Title: PREDICTION OF BRAIN DAMAGE BY BRAIN ENZYME LEVELS IN CEREBROSPINAL FLUID (CSF) OF DOGS AFTER CARDIAC ARREST

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Introduction. There is a need for reliable measurements which would indicate, soon after cardiac arrest (CA), permanent severe brain damage. Based on findings in clinical studies after CA (1-4) increased the activity of brain cytosolic enzymes in cerebrospinal fluid (CSF) reflects neurological deficit and brain damage. We, therefore, adopted this method as an additional parameter in our established animal research program for testing brain resuscitation therapies after CA with post-CPR intensive care and long-term (96 h) outcome.

Methods. Two clinically relevant CA models were used, asphyxial arrest (AA) and ventricular fibrillation arrest (VF). AA was induced in 27 pancuronium-paralyzed, lightly anesthetized dogs by apnea and clamping the tracheal tube. At pulselessness (mechanical asystole), which occurred after asphyxiation time of 6-8 min, arrest times of 0-10 min were added. VF was induced in 25 dogs by external AC shock, and allowed to last for 10 min. Restoration of spontaneous circulation (ROSC) was to be accomplished within 5 min and was according to standard external CPR (SECPR), with IPPV/100% O2, drugs and electric defibrillation. Total insult time was 7'-20'30" in the AA group, and 11'50"-14' in the VF group. The dogs were mechanically ventilated with control of MAP at 115±15 mmHg, PaO2 >100 mmHg and PaCO2 at 30 mmHg for 20 h, and then weaned to spont. resp. Thereafter, intensive care life support was provided with control and monitoring of EKG, MAP, CVP, blood gases, temperature, hct and other variables for 96 h post-insult (PI). Outcome was expressed as neurological deficit (ND), after an established scoring system (0% ND=no deficit, 100% ND=brain death). ND above 40-45% was associated with stupor or coma. The best ND over 96 h was recorded. Cisternal puncture was done with a spinal needle and 1 ml CSF collected before CA and at 24, 48, 72 and 96 h PI, to establish a pattern of CSF-enzyme changes. Punctures were subsequently restricted to approx. 48 h PI as this appeared to be the time of peak activity (2). CSF volume was replaced by MOK CSF. Possible adverse effects of cisternal puncture on brain recovery were ruled out by sham experiments. CSF samples were stored at -20 C and within one week analyzed spectrophotometrically for creatine phosphokinase (CPKBB), lactate dehydrogenase (LDH) and aspartate-amino transferase (ASAT).

Results. Table 1 shows that dogs with short AA (0-1½") were normal, with low enzyme activity, whereas the 7' and 10' AA dogs were all severely damaged, and had high CSF-enzyme activity. In the 3' and 5' AA dogs, outcome was variable (not shown). The 7' AA and 10' VF groups had been used to test 3 different potential brain-damage ameliorating therapies vs advanced intensive care only (standard group) (Table 2). After 7' AA, Dextran 40/Mannitol/MgSO4 (D40/M/Mg) treatment significantly improved ND ($p < 0.05$), with a significant lowering of CPKBB activity ($p < 0.05$). In the VF groups, lidoflazine significantly improved ND ($p < 0.05$), but CPKBB was only numerically lower than in the standard group (NS). Five of 11 lidoflazine treated dogs were normal, but outcome was variable in the others (ND%:19-40). LDH and ASAT showed more inconsistent and variable changes. In the VF group, when ND was correlated with max CSF-enzyme activity, the r-values for CPKBB, LDH and ASAT were 0.77, 0.65 and 0.48 respectively; and in the AA group, 0.56, 0.55 and 0.32. (LDH, ASAT not shown). CPKBB levels above 12 units/L were invariably associated with ND above 15%, whereas dogs which recovered completely had activities below this level. When this activity level occurred within 12-24 h PI, outcome was always poor, with ND usually above 30-40%. After acute experimental focal brain injury, enzymes increased to max levels within a few hrs. After CA, brain damage as reflected by CSF enzyme peaks evolved more gradually.

Summary and Conclusions. After CA in dogs, CPKBB, LDH and ASAT increased in cisternal CSF, and maximal activity correlated with the severity of brain damage. The pattern is similar to that observed after clinical CA (2-4), but the LDH increase is much lower in dogs compared to humans. CPKBB rise was more dependable than the other enzymes in predicting poor outcome. These data indicate the need for a systematic large scale study of CPKBB CSF peaks as possibly reliable predictors of post-CA brain damage, in animals and patients.

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References.

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Table 1 (mean±SD) Standard Post-CPR Therapy

Duration Asphyxial Cardiac Arrest (AA) VF	0 min	1½ min	7 min	10 min
Best ND%	0.3±0.5	3.8±3.8	39±9	33±11
(range)	(0-1)	(0-9)	(28-53)	(16-47)
CPKBB (U/L)	0-5	0-12	20-146	18-98
LDH (U/L)	3-5	5-12	16-74	6-282
ASAT (U/L)	23-26	20-42	32-424	38-283

Range is shown for enzymes.

Table 2 (mean±SD)

	Special Post-CPR Therapies			
Insult	Standard	Lidoflaz.	D40/M/Mg	Verapamil
7' AA				
ND % (n)	41±8(7)	28±11(5)	25±8(5)*	
CPKBB (U/L)	81±53	85±48	33±22	
10' VF				
ND % (n)	33.7±11(11)	18.5±14(10)*		31.3±9.8(4)
CPKBB (U/L)	42±26	35±33		42±14

*$p < 0.05$ vs standard treatment.