

**Impact of Neonatal Cardiovascular Compromise  
and its Treatment on Brain Electrical Activity and  
Short-term Clinical Outcome**

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ  
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا  
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ  
صدق الله العظيم

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# *List of Abbreviations*

Abb.	Full term
<i>AC</i> .....	<i>Adenylate cyclase</i>
<i>ACCM</i> .....	<i>American College of Critical Care Medicine</i>
<i>aEEG</i> .....	<i>Amplitude-integrated electroencephalography</i>
<i>Ao</i> .....	<i>Aorta</i>
<i>A wave</i> .....	<i>Atrial contraction wave</i>
<i>BE</i> .....	<i>Base excess</i>
<i>BLP</i> .....	<i>Bacterial lipopeptide</i>
<i>BP</i> .....	<i>Blood pressure</i>
<i>Ca</i> .....	<i>Calcium</i>
<i>cAMP</i> .....	<i>Cyclic adenosine monophosphate</i>
<i>CBF</i> .....	<i>Cerebral blood flow</i>
<i>CDH</i> .....	<i>Congenital diaphragmatic hernia</i>
<i>CFM</i> .....	<i>Cerebral function monitoring</i>
<i>CI</i> .....	<i>Confidence interval</i>
<i>CHD</i> .....	<i>Congenital heart disease</i>
<i>cGMP</i> .....	<i>Cyclic guanosine monophosphate</i>
<i>CPAP</i> .....	<i>Continuous positive airway pressure</i>
<i>CRT</i> .....	<i>Capillary refill time</i>
<i>CNS</i> .....	<i>Central nervous system</i>
<i>CO</i> .....	<i>Cardiac output</i>
<i>COX</i> .....	<i>Cyclooxygenase enzyme</i>
<i>CPP</i> .....	<i>Cerebral perfusion pressure</i>
<i>CSF</i> .....	<i>Cerebrospinal fluid</i>
<i>CW</i> .....	<i>Continuous-wave mode of Spectral Doppler</i>
<i>DA</i> .....	<i>Ductus arteriosus</i>
<i>Desc Ao</i> .....	<i>Descending aorta</i>
<i>DIC</i> .....	<i>Disseminated intravascular coagulation</i>
<i>DO<sub>2</sub></i> .....	<i>Oxygen delivery</i>
<i>E:A ratio</i> .....	<i>E and A wave velocities ratio</i>
<i>ECMO</i> .....	<i>Extracorporeal membrane oxygenation</i>
<i>EF</i> .....	<i>Ejection fraction</i>
<i>EOS</i> .....	<i>Early onset sepsis</i>
<i>ET-B</i> .....	<i>Endothelin receptor- B</i>

## *List of Abbreviations (cont...)*

Abb.	Full term
<i>ET-A</i> .....	<i>Endothelin receptor-A</i>
<i>ET-1</i> .....	<i>Endothelin-1</i>
<i>E wave</i> .....	<i>Early wave (early diastolic blood flow)</i>
<i>eNOS</i> .....	<i>Endothelial nitric oxide synthase</i>
<i>FDA</i> .....	<i>United States Food and Drug Administration</i>
<i>FiO2</i> .....	<i>Fraction of inspired oxygen</i>
<i>Fn-Echo</i> .....	<i>Functional echocardiography</i>
<i>FoCUS</i> .....	<i>Focused cardiac ultrasound</i>
<i>FO</i> .....	<i>Foramen ovale</i>
<i>FRC</i> .....	<i>Functional residual capacity</i>
<i>FS</i> .....	<i>fractional shortening</i>
<i>GA</i> .....	<i>Gestational age</i>
<i>HFV</i> .....	<i>High frequency ventilation</i>
<i>HRF</i> .....	<i>Hypoxic respiratory failure</i>
<i>Hz</i> .....	<i>Hertz</i>
<i>hrs</i> .....	<i>Hours</i>
<i>iNO</i> .....	<i>Inhaled Nitric Oxide</i>
<i>IVH</i> .....	<i>Intraventricular Hemorrhage</i>
<i>IVC</i> .....	<i>Inferior vena cava</i>
<i>IVS</i> .....	<i>Interventricular septum</i>
<i>K</i> .....	<i>Potassium</i>
<i>LA</i> .....	<i>Left atrium</i>
<i>LA: Ao ratio</i>	<i>Left atrial to aortic root ratio</i>
<i>LOS</i> .....	<i>Late onset sepsis</i>
<i>LPS</i> .....	<i>Lipopolysaccharide</i>
<i>LV</i> .....	<i>Left ventricle</i>
<i>LVEDA</i> .....	<i>Left ventricular end-diastolic area</i>
<i>LVEDD</i> .....	<i>Left ventricular end-diastolic diameter</i>
<i>LVEDV</i> .....	<i>Left ventricular end-diastolic volume</i>
<i>LVESD</i> .....	<i>Left ventricular end-systolic diameter</i>
<i>LVESV</i> .....	<i>Left ventricular end-systolic volume</i>
<i>LVO</i> .....	<i>Left ventricular output</i>
<i>MAP</i> .....	<i>Mean airway pressure</i>

## *List of Abbreviations (cont...)*

Abb.	Full term
<i>MAS</i> .....	<i>Meconium aspiration syndrome</i>
<i>MPI</i> .....	<i>Myocardial performance index</i>
<i>Mv</i> .....	<i>Mitral valve</i>
<i>n</i> .....	<i>Number</i>
<i>NEC</i> .....	<i>Necrotizing enterocolitis</i>
<i>NO</i> .....	<i>Nitric oxide</i>
<i>NSE</i> .....	<i>Neuron-specific enolase</i>
<i>NIRS</i> .....	<i>Near-infrared spectroscopy</i>
<i>NICU</i> .....	<i>Neonatal intensive care unit</i>
<i>OER</i> .....	<i>Oxygen extraction ratio</i>
<i>OI</i> .....	<i>Oxygenation index</i>
<i>OSI</i> .....	<i>Oxygen saturation index</i>
<i>pre-OL</i> .....	<i>Progenitor cells</i>
<i>PaCO<sub>2</sub></i> .....	<i>Arterial partial pressure of carbon dioxide</i>
<i>PaO<sub>2</sub></i> .....	<i>Arterial partial pressure of oxygen</i>
<i>p</i> .....	<i>Pressure gradient</i>
<i>PASP</i> .....	<i>Pulmonary artery systolic pressure</i>
<i>PDA</i> .....	<i>Patent ductus arteriosus</i>
<i>PDE3</i> .....	<i>Phosphodiesterase 3 enzyme</i>
<i>PDE5</i> .....	<i>Phosphodiesterase 5 enzyme</i>
<i>PFO</i> .....	<i>Patent foramen ovale</i>
<i>PGI<sub>2</sub></i> .....	<i>Prostacyclin</i>
<i>PGIS</i> .....	<i>Prostacyclin synthase</i>
<i>PG</i> .....	<i>Prostaglandin</i>
<i>PGs</i> .....	<i>Prostaglandins</i>
<i>PEEP</i> .....	<i>Positive end-expiratory pressure</i>
<i>P/F ratio</i> .....	<i>PaO<sub>2</sub>/ FiO<sub>2</sub></i>
<i>PH</i> .....	<i>Pulmonary hypertension</i>
<i>PIP</i> .....	<i>Peak inspiratory pressure</i>
<i>PLAX</i> .....	<i>Parasternal long axis</i>
<i>PMA</i> .....	<i>Postmenstrual age</i>
<i>PNA</i> .....	<i>Postnatal age</i>
<i>PPHN</i> .....	<i>Persistent pulmonary hypertension of the newborn</i>

## *List of Abbreviations (cont...)*

Abb.	Full term
<i>PROM</i> .....	<i>Premature rupture of membranes</i>
<i>PSAX</i> .....	<i>Parasternal short axis</i>
<i>PVL</i> .....	<i>Periventricular leukomalacia</i>
<i>PVR</i> .....	<i>Pulmonary vascular resistance</i>
<i>PW</i> .....	<i>Pulsed-wave mode of Spectral Doppler</i>
<i>QS</i> .....	<i>Quiet sleep</i>
<i>RA</i> .....	<i>Right atrium</i>
<i>RAP</i> .....	<i>Right atrial pressure</i>
<i>RDS</i> .....	<i>Respiratory distress syndrome</i>
<i>ROC</i> .....	<i>Receiver operating characteristic curve</i>
<i>ROS</i> .....	<i>Reactive oxygen species</i>
<i>RPA</i> .....	<i>Right pulmonary artery</i>
<i>rSO2</i> .....	<i>Regional tissue oxygenation</i>
<i>RSVP</i> .....	<i>Right ventricular systolic pressure</i>
<i>RV</i> .....	<i>Right ventricle</i>
<i>RVO</i> .....	<i>Right ventricular output</i>
<i>RVSP</i> .....	<i>Right ventricular systolic pressure</i>
<i>SaO2</i> .....	<i>Arterial oxygen saturation</i>
<i>SBF</i> .....	<i>Systemic blood flow</i>
<i>SD</i> .....	<i>Standard deviation</i>
<i>sGC</i> .....	<i>Soluble guanylate cyclase</i>
<i>SIMV</i> .....	<i>Synchronized intermittent mandatory ventilation</i>
<i>SNAP II</i> .....	<i>Scoring for acute neonatal physiology</i>
<i>SVC</i> .....	<i>Superior vena cava</i>
<i>SVO2</i> .....	<i>Venous oxygen saturation</i>
<i>SVR</i> .....	<i>Systemic vascular resistance</i>
<i>SWC</i> .....	<i>Sleep-wake cycling</i>
<i>TI</i> .....	<i>Inspiratory time</i>
<i>TTN</i> .....	<i>Transient tachypnea of newborn</i>
<i>TR</i> .....	<i>Tricuspid regurgitation</i>
<i>TV</i> .....	<i>Tidal volume</i>
<i>Tv</i> .....	<i>Tricuspid valve</i>
<i>v</i> .....	<i>Blood velocity</i>

## *List of Abbreviations (cont...)*

Abb.	Full term
<i>Vmax</i> .....	<i>Peak velocity</i>
<i>Vmax TR</i> .....	<i>Peak velocity of tricuspid regurgitation jet</i>
<i>VO2</i> .....	<i>Oxygen consumption</i>
<i>VO2/DO2</i> ...	<i>Oxygen extraction ratio</i>
<i>V/Q</i> .....	<i>Ventilation / perfusion</i>
<i>VTI</i> .....	<i>Velocity time integral</i>
<i>W/AS</i> .....	<i>Wakefulness / active sleep</i>
<i>WMI</i> .....	<i>White Matter Injury</i>
<i>WBC</i> .....	<i>White blood cell</i>

## ABSTRACT

**Background:** Amplitude-integrated electroencephalography (aEEG) has been used in clinical research to study the relationship between changes in neonatal cardiovascular function and brain activity.

**Aim of the Work:** To evaluate the impact of cardiovascular compromise on cerebral cortical activity (aEEG measurements) in non-asphyxiated neonates with persistent pulmonary hypertension of newborn (PPHN) or those with shock and hypotension and to identify neonates at risk for neurologic compromise and the relevance of an abnormal aEEG trace to associated hemodynamic changes, therapeutic interventions and short-term clinical outcome measures in these neonates.

**Study design:** Fifty critically-ill neonates (30-38 weeks' gestation) with cardiovascular compromise; septic shock and hypotension (n=20), persistent pulmonary hypertension of newborn (PPHN) (n=5), or both (n=25), were enrolled into a prospective observational cohort study. All newborns were subjected to thorough history taking and clinical examination. SNAP II scoring and cardiorespiratory therapeutic interventions were recorded. Serum lactate and neuron specific enolase (NSE) levels were measured at enrollment. Functional echocardiographic evaluation and aEEG monitoring were commenced within the first 24 hours of enrollment and repeated 48-72 hours from weaned inotropic support (n=38), with follow-up of the patients to report their final outcome.

**Results:** Total aEEG scores were significantly lower among neonates with severe SNAP II score as compared to those with mild and moderate scores ( $p = 0.021$ ). Initial superior vena cava (SVC) flow, right ventricular output (RVO) values and total aEEG scores were significantly lower ( $p=0.000$ ,  $p=0.000$ ,  $p<0.001$  respectively) in comparison to their corresponding follow-up records. Survivors (n=27) had significantly higher aEEG scores at initial and follow up assessment ( $p=0.002$  &  $p=0.000$ ) and significantly lower serum lactate and NSE levels ( $p=0.000$  respectively), as compared to non-survivors. A significant positive correlation was found between total aEEG score and mean arterial blood pressure ( $r=0.504$ ,  $p=0.000$ ) at initial assessment, meanwhile, follow-up aEEG total scores were inversely correlated with both serum lactate and NSE levels ( $r=-0.455$  &  $p=0.004$ ) and ( $r = -0.488$  &  $p = 0.002$ ) respectively. Logistic regression analysis revealed that serum lactate level of  $> 34.3$  mg/dl was a significantly high risk factor of mortality prediction with odds ratio (95% CI) of 44.00 (5.085 - 380.71),  $p = 0.001$ . ROC curve analysis showed NSE at cutoff value  $> 50$  ng/ml has 83.3% PPV, 88.5% NPV, 86.96% sensitivity and 85.19% specificity for mortality prediction.

**Conclusion:** Significant derangement of brain electrical activity is encountered in critically-ill neonates with cardiovascular compromise. It could be speculated that aEEG monitoring of these neonates might help to predict their short-term clinical outcomes.

**Keywords:** neonatal shock; PPHN; functional echocardiography; amplitude-integrated electroencephalography (aEEG).