11 October 2013

Companies Announcement Office
ASX Limited
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Sydney, NSW 2000

Cortical Dynamics Ltd – Cortical Dynamics Presents Results of Clinical Trial at Anesthesiology 2013 in San Francisco

Please find attached an operational update from BPH Energy Ltd (**ASX: BPH**) investee company Cortical Dynamics Ltd.

Yours sincerely,

Deborah Ambrosini
Director and Company Secretary

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11 October 2013

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Cortical Dynamics Presents Results of Clinical Trial at Anesthesiology 2013 – San Francisco

Cortical Dynamics Ltd ("**Cortical**") will be presenting the Brain Anesthesia Response ("**BAR**") monitor's previously announced clinical trial results at the American Society of Anesthesiologists annual meeting in San Francisco (ANESTHESIOLOGY 2013) incorporating recent further analyses of the clinical data.

The trial conducted at St Vincent's Hospital in Melbourne was a 25 person product validation designed to evaluate the BAR monitor's ability to distinguish between two different doses of the widely used intravenous analgesic fentanyl, in addition to assessing the immunity of the BAR monitor to a range of intra-operative mechanical and electrical artifacts known to complicate the EEG measurement of anaesthetic action.

The presentation entitled, 'The Brain Anaesthesia Response Monitor During Cardiac Surgery: A Double-Blind RCT With Fentanyl' will be presented by Cortical's principle scientist, Dr Mehrnaz Shoushtarian. The presentation is scheduled to occur on Sunday 13th October 2013 from 8:00 am to 9:30 am Pacific Standard time.

About the BAR Monitor

The BAR monitoring system measures a patient's brain electrical activity, the electroencephalogram (EEG), in order to indicate how deeply anaesthetised a patient is during an operation via an adhesive sensor applied to the forehead. The BAR monitor is designed to assist anaesthetists and intensive care staff in ensuring patients do not wake unexpectedly, as well as reducing the incidence of side effects associated with the anaesthetic.

The BAR monitor improves on currently used EEG monitors by utilising advances in understanding of how the brain's electrical activity is produced, and how it is affected by anaesthetic and sedative drugs. The BAR's unique physiological approach is aimed at independently monitoring the hypnotic and analgesic states associated with anaesthesia, a feature no known existing EEG based depth-of-anaesthesia monitor is able to achieve. Objectively monitoring of hypnotic and analgesic state may lead to improved anaesthetic and surgical outcomes, by reducing recovery times and minimising drug costs.

In 2012 Cortical completed its first human clinical trial using the BAR monitoring system which was conducted at St Vincent's Hospital, Melbourne.

Cortical has developed an extensive patent portfolio encapsulating the BAR monitoring system and its physiologically based algorithms, with a total of thirteen patents granted throughout Australia, New Zealand, the United States, Japan and the People's Republic of China.

About Cortical Dynamics

Cortical Dynamics Ltd is a medical technology company that was established in 2004 to commercialise intellectual property relating to brain function monitoring developed by Professor David Liley and his scientific team at Melbourne's Swinburne University of Technology.

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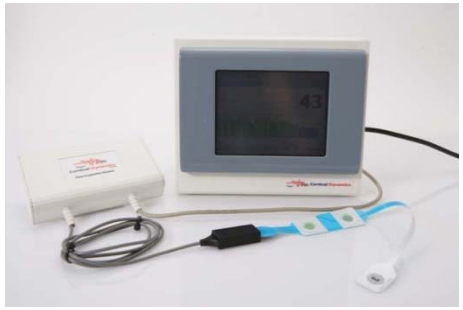
The Brain Anaesthesia Response Monitor During Cardiac Surgery: a Double-Blind RCT with Fentanyl

Mehrnaz Shoushtarian, Desmond P McGlade, Louis Delacretaz, David TJ Liley

Cortical Dynamics Ltd, Perth, Australia
St. Vincent's Hospital, Melbourne, Australia



Disclosure

- This study was supported by funding from Cortical Dynamics Ltd.

- Mehrnaz Shoushtarian, Louis Delacretaz and David Liley are employed by Cortical Dynamics Ltd., Australia.

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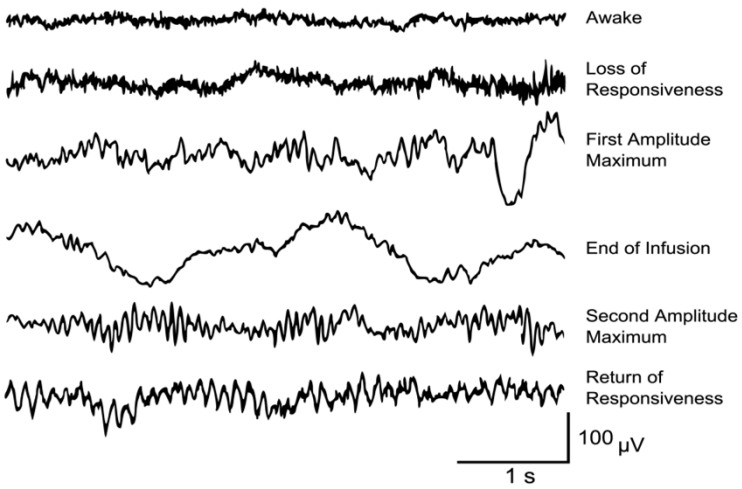
Introduction



Kuizenga et al. (1998), Br. J. Anaesth.

- All current EEG based depth of anaesthesia monitors use QEEG, MLAEP, or a combination, to select features which best correlate with clinical endpoints
- All current measures are heuristically derived

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BAR Monitor

Liley Model

$$\tau\,\partial h(r,t+\xi)/\partial t \;=\; -h(r,t+\xi)+\Psi(h)I(r,t)$$

Passive electrical properties
and reversal potentials

$$(\mathrm{I}\partial/\partial t+\gamma)^2 I(r,t) \;=\; \gamma\Gamma\{N^{\beta}S(h)+\phi(r,t)+p(r,t)\}$$

Transmitter kinetics, intra-cortical
connectivity and cable delays

$$\{(\mathrm{I}\partial/\partial t+v\Lambda)^2-\frac{3}{2}v^2\nabla^2\}\phi(r,t) \;=\; N^{\alpha}v^2\Lambda^2 S_e(h_e)$$

Conduction delays and
cortico-cortical connectivity

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BAR Monitor

Liley Model

	Definition	Units
h_k^r	resting membrane potential	mV
τ_k	passive membrane decay time	ms
h_{ek}^{eq}	excitatory reversal potential	mV
h_{ik}^{eq}	inhibitory reversal potential	mV
Γ_{ek}	EPSP peak amplitude	mV
Γ_{ik}	IPSP peak amplitude	mV
$1/\gamma_{ek}$	EPSP rise time to peak	ms
$1/\gamma_{ik}\,(1/\gamma_{ik}^0)$	IPSP rise time to peak (at c = 0)	ms
N_{ek}^{α}	no. of excitatory cortico-cortical synapses	–
N_{ek}^{β}	no. of excitatory intracortical synapses	–
N_{ik}^{β}	no. of inhibitory intracortical synapses	–
v_{ek}	axonal conduction velocity	$\frac{\mathrm{mm}}{\mathrm{ms}}$
$1/\Lambda_{ek}$	decay scale of cortico-cortical connectivity	mm
$S_k^{\max}$	maximum firing rate	ms^{-1}
μ_k	firing threshold	mV
σ_k	standard deviation of firing threshold	mV
p_{ek}	extracortical synaptic input rate	ms^{-1}
c	aqueous isoflurane concentration	mM

BAR Monitor

Liley Model

established physiological principles

↓

full non-linear theory of EEG

↓

linear approximation (transfer function)

↓

(8,5)-ARMA time series model

- Cortical State (CS): Resonant state of cortex
- Cortical Input (CI): Input to cortex

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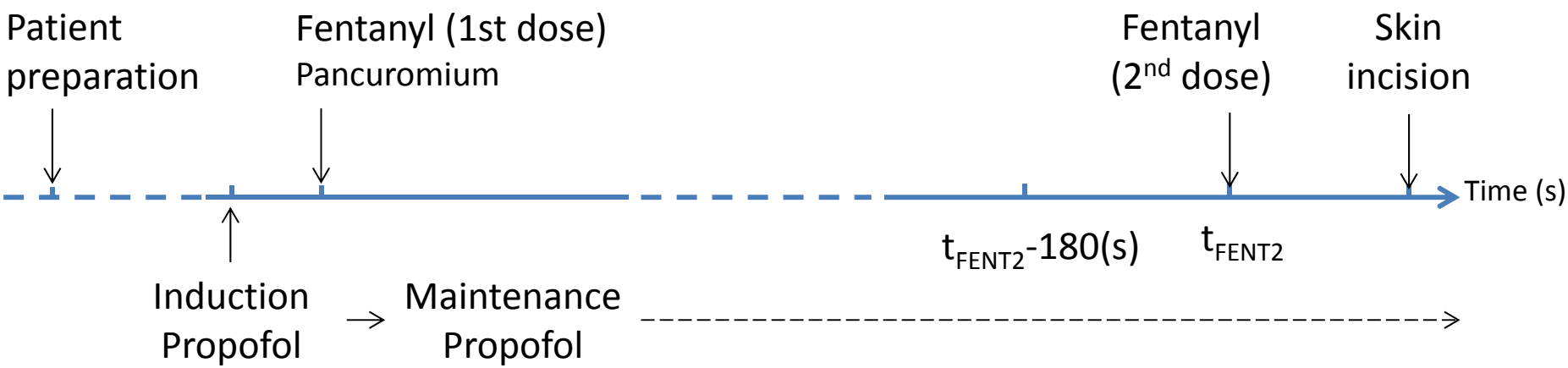
Hypotheses

- CI would differentiate between two patient groups receiving different doses of fentanyl
- In the presence of propofol, CS would correlate well with the Bispectral Index (BIS™)

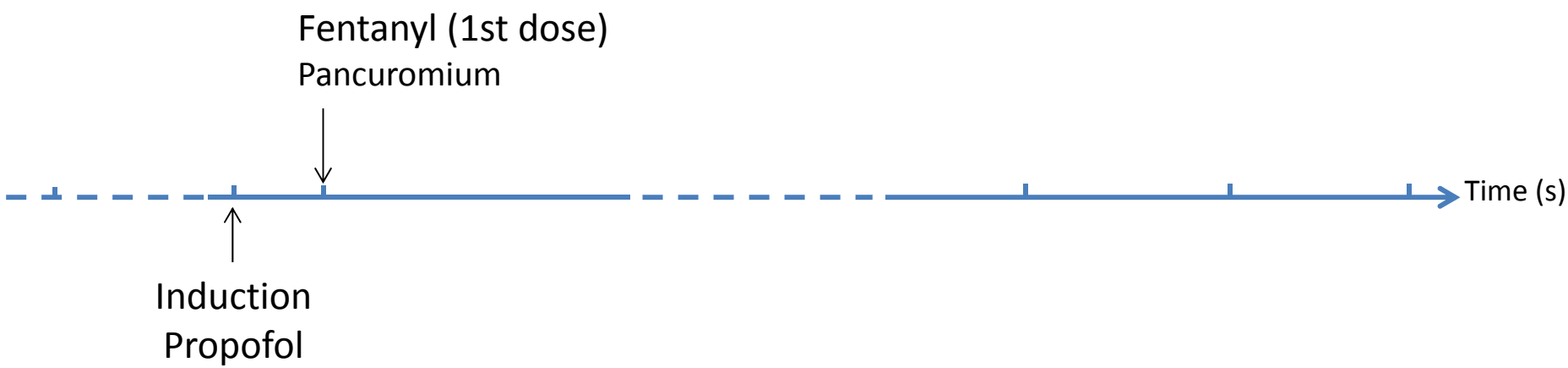
Methods

Recruitment and Randomisation	25 patients primary CABG low risk factors Fentanyl Low Dose 12 μg/kg total (8 μg/kg + 4 μg/kg) Fentanyl Moderate Dose 24 μg/kg total (16 μg/kg + 8 μg/kg)
Premedication **Preoperative Preparation**	Lorazepam 2 mg, Oxycontin 10 mg BAR and BIS Sensors applied IV, Arterial and Pulmonary Artery Catheters inserted Midazolam 0.5 mg to maintain OAA/S 4 (mild sedation only)
Induction and Maintenance	Propofol 1 mg/kg over 60 seconds then 6 mg/kg/h, titrated to BIS 40-60
Following Induction →	Fentanyl Dose 1, Pancuronium 0.12 mg/kg; intubate after 3 minutes
Prior to Skin Incision →	Fentanyl Dose 2
Haemodynamic Management	Vasoactive agents used to maintain SBP 100-140 mmHg and HR 45-90

Methods


Patient preparation
Fentanyl (1st dose)
Pancuromium
Fentanyl (2nd dose)
Skin incision
Time (s)
t_{FENT2}-180(s)
t_{FENT2}
Induction Propofol
Maintenance Propofol

Methods



- Correlations between BIS and CS following induction

Methods

- Relative difference in BIS, CI and CS at time of skin incision and 3 minutes before calculated

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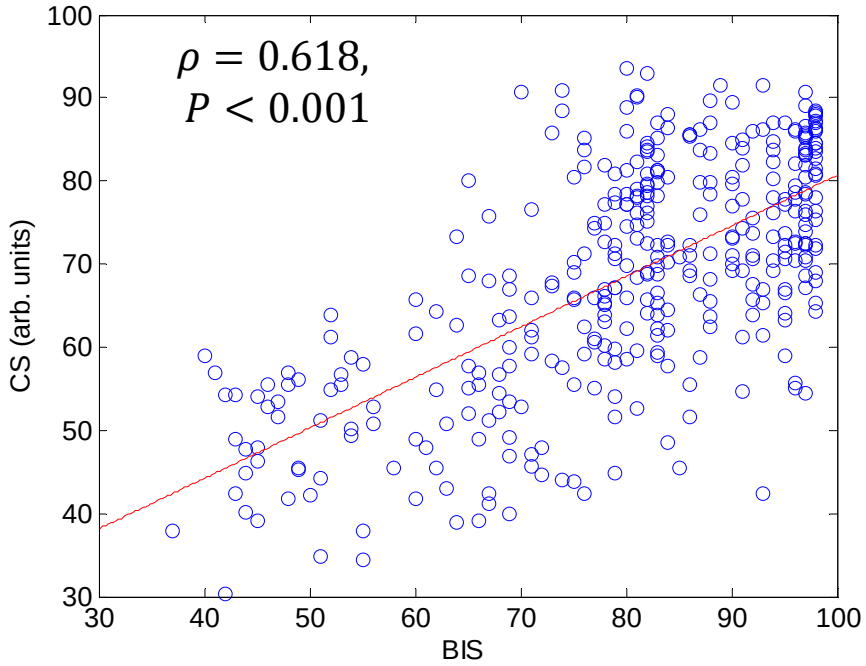
Results

- Following induction, a significant correlation between CS and BIS was found.
- Prediction probability:
  P_k = 0.721, SE = 0.014



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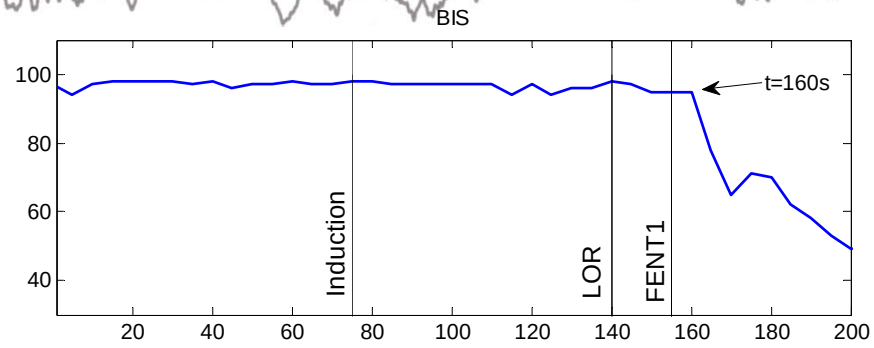
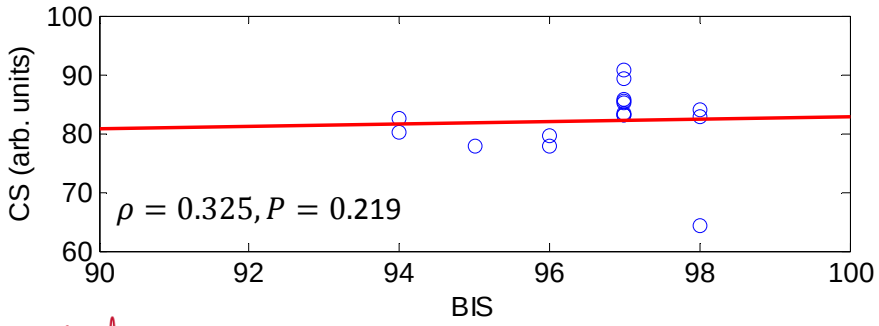
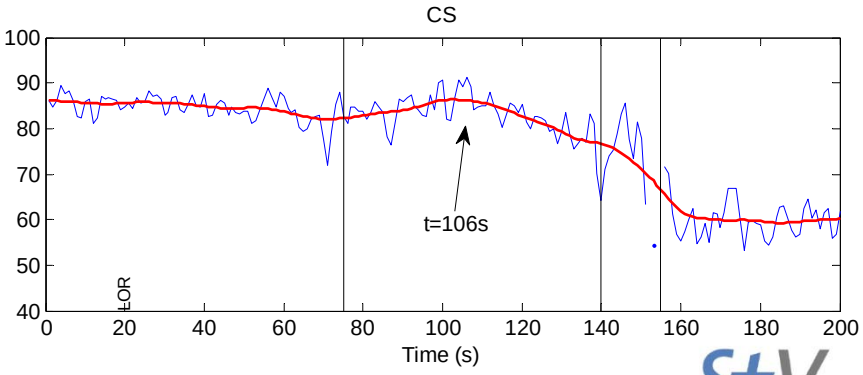
Results







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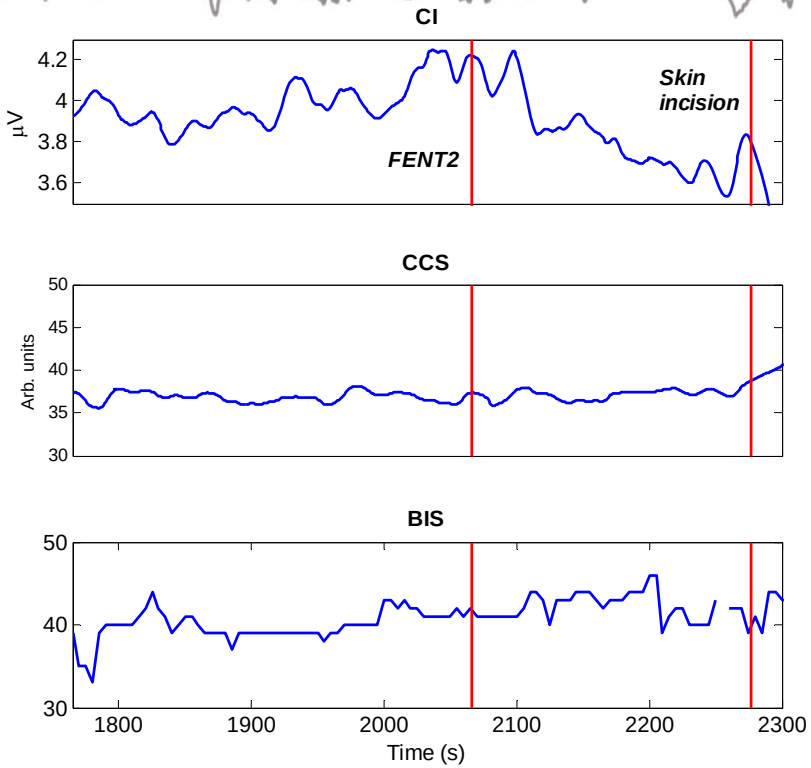
Results



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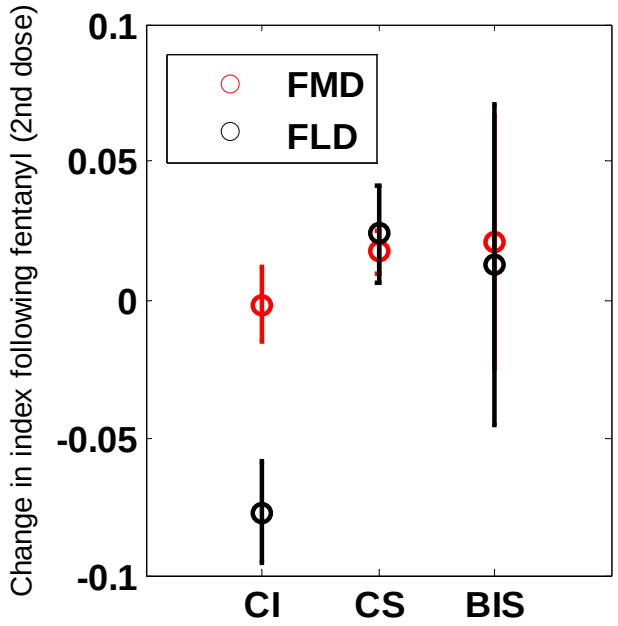
Results

- The relative change in CI was greater in the FLD group compared with the FMD group ($F(1, 18) = 10.7$, $P = .004$).
- BIS and CS showed no significant difference between the groups.



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Conclusion

- The fall in CS following anaesthesia induction with propofol showed significant correlation with BIS and is indicative of its utility as a monitor of hypnosis.
- The ability of the CI index to differentiate the two study groups according to fentanyl dose indicates that the BAR Monitor may be useful in the titration of intraoperative opioid analgesic agents.