

Novel Drug Delivery Systems in Anaesthesiology

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Children's Hospital
SingHealth

Disclosure

- Received Medical Technology related grants
- Singhealth Foundation Grant (Transitional Award) (DIVA)
- **NMRC** Clinical Trials Grant (Late Phase) (EPIVA)
- **NHIC** I2D Grant (INTRAVA morphine)
- Singhealth Foundation Grant (Transitional Award) (INTRAVA remifentanil) (Mentor)

- **NMRC** Transition Award
- Khoo Student Research Award
- JOAM Medical Student Research Award

- No patent or financial disclosures

Spinal Anaesthesia for Caesarean Section

- Caesarean section is one of the most common surgical procedures
- Spinal anaesthesia is now widely used
- **Hypotension** due to sympathetic blockade
- Defined as BP <80% baseline systolic BP
- Occurs in up to 70% of patients



Effects of Hypotension

- Mother
 - Nausea and vomiting
 - Altered consciousness
 - Cardiovascular collapse
- Fetal
 - Fetal acidosis
 - Lower umbilical cord pH
 - Hypoxemia



Various strategies have been attempted..

- Left uterine displacement to prevent aortocaval compression
- Intravenous fluid administration
- **Vasopressor** therapy (phenylephrine, ephedrine)
- **Close monitoring** of maternal blood pressure and haemodynamics
- **No strategy has been shown to totally eliminate occurrence of maternal hypotension**



Choice of Vasopressors

- Short acting vasopressors
- Bolus administration used in our centre

Phenylephrine
Increase BP
Decrease heart rate



Low BP with normal heart rate

Ephedrine
Increase BP
Increase heart rate



Low BP with low heart rate

Blood Pressure Monitoring

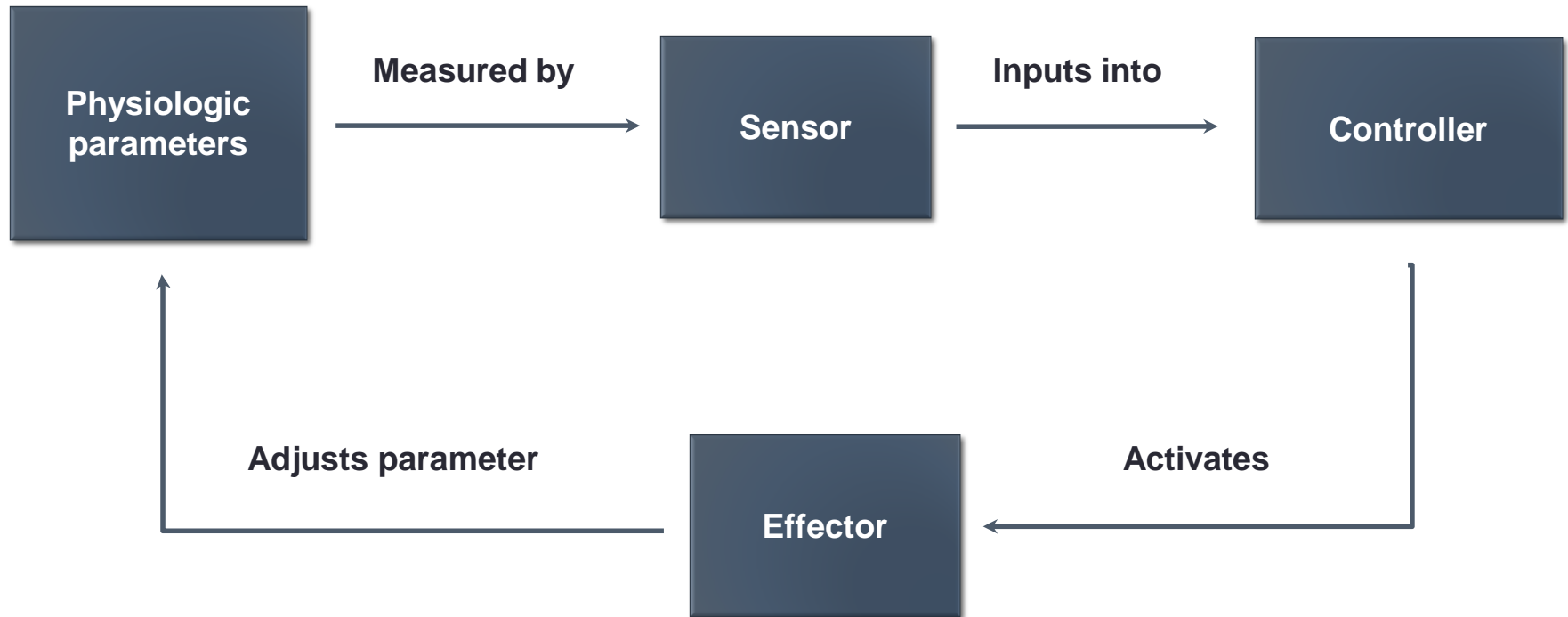
- Current standard is using intermittent BP monitoring
- **Non-invasive continuous** arterial pressure monitoring (CNAP)
- **Aim to reduce lag time** between detecting hypotension and administering vasopressor
- **Aim to maintain BP** near baseline systolic BP level

Challenge for Anesthetists

- Maintain BP within **tight limits**
- **Handling rapid changes** in physiological responses to spinal anaesthesia
- Effectiveness of therapy depends on
 - Continuous monitoring
 - Timely intervention



Our Solution – Closed Loop Feedback System



Less Medications

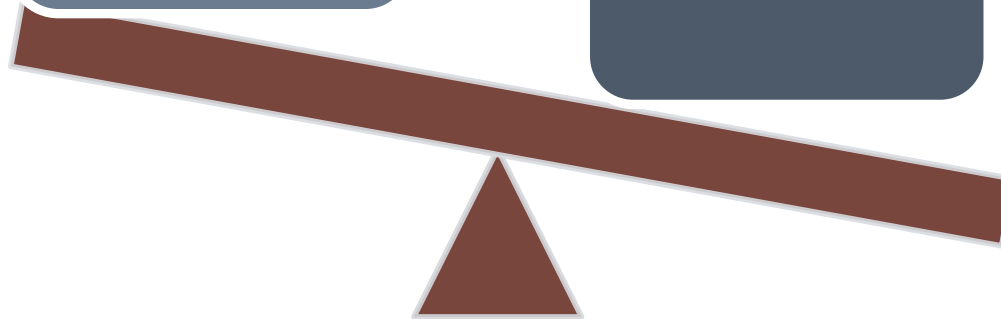
Maternal side effects

Fetal side effects

More Medications

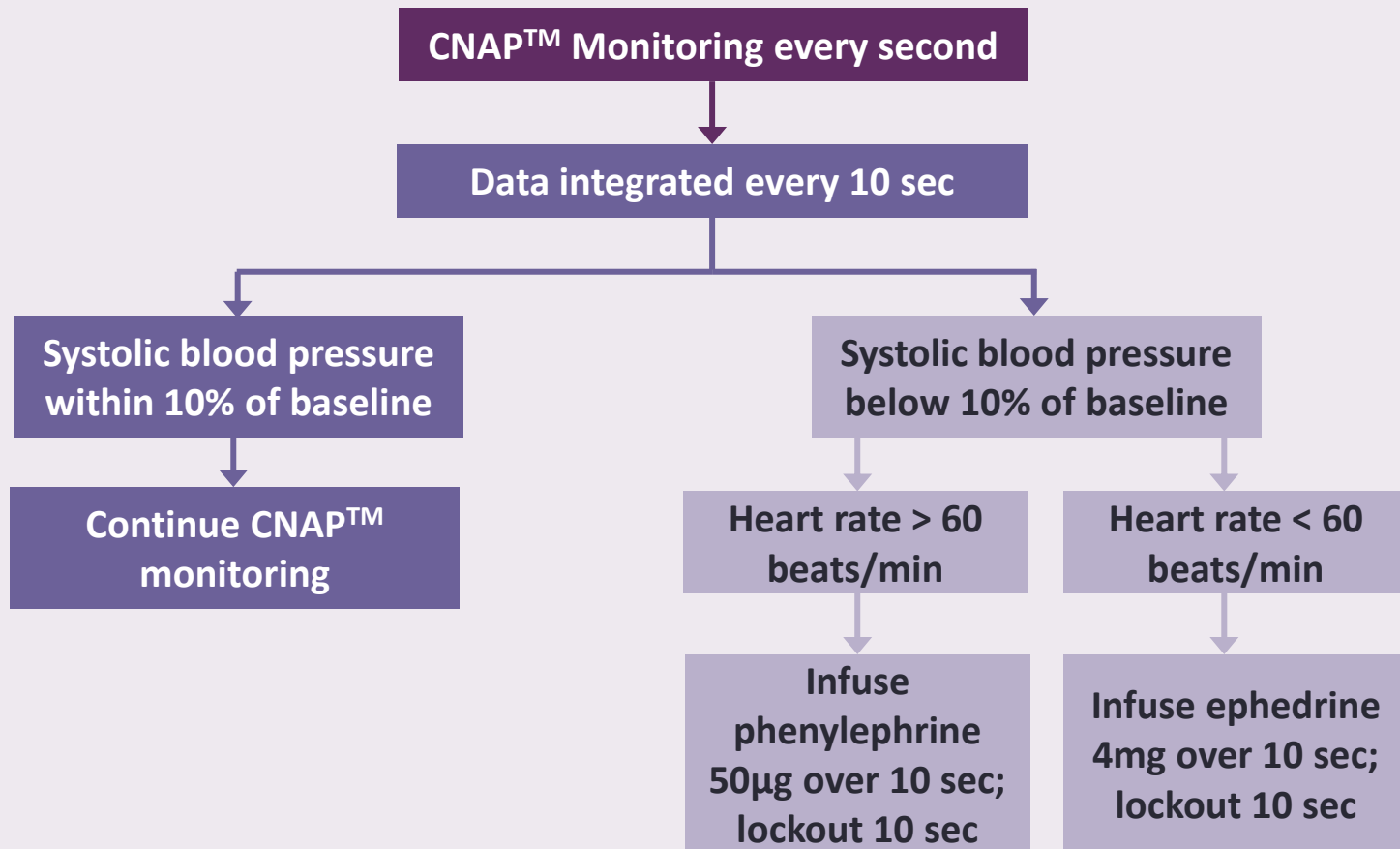
Hypertensive response

Headache

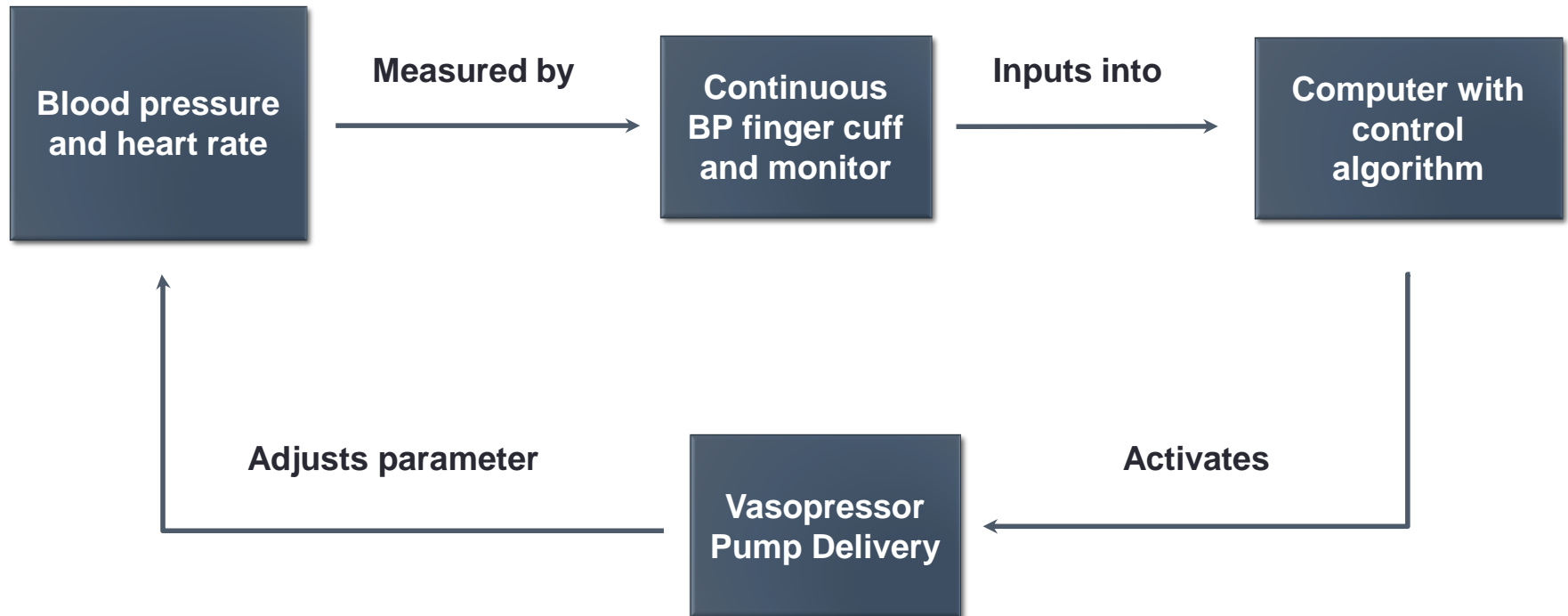


The Control Algorithm

- Basic on-off algorithm
- Dual vasopressors used (phenylephrine, ephedrine)



Our Solution – Double Intravenous Vasopressor Automated (DIVA) system



Prototype of DIVA

World's first automated blood pressure management system to enhance patient safety during c-section

CNAP
Vital signs
monitor

Phenylephrine

Ephedrine

Algorithm (laptop)



KKH anaesthetist demonstrates the use of the DIVA System in managing a patient's blood pressure during caesarean section under spinal anaesthesia

RCT

- Double blinded RCT comparing
 - Manual bolus delivery (Control)
 - DIVA system (Experiment)

	Control	Experiment
Haemodynamic monitoring	Every minute	Continuous
Vasopressor threshold	SBP below 90% baseline	Same as control
Dosing regime	50µg phenylephrine or 4mg ephedrine	Same as control
Mode of delivery	Manual bolus	DIVA bolus



Lower Incidence of Hypotension and Nausea

Parameter	Experiment	Control	<i>p</i>
Number of patients with Hypertension	8 (7.6%)	14 (13.1%)	0.260
Number of patients with Hypotension	37 (34.9%)	63 (58.9%)	0.001
Incidence of Nausea	1 (0.9%)	11 (10.2%)	0.005
Incidence of Vomiting	0 (0.0%)	3 (2.8%)	0.246

Neonatal Outcomes are Comparable

Parameter	Experiment	Control	<i>p</i>
pH difference (umbilical artery – vein)	0.0715 [0.057 to 0.095]	0.0770 [0.048 to 0.097]	0.813
Lactate difference (umbilical artery – vein)	0.3400 [0.060 to 0.620]	0.3900 [0.073 to 0.783]	0.389
APGAR score at 1 minute	9 [9 to 9]	9 [9 to 9]	0.991
APGAR score at 5 minute	9 [9 to 9]	9 [9 to 9]	1.000
Neonatal birthweight (g)	3204 (400)	3166 (415)	0.501

Better Accuracy of DIVA to Maintain Baseline SBP

Parameter	Experiment	Control	<i>p</i>
Median absolute performance error (MDAPE) (%)	8.7	9.8	0.013
Median performance error (MDPE) (%)	-5.4	-5.2	0.264
Wobble (%)	6.2	6.4	0.684

DIVA Conclusions

- **Lower incidence of hypotension**
- **Lower incidence of maternal nausea**
- Similar incidence of reactive hypertension
- Similar good neonatal outcomes
- **DIVA maintains systolic BP closer to baseline with higher accuracy**
- Enables anaesthetist to focus on other patient's needs

DIVA system research

竹脚医院新研发 剖腹产妇血压测量有望更精准



这套双静脉血压协调自动化系统相信是世界首创，可以连续每秒测量产妇血压和心跳，每15秒整合数据，一旦发现血压或心跳低于一定水平，会自动为产妇注射药物。

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剖腹产子使用的局部麻醉药会导致一些产妇血压骤降，必须注射药物恢复血压。不过，目前人工监控和注射过程不够及时精准。干嘉木坡医院设计出相信是世界首创的自动测量和注射系统。

竹脚医院设计的这套双静脉血压协调自动化系统（Double Intravenous Vasopressor Automated System，简称DIVA）是医院自行开发的计算机程序，可连续每秒测量产妇血压和心跳。每15秒整合数据，一旦发现血压或心跳低于一定水平，会自动为产妇注射药物。

如果产妇收缩血压（即数值较高的血压）比本身的基础血压（baseline pressure）低超过10%，自见心跳速率于每分钟60下或以上的正常值，系统会自动通过针管从双静脉注射止血升血压素（phenylephrine，或称爱德林）来提升血压。如果低血压的同时心跳低于每分钟60下，系

统则会自动注射可同时提升血压和心跳的麻黄素（ephedrine）。

约六成剖腹产产妇生产时出现低血压

这个系统还在该注射时间15秒，药物注射后等30秒，待血压和心跳恢复正常。

妇科麻醉科顾问医生孙丹良说，文献显示，大约六成剖腹产产妇在生产时会出现低血压。这导致产妇心脏停跳，严重的还会影响供给胎儿的血量输送。

造成低血压的原因并不是因为产妇失血过多，而是剖腹产常用的脊髓麻醉（spinal anaesthesia）均具有收缩血管的作用，导致回心血量锐减，血压因此骤降。

跟自然分娩经常选用的硬膜外（epidural）麻醉一样，脊髓麻醉也是局部麻醉。不同的是，脊髓麻醉是将少量麻醉药用针注入椎管外的液体，阻止疼痛讯号传递，而硬膜外麻醉是将量较多的麻醉药注入椎管外。通过导管注入延长药效。

孙丹良指出，剖腹产手术一般在一小时完成，因此麻醉药效更快，产出出现低血压风险也比自然分娩高。

竹脚医院是本地最大的妇产专科医院，每天接生30至35名宝宝，其中约三成是透过剖腹产接生。

孙丹良说，目前做法是由一名麻醉师在生产时随时待命，不过她指出，还差控制产妇血压并垂直注射升压药，而目前的仪器只能每分钟测一次血压，不比每秒测量来得精准。

这套双静脉血压协调自动化系统有两支针管，如果产妇血压骤降，装有去氧肾上腺素的针管（上方）能自动给产妇注射。一旦血压和心跳速度都低，装有麻黄素的针管（下方）则自动注射。其独创之处是将各环节整合成一套自动化系统。（陈国庄摄）

Straits Times Interactive Online
29 Apr 2013

KKH designs automated system to monitor blood pressure during C-sections

Published on
Apr 29, 2013
6:20 PM



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NEWS POST



Dr Sng Ban Leong, consultant at the Department of Women's Anaesthesia, presents the Double Intravenous Vasopressor Automated System. KK Women's and Children's Hospital have designed the automated blood pressure management system to enhance patient safety during Cesarean procedures. — ST PHOTO: RACHEL TAN

A Diva to manage mum's blood pressure

KKH docs develop automatic system for use during caesarean births

By RACHEL TAN

AN AUTOMATIC system to manage blood pressure in mothers going through caesarean births has been developed by doctors at a Singapore hospital, in what they say is a world first.

The Double Intravenous Vasopressor Automated System - or Diva - is still in development stage, but doctors at the KK Women's and Children's Hospital (KKH) hope it will lead to safer caesarean sections.

About 30 per cent of patients at the hospital, which delivers 30 to 35 babies every day, undergo caesarean births.

Not only does Diva allow hands-off and more accurate blood pressure and heart rate monitoring, but - through a computer programme - it also delivers the precise amount of medication needed to stabilise the patient more quickly.

"The baby's blood pressure and oxygen supply is very dependent on the mother's blood pressure, so it's important to regulate it," said Dr Sng Ban Leong, a consultant at KKH's Department of Women's Anaesthesia.

Up to 60 per cent of expectant mothers experience low blood pressure under spinal anaesthesia. This could cause pre-delivery nausea and, in more severe cases, it reduces blood flow to the placenta - harming the baby.

Until the development of Diva, managing blood pressure levels required an anaesthetist to manually administer vasopressors, which raise blood pressure by constricting blood vessels.

Now, blood pressure and heart rate data can be sent to a laptop from two finger cuffs worn by the patient, and a programme will determine the dosage of vasopressor needed.

The speed at which it reacts is faster than conventional monitoring, which occurs at 60-second intervals and could delay the detection of rapid changes in blood pressure.

Diva also frees up the anaesthetist to do other things.

"With this automated close-loop system, the anaesthetist is able to focus on more important aspects of patient care - to deliver more holistic patient care," said Professor Alex Sia, chairman of the medical board and director of KK Research Centre.

A 2011 study, jointly carried out by KKH and Duke-NUS Graduate Medical School and involving 55 women, showed that the Diva system was more efficient than conventional methods at maintaining blood pressure during caesarean sections under spinal anaesthesia.

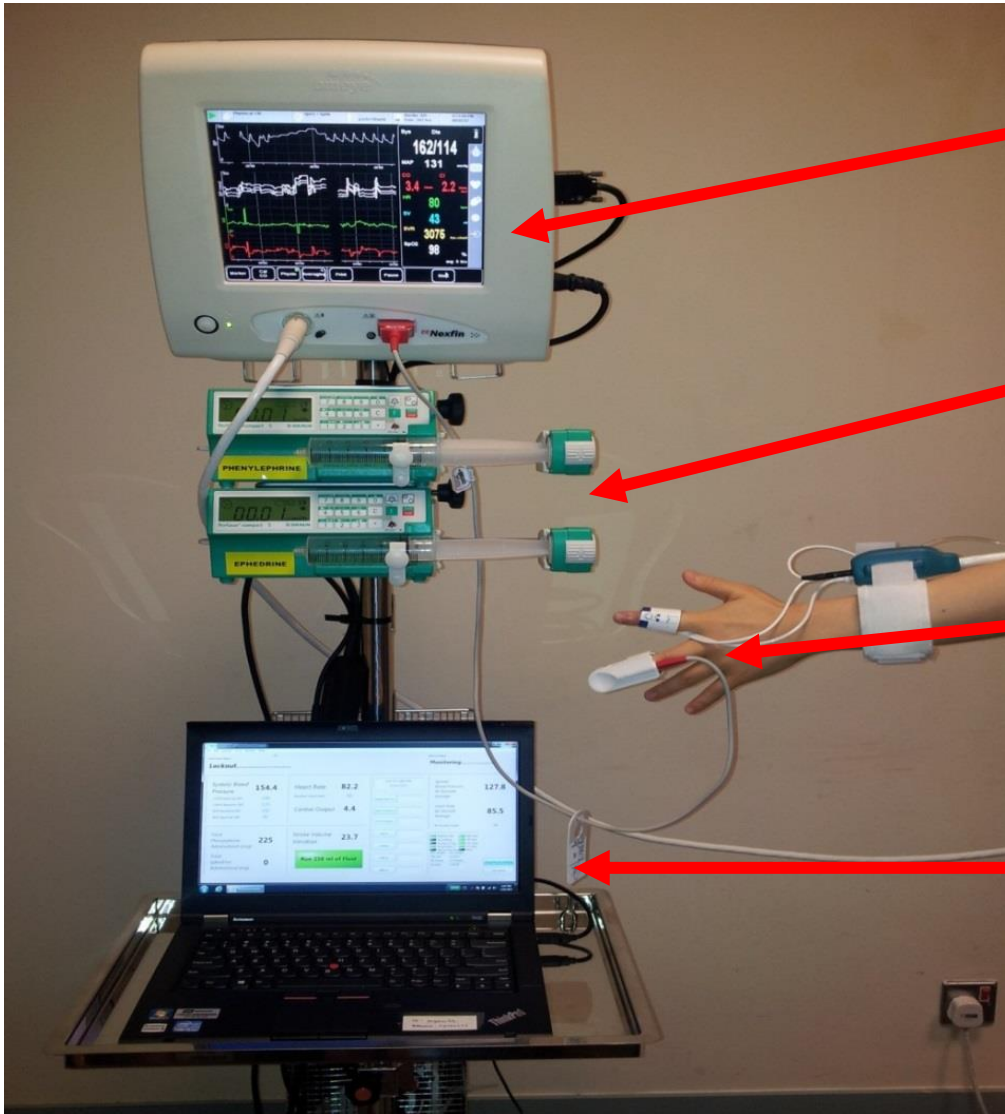
KKH, however, could not give a timeframe as when Diva will come into operation.

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Moving Forward – DIVA 2.0

- Previous study uses on-off algorithm - unable to titrate vasopressor to the severity of hypotension
- **Modified 2-Step algorithm to be responsive to the severity of hypotension**
 - 90 to 100% of baseline SBP → 25mcg phenylephrine
 - below 90% of baseline SBP → 50mcg phenylephrine
- Blood pressure is not the only determinant of tissue perfusion
- **Continuous non-invasive cardiac output monitor (Nexfin)**

DIVA 2.0 Setup



Nexfin cardiac
output monitor

Vasopressor
delivery

Finger cuff

Algorithm
(laptop)

DIVA 2.0 Pilot Study

- Modified DIVA system maintains systolic BP closer to baseline
- Minimal intervention from the attending anaesthetist
- Good clinical maternal and fetal outcomes

Anaesthesia 2015, 70, 691-698

doi:10.1111/anae.13008

Original Article

Assessment of an updated double-vasopressor automated system using Nexfin™ for the maintenance of haemodynamic stability to improve peri-operative outcome during spinal anaesthesia for caesarean section

B. L. Sng,^{1,2} H. Wang,³ P. N. Assam^{4,5} and A. T. Sia^{1,6,7}

Drug Delivery Systems for Labour Pain



Labour Epidural
Analgesia

Intravenous
Remifentanil
Patient Controlled
Analgesia (PCA)



Decrease Patient Demands
Less Medications

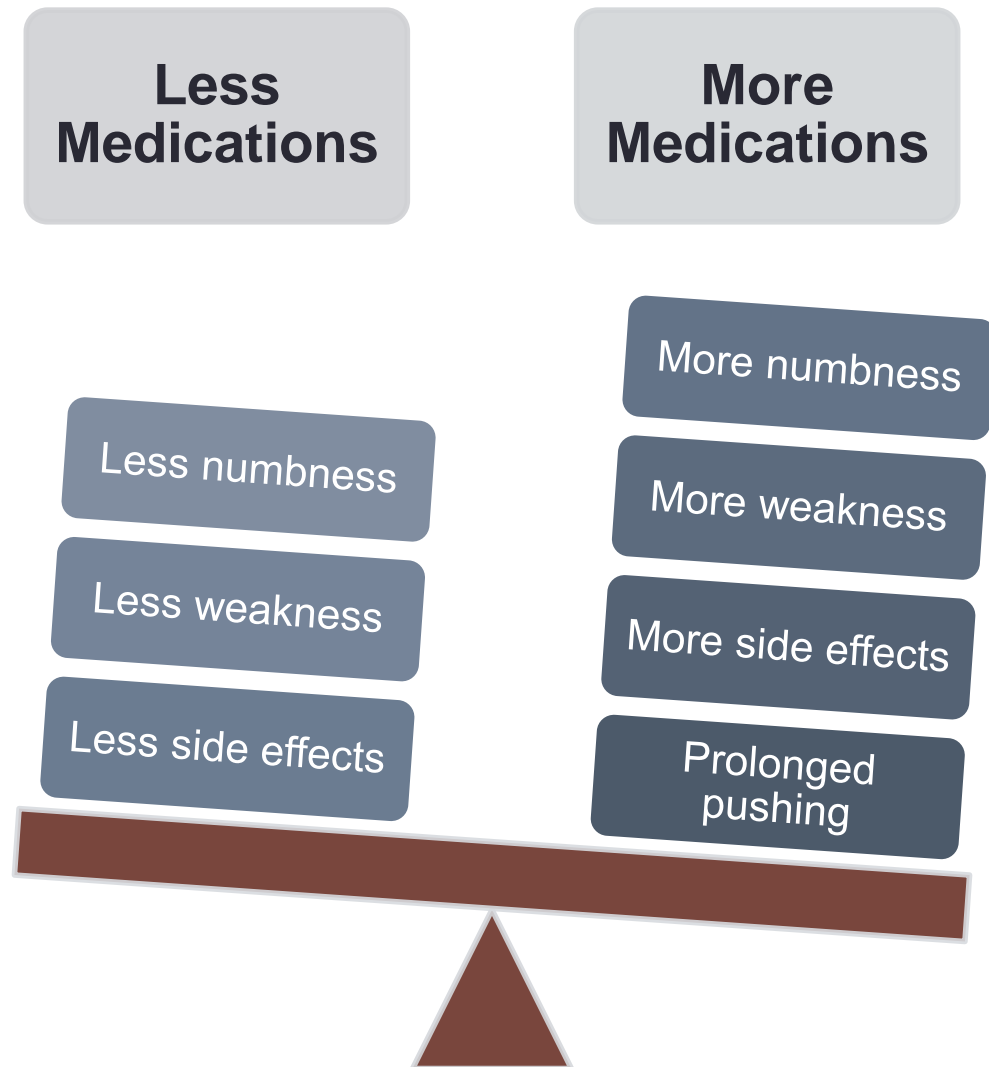
Increase Patient Demands
More Medications

EARLY LABOUR

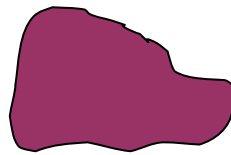
LATE LABOUR

Personalised Titration of Medications

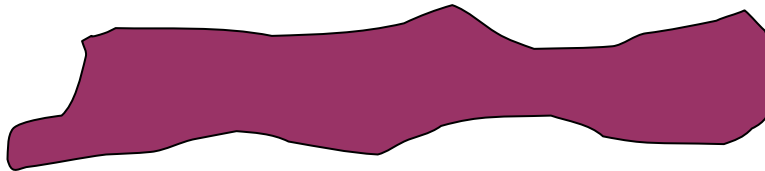
Labour Epidural Analgesia



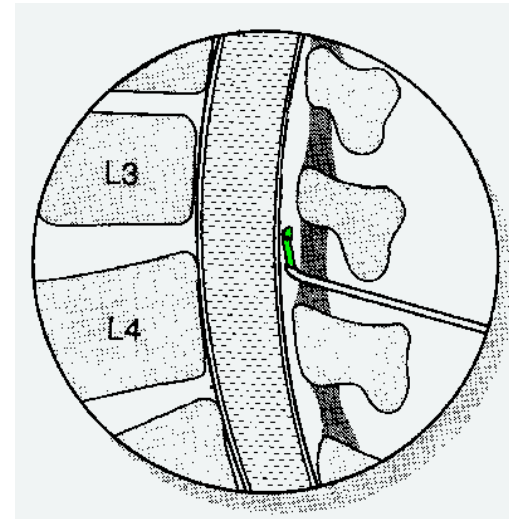
Spread in Epidural Space



**Continuous
infusion**



Automated Bolus



EPIVA Epidural Pump

KKH testing new way to reduce pain in childbirth



The smart pump aims to reduce "breakthrough pain" - which occurs when a dose of epidural loses its efficacy and a patient feels pain while waiting for the next dose - by tracking how often patients press a button to release more doses. PHOTO: KK WOMEN'S AND CHILDREN'S HOSPITAL

Intravenous Remifentanyl PCA

Less Medications

More Medications

More labour pain

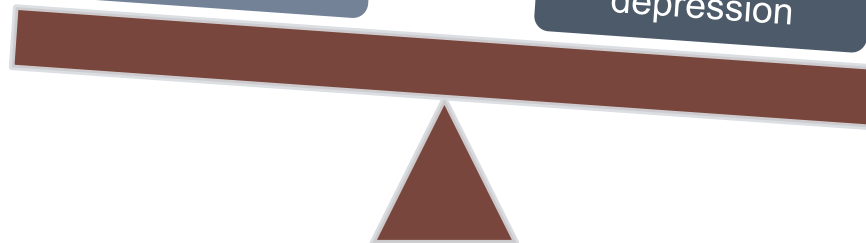
More hypertensive responses

More pain relief

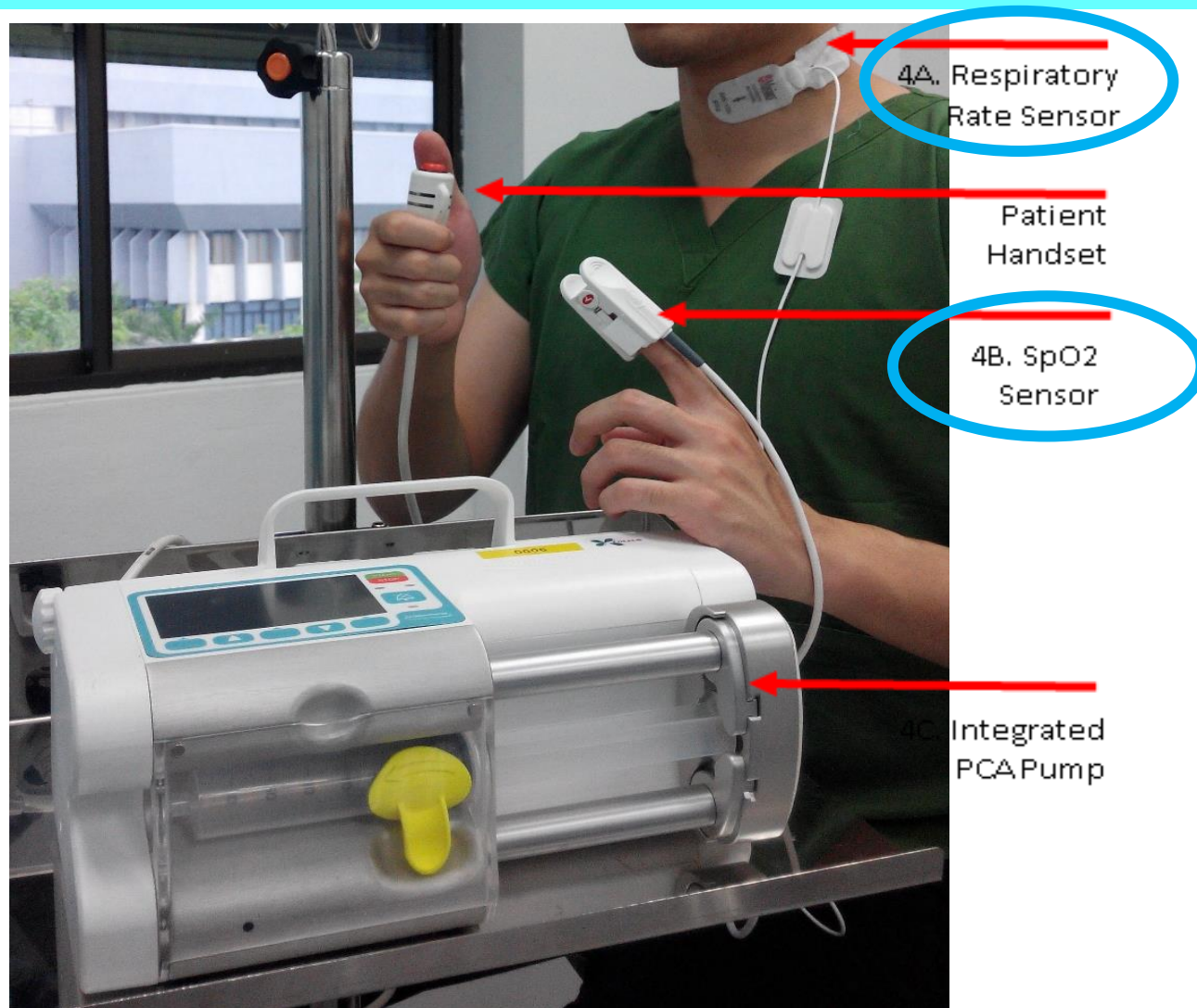
More oxygen desaturation

More bradycardia

More respiratory depression



INTRAVA Pump



Challenges of med tech

- Ensuring algorithm decision tree → clinically driven, future proof
- Communication with engineering
- Communication with industry
- Ensuring regulatory developments and approvals
- Ensuring staff training and buy in
- Be prepared to be called 24/7, at least for a while

Conclusion

- New technology **closed-loop feedback** system that provide solutions to clinical gaps in monitoring and drug delivery
- Drug delivery **effect and safety** must be balanced
- Find the appropriate **monitoring system** that is accurate, responsive and acceptable by patients
- **Partnership** between academic medicine institutions and industry to develop medical technologies that benefit patients

THANK YOU

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KKH Research Centre

Duke NUS Medical School

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