Ongoing data collection and analysis has the potential to help guide future research in the field of paediatric acute pain management.

Authors' contributions

Drafted, revised, and finalised the manuscript: both authors.

Declarations of interest

The authors declare that they have no conflicts of interest.

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New evidence to inform decisions and guidelines in difficult airway management

Alistair F. McNarry[1,*] and Takashi Asai[2]

[1]Department of Anaesthesia, NHS Lothian, Edinburgh, UK and [2]Department of Anesthesiology, Dokkyo Medical University Saitama Medical Centre, Koshigaya, Japan

*Corresponding author. E-mail: althegasman@btinternet.com

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In the event of failed tracheal intubation and difficult face mask ventilation after the induction of general anaesthesia, guidelines for 'difficult airway management'[1–4] recommend the insertion of a supraglottic airway. However, if this does

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not achieve effective oxygenation, they recommend progression to performance of an emergency front-of-neck airway (eFONA). Despite this unanimity, recommendations for eFONA are derived from low-level evidence,[2] and thus it is inevitable that many column inches have been devoted to debating which method of eFONA or which ventilation mode should be chosen in the 'cannot intubate, cannot oxygenate' situation.[5,6] In this issue of the *British Journal of Anaesthesia*, Laviola and colleagues[7] provide a new type of evidence to inform decision making around ventilatory strategies for eFONA.

Laviola and colleagues[7] carried out a study *in silico*. The phrase *in silico* is pseudo-Latin for '*in silicon*', referring to modelling and simulating medical process on computers (with silicon chips), to differentiate it from *in situ*, *in vivo*, *ex vivo*, or *in vitro*. They used the Interdisciplinary Collaboration in Systems Medicine simulation suite, which generates computational models of how the human body will perform, to create 50 virtual patients (with various organ functions) who had become severely hypoxaemic (arterial haemoglobin oxygen saturation of 40%) because of upper airway obstruction after induction of anaesthesia. In these virtual patients, they assessed oxygenation and cardiopulmonary effects of five different eFONA devices with varying internal diameter of 1.8–6.0 mm. With more than 7000 simulations, they found that re-oxygenation was achieved in all ventilation strategies within 1 min. A smaller airway (ID, <3 mm), but not a larger airway, quickly caused hyperinflation of the lungs resulting in pronounced cardiocirculatory depression (cardiac output <3 L min^{-1} and MAP <60 mm Hg) and impeding oxygen delivery if tidal volume was >200 ml and ventilation frequency was >8 breaths min^{-1}.[7]

There is clearly a need for an increased level of evidence around eFONA, so we are therefore obliged to ask what type of studies should we carry out, and what is the role of *in silico* studies (such as reported by Laviola and colleagues[7])? Firstly, we must assess the efficacy of each procedure (e.g. cannula cricothyroidotomy or scalpel–bougie cricothyroidotomy) and of each ventilation mode. Even if one procedure has been found faster than others, it does not necessarily mean that it should become the procedure of choice. The standard against which these interventions must be judged is that of effective (re-)oxygenation, and then on minimising complications. Therefore, we must consider these interventions as a whole to confirm both the effectiveness of the procedure and of the ventilation mode.

High-level evidence should be obtained from randomized controlled trials (RCTs) and meta-analysis thereof, but it would be virtually impossible to recruit sufficient numbers of patients who require rarely performed life-saving procedures, impractical to obtain written informed consent from possible participants, and unethical to allocate patients to possibly less effective life-saving emergency procedures. Therefore, decision making around eFONA is made based on surrogate endpoints or on cohort studies.[8,9] However, these studies may not be able to provide absolute answers. One such study by Fennessy and colleagues[10] using ultrasonography indicated that the optimal incision length for emergency cricothyroidotomy would be an 80 mm incision commencing 30 mm above the suprasternal notch. This finding is in keeping with the Difficult Airway Society (DAS) Guidelines[1] but is not *prima facie* evidence for them. In addition, there is growing evidence that use of jet ventilation through a small-bore needle is frequently ineffective and is associated with a higher incidence of life-threatening complications, but this is not in itself evidence for the scalpel technique. Given these issues among others, cohort studies alongside systematic reviews thereof are usually unable to draw firm conclusions.[11,12]

Appropriately preserved cadavers can provide life-like conditions, which may then be suitable for assessing the effectiveness of each procedure.[13] However, they do not facilitate study of the efficacy of each procedure in terms of effective oxygenation or adverse effects on cardiopulmonary function. Recently, simulation studies in manikins, in anaesthetised animals, or in an animal wet laboratory environment[14–16] have provided evidence as to which procedure might be more effective, easier to perform with less complications, and easier to master. Nevertheless, manikins and animal models may not be good surrogates for real patients, so contradictory results may be obtained.[14,16]

In silico simulation studies have a potential role, particularly in this area where clinical studies are difficult or insufficient. The coronavirus disease 2019 (COVID-19) pandemic triggered extensive use of computer simulations, calculations, and predictive modelling to provide insight into the spread of the virus and to guide government policies, despite their recognised inadequacies and the numerous unknown variables.[17,18] That experience underlines the pros and cons of *in silico* studies: they allow for the provision of evidence where none has previously existed, for the generation of evidence in scenarios where it may be impossible to gather data, and for the assimilation of information in a variety of situations that would take a long time to gather in a laboratory even if it were possible. The *in silico* study reported by Laviola and colleagues[7] has added a new type of evidence to the area of difficult airway management. However, for this new evidence to be considered valid, the underlying assumptions of the simulations must be considered. Use of *in silico* simulation is not new and the validity of the physiological model used has been established *in vivo*.[19] The authors have previously provided useful information about the efficiency of airway management and oxygenation in areas where clinical studies are not practical.[20,21]

Simulation is of course not new to anaesthesia. The role of simulators and simulation in anaesthesia training has been recognised for more than 50 yr,[22] initially as a tool for training, not just in technical skills but also in comprehension of facts, grasp of concepts, and a quick response.[23] The report of the Fourth National Audit Project (NAP4) of the Royal College of Anaesthetists (RCoA) and the DAS in 2011[24] identified that, although infrequent, anaesthetic airway complications remained commonly associated with poor standards of care. Human factors issues have been identified,[24,25] (and their role repeatedly reported[1,5]) as contributing to serious consequences associated with airway management. These are at least in part the comprehension of facts, grasp of concepts, and respect for co-workers that Spence noted in his 1997 editorial.[23]

The role of simulation and simulators is not only the teaching of technical skills, but also improving understanding as to how stress can affect decision making and behaviour, and how training in non-technical skills can improve performance. Successful management of a difficult airway, and in particular eFONA, is a high-stakes procedure. The need for a training system has been repeatedly emphasised,[24,26] with

some colleges mandating it.[27] This will require the use of a simulated environment.

The challenge is to integrate simulation training in a manner similar to that of safety-critical industries such as airlines or nuclear power; however, this raises the question of how much the environment should be informed by simulation. When considering COVID-19 modelling, Chin and colleagues[18] suggested that 'models need to be subjected to prespecified real time performance tests'. We should consider what their equivalent should be in the sphere of rarely performed techniques.

No simulated environment can perfectly reflect the attributes of every human being. However, virtual reality (*in silico*) simulators have already been developed for training in the technical and non-technical aspects of flexible bronchoscopy.[28] Recognising their shortcomings, it is now time to appreciate that *in silico* simulation can provide useful physiological information that can inform which techniques are best to perform in eFONA, not just how best to perform the chosen technique.

Although we believe that future guidelines must continue to consider human factors, transition triggers,[3] cohort studies, case reports, and manikin or *ex vivo* studies, we believe that they should also now consider the answers provided by complex simulation modelling. It is time for us as a profession to recognise and investigate the potential influence of complex physiological modelling on the conduct and the successful of rarely performed clinical skills.

Authors' contributions

Both authors contributed equally to the drafting of the article, revisions, and final approval of the submitted article.

Declarations of interest

AFMcN is the Royal College of Anaesthetists–Difficult Airway Society (RCoA–DAS) Airway Leads Advisor. TA is an editor of the *British Journal of Anaesthesia*.

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Applying the adverse outcome pathway concept to questions in anaesthetic neurotoxicity

Jennifer Waspe[1,2,*], Timothy J. A. Chico[1] and Tom G. Hansen[3,4]

[1]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield Medical School, Sheffield, UK, [2]The University of Sheffield, Sheffield, UK, [3]Department of Anaesthesia and Intensive Care, University Hospital Odense, Odense, Denmark and [4]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

*Corresponding author. E-mail: J.waspe@sheffield.ac.uk

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Adverse outcome pathways (AOPs) aim to improve research synthesis through structured, multilevel integration of basic science and data from human trials.[1] The AOP approach is endorsed by the Organisation for Economic Co-operation and Development (OECD)[1] and used by toxicologists to aid evidence synthesis in the face of an ever-increasing volume of highly specialised biomedical data.

The AOP concept gained acceptance in regulatory toxicology after a landmark report from the US National Academy of Sciences in 2007.[2] That report recognised that existing practices were insufficient for effective and timely risk assessment of chemicals because of the rapidly expanding chemical industry.[2–4] The central tenet of the proposed strategy to improve risk assessments was to develop *toxicity pathways*—a process of delineating the sequence of key events at different biological levels (molecular, cellular, tissue, and organ) resulting from chemical perturbation of a biological process or system.[2] The AOP concept evolved from this, broadening the approach to include effects at the level of an organism or population.[5,6]

So far, AOPs have been developed to address endpoints relevant to regulation and safety of chemicals. However, the approach has far wider application than within toxicology. The systematic organisation and appraisal of biomedical data at the core of AOP development echo methods of literature analysis that are already central to clinical research, but do not encompass mechanistic data. Adoption of the AOP framework as a complement to systematic review and meta-analysis would significantly aid integration of preclinical and clinical data sets.

There are particular advantages in applying an agnostic science-based strategy, such as AOPs, in anaesthetic research, specifically in paediatric neurotoxicity. In 2017, conclusions drawn about the safety of anaesthesia in children less than 3 yr old instigated regulatory involvement from the US Food and Drug Administration.[7] Ultimately, a warning was issued, highlighting concerns that the developing brain could be adversely affected by prolonged exposure to anaesthetic drugs. This has since generated contention amongst experts and international discussion about how to advance research in this complex field.[8]

For a subject area where expert opinion is staunchly divided, the opportunity to display available evidence in a single integrated platform is appealing. Using the AOP framework, knowledge of the current distribution of evidence would be more accessible, enabling transparent data analysis and identification of critical knowledge gaps. It is hoped that this would facilitate harmonisation of expert opinion, aid future trial design, and in time may also be used to inform regulatory decision-making.

Structure of the AOP framework

An AOP provides a clearly accessible, multiscale overview of the known molecular and cellular events linking a biological