Whole body endogenous nitric oxide production in patients with decompensated liver disease

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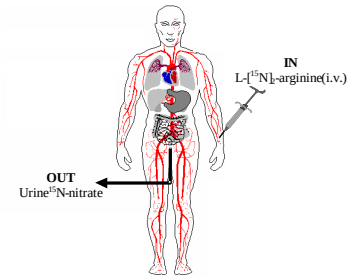
Background

- Patients with cirrhosis have a hyperdynamic circulation.
- Inducible NO synthase (iNOS) is viewed as responsible responding to endotoxins and/or cytokines. The resulting increased NO production leads to hypo-responsive blood vessels.
- In man, point estimates of blood or urine nitrite or nitrate, used to infer the involvement of NOS, do not simply reflect the rate of production of endogenous NO.
- **Many of the problems associated with measuring NO in man can be overcome using L-[^{15}N]$_2$-arginine**. The ^{15}N label (stable, non-radioactive) is carried from L-arginine to NO via NOS. NO is further metabolised and excreted as ^{15}N-nitrite and ^{15}N-nitrate ($^{15}NO_x$) (Demoncheaux *et al.* 2005).

Whole body NOS-dependent NO production



Subject profile

- Ten patients with alcoholic liver cirrhosis (mean age 48.5 ± 2.5 years) and ten age and sex matched healthy volunteers (mean age 48.2 ± 1.8 years) were recruited.
- Informed consent was obtained from all patients and volunteers. The study was approved by the South Sheffield Research Ethics Committee.
- Patient were ambulant with normal serum creatinine (<120 μmol/l). To avoid depressing effect of alcohol on vascular haemostasis, patients with alcoholic liver disease were abstinent from alcohol for at least 4 weeks. None of the patients were on vasoactive or non-steroidal anti-inflammatory drugs in the week before the study.
- Subjects abstained from eating nitrate containing foods, such as green vegetables and preserved red meat, as well as smoking tobacco for at least 36 hours before and during the study.

Results

- **All patients had decompensated liver cirrhosis and portal hypertension (Table).**
- **113.4 ± 38.1 and 118.0 ± 31.9 nmol $^{15}NO_x$** / mmol creatinine were recovered over 36 hours in the urine of patients and control subjects respectively. **These results were not statistically different.**
- **Neither urinary nor blood non-labeled NO_x (e.g. $^{14}NO_x$) concentrations were different between patients and control subjects**:
  - 42.8 ± 13.6 vs. 62.5 ± 17.0 μmol/mmol creatinine over 36 hours (urine).
  - 122.6 ± 18.3 vs. 136.4 ± 22.7 μmol/l (blood).
- **Patients and control subjects had normal kidney function** with glomerular filtration rates of 95.7 ± 12.0 and 129.1± 16.8 ml/min respectively.

Table. Biochemical profile of patients and control subjects (mean ± SEM)

Factors		Patients	Controls	P value
Age (yr)		48.5 ± 2.5	48.2 ± 1.8	NS
Sex (M/F)		7/3	7/3	
Whole body NO production (nmol/mmol creatinine)	0-12h	154.6 ± 65.3	139.8 ± 54.1	NS
	12-24h	115.6 ± 32.1	148.2 ± 38.8	NS
	24-36h	70.1 ± 27.6	65.9 ± 16.9	NS
Serum nitrite and nitrate (μmol/l)		122.6 ± 18.3	136.4 ± 22.7	NS
Urine nitrite and nitrate (μmol/mmol creatinine)		42.8 ± 13.6	62.5 ± 17.0	NS
Serum creatinine (μmol/l)		75.8 ± 6.6	85.8 ± 7.3	NS
Urine creatinine (mmol/l)		8.7 ± 1.7	9.8 ± 1.1	NS
Glomerular Filtration Rate (ml/min)		95.7 ± 12.0	129.1 ± 16.8	NS
Prothrombin time (sec)		15.1 ± 1.4	N/A	
Serum albumin (g/l)		24.7 ± 1.7	N/A	
Serum bilirubin (μmol/l)		87.5 ± 25.7	N/A	
Pugh score		9.3 ± 0.6	N/A	

Conclusions

- We have confirmed that whole body conversion of arginine to NO can be measured using safe, *non-gamma emitting* ^{15}N labelled L-arginine.
- We have demonstrated that global NOS-dependent NO production is not different between patients with advanced liver disease and age and sex matched healthy subjects. These results are independent of exogenous sources of nitric oxide.

References:
Demoncheaux *et al.* J. Vasc Res 2005, in press.