concentrations reflect the rate of synthesis and degradation
(*Dame et al 1998*)



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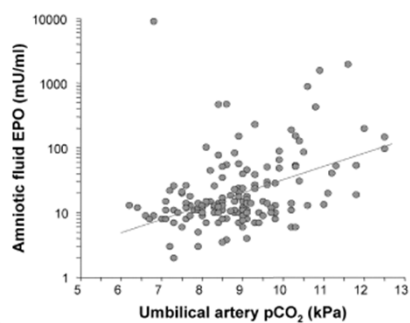
Erythropoietin (EPO)



Teramo et al Diabetologia 2004

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Erythropoietin (EPO)

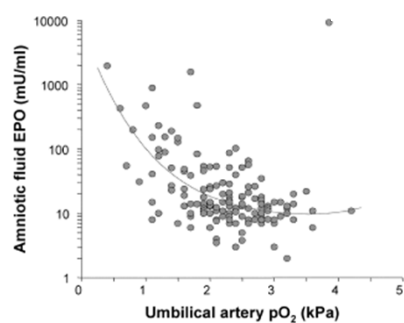


Teramo et al Diabetologia 2004

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Erythropoietin (EPO)



Teramo et al Diabetologia 2004

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EPO and placental insufficiency

Group 1 (n=9)

Normal umbilical artery (UA) velocimetry
Normal ductus venosus (DV) velocimetry

Group 2 (n=18)

Abnormal UA velocimetry
Normal DV velocimetry

Group 3 (n=11)

Abnormal UA velocimetry
Abnormal DV velocimetry

Girsen et al, AJOG 2007

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Results

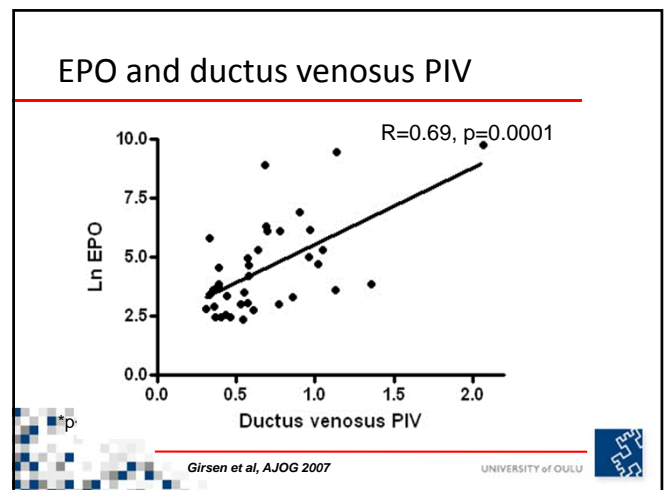
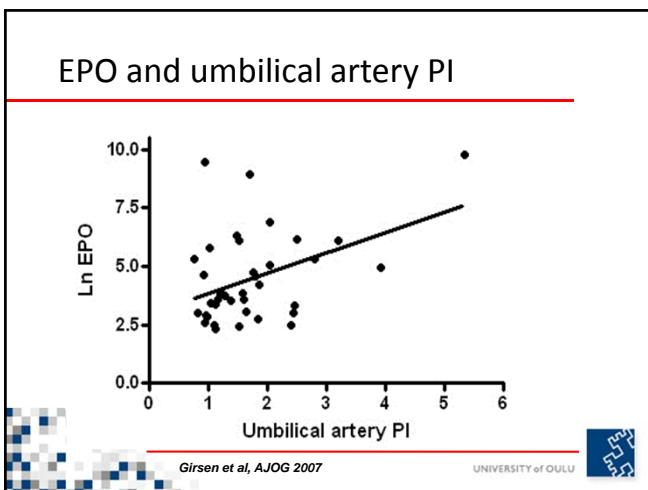
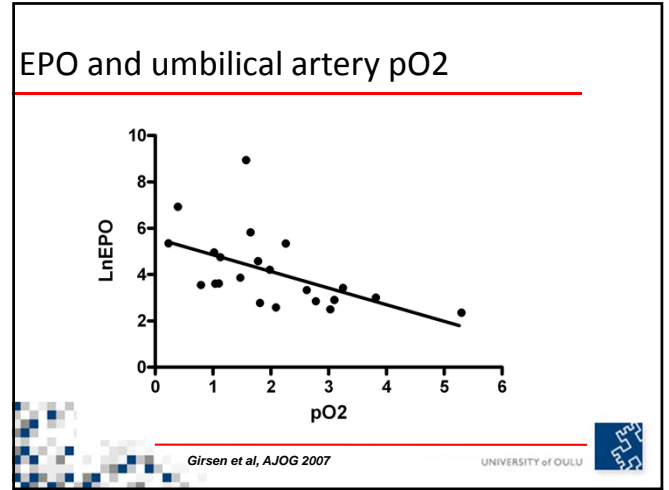
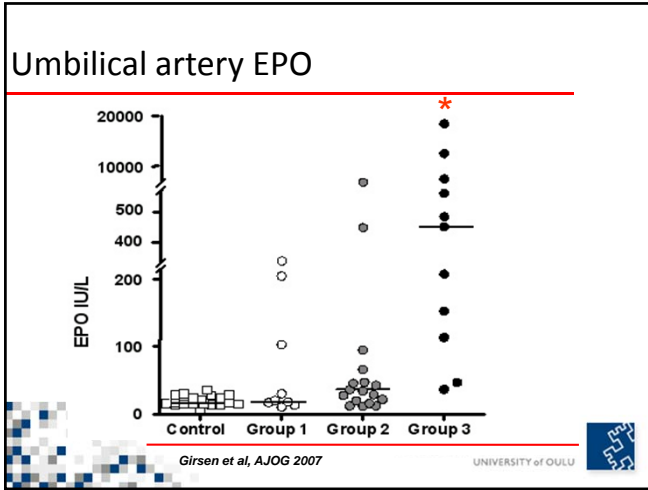
	Group 1	Group 2	Group 3
GA delivery (w)	37.9 (1.1)	33.8 (3.9) *	34.5 (3.2) *
Birth weight (g)	2367 (379)	1735 (773)*	1643 (497)*
UA pH	7.25 (0.05)	7.27 (0.05)	7.22 (0.05)
UA pO ₂	2.94 (1.11)	1.84 (0.94)*	1.08 (0.69)*
UA pCO ₂	6.26 (1.14)	6.83 (0.94)	7.36 (0.42)
UA BE	-6.85 (3.45)	-4.31 (3.22)	-4.28 (2.23)
Apgar 5 min	9 (7-10)	8 (3-10)	8 (6-9)

*p < 0.05 vs. Group 1

Girsen et al, AJOG 2007

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Conclusions

Human fetal EPO secretion is increased in proportion to the severity of fetal cardiovascular compromise in intrauterine growth restriction

Growth-restricted fetuses with increased systemic venous pressure demonstrate abnormal EPO concentrations at birth indicating intrauterine hypoxemia

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Girsen et al, AJOG 2007

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