ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2017 August 4; 6(3): 140-178

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

A peer-reviewed, online, open-access journal of critical care medicine

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2016-2019

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INDEXING/ABSTRACTING

World Journal of Critical Care Medicine is now indexed in PubMed, PubMed Central.

FLYLEAF **I-III** Editorial Board

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Critical Care Medicine
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
August 4, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.f6publishing.com

World J Crit Care Med 2017 August 4; 6(3): 140-152

DOI: 10.5492/wjccm.v6.i3.140

ISSN 2220-3141 (online)

REVIEW

Immunomodulatory effects of anesthetics in obese patients

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Author contributions: Heil LBB and Silva PL designed and conducted the literature review, wrote the manuscript, and prepared the tables; Silva PL prepared the figures, and supervised all the process; Pelosi P and Rocco PRM wrote the manuscript and supervised all the process.

Supported by Brazilian Council for Scientific and Technological Development (CNPq); Carlos Chagas Filho Rio de Janeiro State Foundation (FAPERJ); Department of Science and Technology (DECIT); Brazilian Ministry of Health; and Coordination for the Improvement of Higher Level Personnel (CAPES).

Conflict-of-interest statement: The authors have no conflict of interest.

Manuscript source: Invited manuscript

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Received: January 26, 2017
Peer-review started: February 8, 2017
First decision: April 17, 2017
Revised: June 27, 2017
Accepted: July 7, 2017
Article in press: July 10, 2017
Published online: August 4, 2017

Abstract

Anesthesia and surgery have an impact on inflammatory responses, which influences perioperative homeostasis. Inhalational and intravenous anesthesia can alter immune-system homeostasis through multiple processes that include activation of immune cells (such as monocytes, neutrophils, and specific tissue macrophages) with release of pro- or anti-inflammatory interleukins, upregulation of cell adhesion molecules, and overproduction of oxidative radicals. The response depends on the timing of anesthesia, anesthetic agents used, and mechanisms involved in the development of inflammation or immunosuppression. Obese patients are at increased risk for chronic diseases and may have the metabolic syndrome, which features insulin resistance and chronic low-grade inflammation. Evidence has shown that obesity has adverse impacts on surgical outcome, and that immune cells play an important role in this process. Understanding the effects of anesthetics on immune-system cells in obese patients is important to support proper selection of anesthetic agents, which may affect postoperative outcomes. This review article aims to integrate current knowledge regarding the effects of commonly used anesthetic agents on the lungs and immune response with the underlying immunology of obesity. Additionally, it identifies knowledge gaps for future research to guide optimal selection of anesthetic agents for obese patients from an immunomodulatory standpoint.

Key words: Anesthesia; Immune system; Perioperative care; Obesity; Inflammation

Core tip: Anesthetic agents have been studied not only for their effects on anesthesia and analgesia, but also their action on the lungs and immune system. Obesity is associated with a chronic state of low-grade systemic inflammation, and may predispose to development of comorbidities. Although efforts have been made to develop guidelines for anesthesia in obesity, to date, no ideal drug combination has been found. Optimization of the immunomodulatory properties of anesthetic agents may enable perioperative modulation of inflammatory response in obese patients and improve postoperative outcomes.

Heil LBB, Silva PL, Pelosi P, Rocco PRM. Immunomodulatory effects of anesthetics in obese patients. *World J Crit Care Med* 2017; 6(3): 140-152 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i3/140.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i3.140

INTRODUCTION

Obesity and associated comorbidities are increasing at epidemic proportions globally[1], with a substantial impact on postoperative outcomes for affected individuals undergoing minor or major surgical procedures that require anesthesia. Intravenous and inhalational anesthetics (IAs) have been shown to modulate the innate and adaptive immune responses, as well as indirect effectors of immunity[2,3].

Since obesity results in chronic low-grade inflammation or metainflammation[4] associated with increased circulating proinflammatory factors, it has been proposed that anesthetic agents may modulate the already altered immune function in obesity, with particular emphasis on pulmonary inflammation.

This review article aims to integrate current knowledge regarding the effects of commonly used anesthetic agents on the lungs and immune response with the underlying immunology of obesity. Additionally, it provides insights and future perspectives into the safe use of anesthetics as immunomodulators for obese patients. Better knowledge of the impact of anesthetic agents on the immune system, especially in the setting of obesity, may improve perioperative management and outcome.

IMMUNE AND INFLAMMATORY CHANGES DUE TO OBESITY: THE ROLE OF IMMUNE CELL INFILTRATION IN ADIPOSE TISSUE

Healthy adipose tissue (AT) is composed of a type-2 polarized immune system, which maintains AT macrophages (ATM) in an M2-like (pro-resolution) state. While in this form, AT is mainly composed of eosinophils, invariant-chain natural killer T (iNKT) cells[5], and regulatory T (Treg) cells[6], which produce interleukin (IL)-4, IL-13, and IL-10. Adipocytes also contribute to the type 2 immune response through production of adiponectin, which exhibits a strong anti-inflammatory effect[7]. These type 2 immune cells are supported by a stromal structure, which promotes immune cell viability through the production of several cytokines, with IL-33 playing a particularly important role[8,9]. Moreover, in order to sustain this environment, AT cells engage in extensive cross-talk to (re)model AT structure and phenotype[10].

The early phases of the diet-induced obesity (DIO) period are characterized by an increase in the amount of fat per adipocyte and an accumulation of immune cells. Acute changes in the microenvironment, such as alterations in oxygen supply and consumption, contribute to triggering a rapid increase in the number of neutrophils[11]. Adipocytes become hypertrophic and hyperplastic. This is associated with a shift in adipokine production from adiponectin to leptin, monocyte chemo-attractant protein-1 (MCP-1), and IL-6, as well as resistin, visfatin, tumor necrosis factor (TNF)-α, retinol binding protein 4 (RBP4), lipocalin-2, and CXCL5[12]. Leptin directly increase the production of several proinflammatory cytokines, such as IL-6, TNF-α, the chemokines CCL2/MCP-1, and leukotriene B_4 (LTB_4) in peripheral blood monocytes and resident tissue macrophages[13]. Leptin can also induce the production of reactive intermediates in macrophages, neutrophils, and endothelial cells, as well as potentiate interferon (IFN)-γ induced expression of nitric oxide (NO) synthase[14-16], whereas adiponectin, IL-10, and omentin, which have anti-inflammatory effects, are downregulated[17]. In addition, innate inflammatory molecules such as acute phase reactants, C-reactive protein (CRP)[18], complement components C2, C3, and C4[19,20], and other immune-modulating mediators produced in AT contribute to the intricate connection between fat and its tissue-resident immune cells.

The adaptive immunity role is mediated by T-lymphocyte infiltration during early AT inflammation, preceding macrophage recruitment[21,22]. Most of these are $CD4^+$ lymphocytes that differentiate to TH1-cells, governing the local inflammatory process through the release of proinflammatory cytokines like IFN-γ and TNF-α. T-cell recruitment is usually mediated by chemokines released from endothelial cells, stromal cells, or macrophages. While, on the one hand, T-cell derived IFN-γ promotes the recruitment of monocytes by MCP-1 secretion from preadipocytes, it also activates other cells, including macrophages[21].

Resident and recruited ATM are the most common immune cell types in AT, and their infiltration is associated with AT inflammation[23,24]. Recruited AT macrophages induce tissue inflammation when their

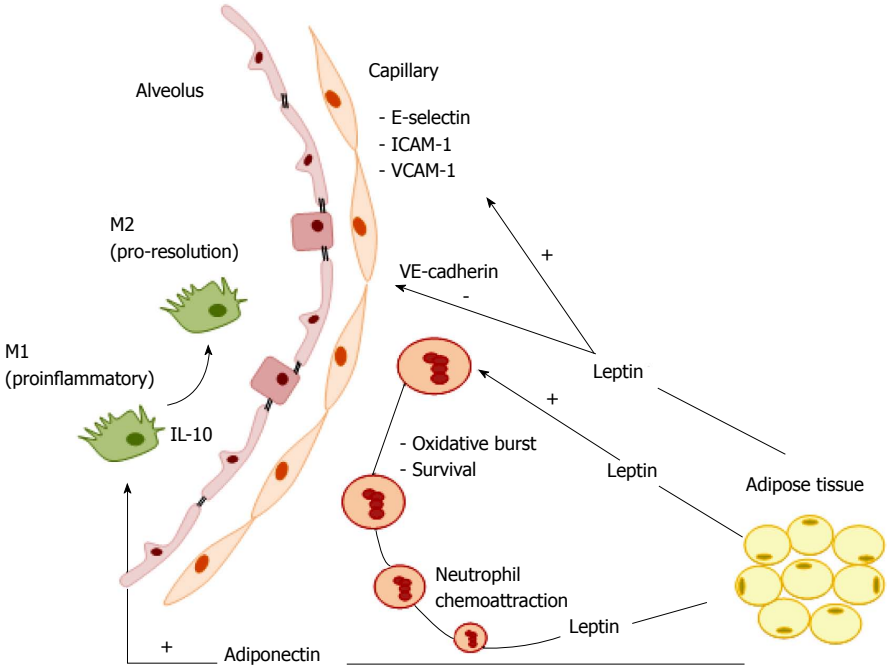

Figure 1 Model of obesity-associated pulmonary inflammation. Lung immune cells and inflammation due to obesity. Leptin is implicated in inflammatory respiratory diseases as a neutrophil chemoattractant. The association between obesity and LPS-induced lung inflammation involves an increase in monocytes and lymphocytes, as well as in intracellular adhesion molecule (ICAM)-1 expression in alveolar macrophages, suggesting their polarization toward a pro-inflammatory M1 phenotype. Obesity impairs vascular homeostasis, facilitating increased susceptibility to inflammatory lung vascular diseases by affecting structural cells in the alveolar-capillary membrane. The lung endothelium of obese mice has been shown to express higher levels of leukocyte adhesion markers (E-selectin, ICAM-1, VCAM-1) and lower levels of junctional proteins (VE-cadherin and β-catenin). Adiponectin has anti-inflammatory properties, mainly by its effects on toll-like receptor (TLR) pathway-mediated NF-κB signaling, which regulates the shift from M1 to M2 macrophage polarization, and suppresses differentiation of M1 macrophages by downregulating the pro-inflammatory cytokines TNF-α, MCP-1, and IL-6. Adiponectin also promotes expression of the anti-inflammatory factor IL-10 in macrophages via cAMP-dependent mechanisms. TNF: Tumor necrosis factor; IL: Interleukin; LPS: Lipopolysaccharide.

polarization shifts from an M2 type to an activated proinflammatory M1 state. Stimuli for this shift toward the M1 phenotype includes systemic factors, such as increase in free fatty acids (FFAs), which stimulates toll-like receptors (TLR)-4 on macrophages[25], and activation of the inflammasome, which is responsible for production of the proinflammatory cytokines IL-1β and IL-18[26]. In addition, IFN-γ is a potent local inducer of M1 polarization during ATM inflammation[27].

The link between metabolism and immunity at the intracellular level occurs through activation of nuclear factor-κB (NF-κB) and its cytoplasmic inhibitor IκκB. Likewise, other inflammatory factors, such as c-Jun N-terminal protein kinases (JNK), are activated[28,29]. These proinflammatory mediators are produced in excess, spilling into the peripheral circulation and contributing to the low-grade systemic inflammation that ultimately influences the development of obesity-associated comorbidities, including the pulmonary immune response, thus contributing to pulmonary inflammation[12,30].

AT immune cells contribute to the maintenance of homeostasis and development of chronic inflammation and are responsible for the mechanisms underlying obesity-associated complications and impairment of normal immune system functioning, thus further perpetuating chronic disease development and metabolic complications.

LUNG IMMUNE CELLS AND OBESITY-ASSOCIATED INFLAMMATION

Several mediators elicited by obesity alter immune and inflammatory responses in the lung, and may induce obesity-associated changes to adipokines and lung immune cells.

Leptin

Several lung cell types, such as leukocytes, airway smooth muscle cells, alveolar epithelial cells, and macrophages, express the functional leptin receptor, which, when bound to its main ligand (systemic leptin), participates in triggering inflammatory respiratory diseases. Lungs represent a target organ for leptin signaling. In this line, leptin stimulates neutrophil and macrophage release of cytokines (TNF-α, IL-6, IL-12), eicosanoids, and NO and induces neutrophil oxidative burst[31]. Endogenous leptin has two main effects in the lungs (Figure 1). First, it acts as a neutrophil chemoattractant to the lungs[32]. Once neutrophil levels are increased, leptin lengthens neutrophil survival by delaying or inhibiting apoptosis[33]. Additionally, obese patients with increased levels of leptin exhibited increased susceptibility to respiratory infections, in an association that may be independent and

likely additive to metabolic syndrome-related factors[34]. Furthermore, the proinflammatory effects of leptin may contribute to a higher incidence of asthma in the obese population[35]. In chronic obstructive pulmonary disease[36,37], the higher the leptin production, the greater the severity of the disease[38,39]. In the setting of obesity, not only immune cells but also structural cells in the alveolar-capillary membrane are altered. In obese mice, the lung endothelium was found to express higher levels of leukocyte adhesion markers (E-selectin, ICAM-1 and VCAM-1) and lower levels of junctional proteins (VE-cadherin and β-catenin) (Figure 1), providing further evidence that obesity may impair vascular homeostasis and increase susceptibility to inflammatory lung vascular diseases[40].

In short, leptin plays an important role in respiratory immune responses and pathogenesis of inflammatory respiratory conditions by acting on different cell types in the lung.

Adiponectin

Adiponectin is a well-defined obesity marker that has anti-inflammatory properties. Its predominant immune-related functions involve suppression of inflammation by clearance of apoptotic cell debris[41] and promotion of an anti-inflammatory phenotype in the lung by blunting oxidative stress, inflammation, and angiogenesis. However, several of these immune-related functions depend on the respective adiponectin receptor. AdipoR1, AdipoR2, T-cadherin, and calreticulin are detected in several lung cells[42]. The structure of adiponectin resembles those of complement factor C1q and of surfactant proteins, which act as pattern recognition molecules limiting lung inflammation[43]. Adiponectin receptors are also involved in the regulation of macrophage proliferation and function. AdipoR1 mediates adiponectin suppression of NF-κB activation and proinflammatory cytokine expression in macrophages[44,45], AdipoR2 is involved in adiponectin-mediated M2 polarization[46], and T-cadherin has been shown to play an essential role in the stimulatory effects of adiponectin on M2 macrophage proliferation[47]. The anti-inflammatory effects of adiponectin are mainly guided by the toll-like receptor (TLR) mediated NF-κB signaling pathway, which modulates a shift in macrophage polarization from M1 to M2 (Figure 1) and suppresses differentiation of M1 macrophages by downregulating the proinflammatory cytokines TNF-α, MCP-1, and IL-6[48,49]. Moreover, adiponectin increases expression of the anti-inflammatory factor IL-10 in macrophages *via* cAMP-dependent mechanisms[50]. Adiponectin has also been proposed to regulate energy and metabolism by targeting innate-like lymphocytes (ILC2)[10,51], natural killer T (NKT)[52], and gamma delta T (γδT)cells[53].

Adiponectin senses metabolic stress and modulates metabolic adaptation by targeting functions of the innate immune system, including macrophage polarization and lymphocyte activity.

ANESTHESIA, ANESTHETICS, AND IMMUNOMODULATION

Anesthesia and the surgical stress response result in several immunological alterations, which cannot be easily separated. The pharmacological effects of anesthetic drugs (sedation, anesthesia, and analgesia) have been widely studied, as have their actions on several cell types, including inflammatory cells, by altering cytokine release[54]; cytokine receptor expression[55]; phagocytosis or cytotoxic actions[56]; and transcription or translation of protein mediators[57,58]. Depending on the clinical setting, immunosuppression and activation can be either detrimental or beneficial. These effects are clinically important because the balance between pro- and anti-inflammatory cytokine secretion is associated with surgical outcomes.

Immune cells are categorized into two lines according to their maturation site: The myeloid lineage, which includes macrophages, dendritic cells (DCs), mast cells, and granulocytes (neutrophils, eosinophils and basophils); and the lymphoid lineage, which is composed of T and B lymphocytes, natural killer (NK) cells, and NK T cells[59,60]. Myeloid cells are considered the main players in innate immunity, and play important roles in adaptive immunity as well; they serve as antigen presenters and macrophages, mast cells, and neutrophils produce several cytokines, thus activating T and B lymphocytes[60]. Immunomodulation can have a dichotomous sense whereby suppression of the immune response can prevent further injury, as observed in models of acute inflammation[61], but also prevent the body from counteracting infections and increase the risk of opportunistic infections. In these scenarios, both inhalational and intravenous anesthetic agents may jeopardize or improve immune function.

IA agents

The action of IAs on immune cells has been extensively reviewed in preclinical studies[2,62,63]. *In vitro* experiments on immune cells revealed generally transient, dose- and time-dependent effects predominantly on neutrophil function[64-66], lymphocyte proliferation[67], suppression of inflammatory cytokines in rat alveolar cells, and decrease in the expression of inducible NO synthase by inhibition of voltage-dependent calcium channels, reducing intracellular calcium concentrations[68]. However, in an ischemic setting, the suppression of neutrophil adhesion had a positive effect against the deleterious effects of polymorphonuclear cells, improving cardiac function[69-72]. Furthermore, exposure to the isoflurane attenuated villus, hepatic, and renal injuries in a mouse model of intestinal ischemia; these effects were mediated *via* plasma membrane phosphatidylserine externalization and subsequent release of the anti-inflammatory and anti-apoptotic cytokine transforming growth factor β1 (TGF-β1)[73]. In both studies, the proposed mechanisms for protection rely on modulation

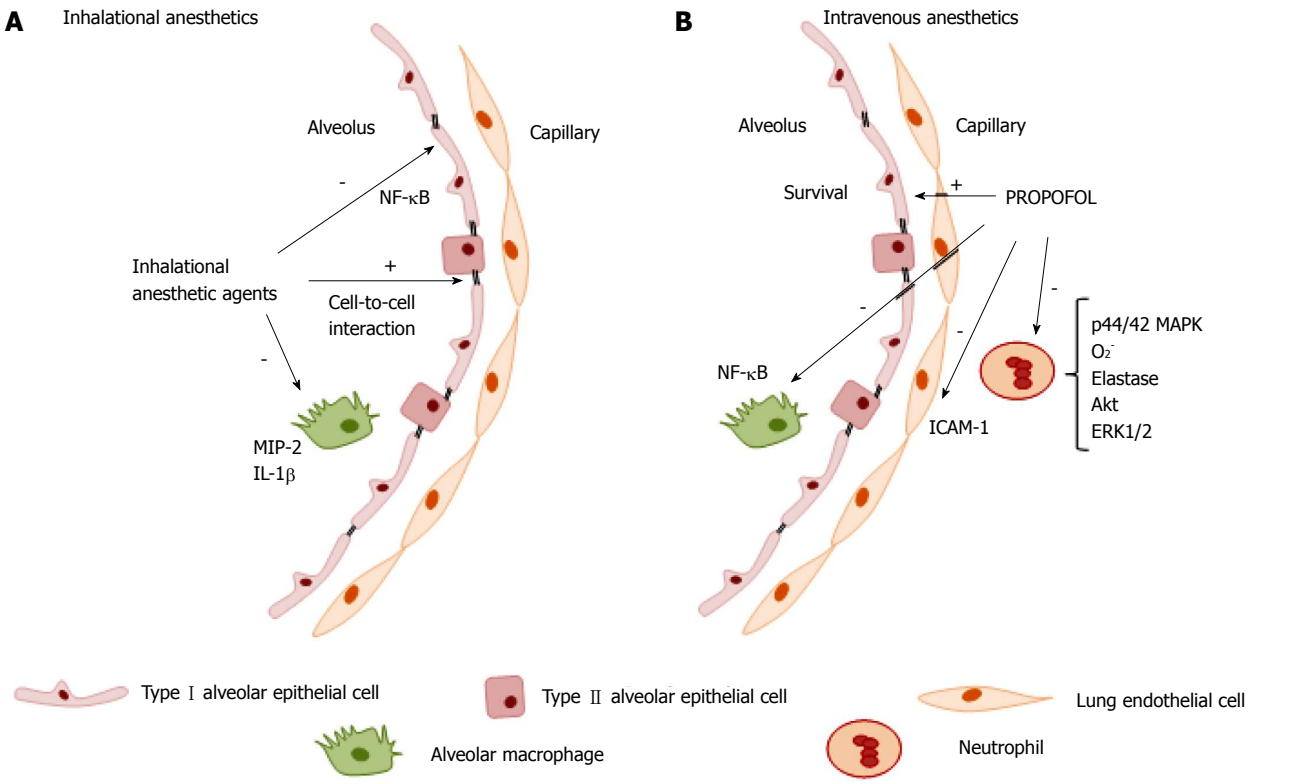

Figure 2 Modulatory effects of anesthetic agents on lung immune cells. A: Inhaled anesthetics: Decreased neutrophil influx, synthesis, and expression of macrophage inflammatory protein (MIP)-2, IL-1β, and stress proteins heme oxygenase (HO-1) and heat shock protein (HSP-70). Reduction of pro-inflammatory cytokine release, inhibition of iNOS expression and activity by blockade of NF-κB activation in lung tissue, inhibition of proapoptotic procaspase protein expression, and maintenance of alveolar epithelial adherence by attenuating reduction of zona occludens 1 (ZO-1) levels; B: Intravenous anesthetic (propofol): Impairs neutrophil activity by inhibition of phosphorylation of the mitogen-activated protein kinases p44/42 MAPK signaling pathway and disrupts the downstream signaling pathway involving calcium, Akt, and ERK1/2, which decreases superoxide generation, elastase release, and chemotaxis.

of endothelial and neutrophil adhesion molecules and reduction of neutrophil migration and margination into tissues[74]. In human endothelial cells, the effects of isoflurane against TNF-α-induced apoptosis are mediated by the phosphorylation of extracellular signal-regulated kinase (ERK MAPK) and induction of sphingosine kinase 1 (SK1) to increase production of the lysophospholipid S1P, a cytoprotective signaling molecule product of sphingomyelin hydrolysis that functions as an extracellular ligand for specific G protein-coupled receptors and as an intracellular second messenger[75]. In the context of acute inflammatory lung injury (Figure 2A), isoflurane has been shown to decrease neutrophil influx, as well as the synthesis and expression of macrophage inflammatory protein (MIP)-2, IL-1β, and the stress proteins heme oxygenase (HO-1) and heat shock protein (HSP-70)[76-79]. These studies showed reduction of proinflammatory cytokine release through several mechanisms: (1) inhibition of NF-κB translocation into the nuclei of human epithelial cells[58,76]; (2) inhibition of inducible nitric oxide synthase (iNOS) expression and blockade of NF-κB activation in a mouse model of lung injury; (3) inhibition of proapoptotic procaspase-8, procaspase-3, and inactivated proapoptotic protein Bax expression; (4) promotion of phosphatidylinositol-3-kinase/Akt activation and enhanced expression of the antiapoptotic B-cell lymphoma-2 (Bcl-2)-related protein homeostasis[80]; and (5) maintenance of alveolar epithelial adherence by attenuating reduction of zona occludens 1 (ZO-1) levels[81].

Intravenous anesthetic agents

The intravenous anesthetics (IVAs) ketamine and dexmedetomidine, although very important in clinical practice, have well-recognized and characterized immunomodulatory effects and will not be covered in the present review. The immunomodulatory effects of propofol have been investigated since it is widely used for general anesthesia and for sedation at sub-anesthetic doses. *In vitro* studies have shown that use of propofol at clinically relevant plasma concentrations impairs several monocyte and neutrophil functions, such as chemotaxis[82,83], phagocytosis[84], respiratory oxidative burst activity[85] cellular killing processes, and bacterial clearance[56,86] (Figure 2B). Some of these inhibitory properties are related to its lipid vehicle[87]. However, at the intracellular signal transduction level, Nagata *et al*[88] have proposed that some of the inhibitory effects of propofol on neutrophil activity may be mediated by inhibition of the phosphorylation of the mitogen-activated protein kinases p44/42 MAPK signaling pathway. A role of other pathways (such as p38 MAPK) in neutrophil chemotaxis has also been posited. Recently, Yang *et al*[89]

proposed a novel mechanism for the anti-inflammatory effects of propofol on fMLF-activated human neutrophils. Propofol decreased superoxide generation, elastase release, and chemotaxis, in a mechanism mediated by competitive blockade of the interaction between fMLF and its formyl peptide receptor (FPR)1, thus disrupting the downstream signaling pathway involving calcium, Akt, and ERK1/2. This provides additional evidence of the potential therapeutic effect of propofol to attenuate neutrophil-mediated inflammatory diseases[89]. In an animal model of endotoxemia, the anti-inflammatory effect of propofol decreased TNF-α, IL-1, and IL-6 levels[90]. Further research in murine macrophages suggests that propofol suppresses lipopolysaccharide (LPS)/TLR4-mediated inflammation through inhibition of NF-κB activation[91] and does not affect MAPKs, including ERK1/2, p38 MAPK, or JNK. The antioxidant properties of propofol, capable of regulating reactive oxygen species (ROS)-mediated Akt and NF-κB signaling, have also been considered. In a clinical study of patients undergoing craniotomy, propofol prevented the decrease in Th1/Th2 cell ratio seen with isoflurane anesthesia[92]. However, no differences in neutrophil function or cellular markers in lymphocytes and monocytes have been observed in patients with severe brain injury requiring long-term sedation with propofol[93].

Studies have demonstrated several effects of propofol in the pulmonary immune response to acute inflammation. It protected cultured alveolar epithelial cells from apoptosis and autophagy by prevention of LPS-induced mitochondrial dysfunction and inhibition of LPS-induced activation of apoptotic signals (caspase 9 activity, ROS overproduction, and Ca^{2+} accumulation)[94,95]; attenuated iNOS mRNA expression, NO, and TNF-α, which was associated with improved survival in a murine model of endotoxin-induced acute lung injury[94]; decreased neutrophil influx into the lungs through reduction of ICAM-1 expression[96]; reduced apoptosis of lung epithelial cells by downregulation of LPS-induced cytokines (IL-6, IL-8, TNF-α); and reduced levels of hypoxia-inducible factor (HIF)-1α, a transcription factor essential for regulating oxygen homeostasis[97]. The lipid carrier vehicle or other constituents of propofol formulations may also contribute to these immunomodulatory effects[87,98].

Many IVAs, including propofol, barbiturates, and benzodiazepines, produce their sedative and anesthetic effects on the central nervous system by inhibition of the $GABA_A$ receptor[99]. It is also known that immune system cells are capable of synthesizing and releasing GABA neurotransmitters, which are parts of the neuronal GABA signaling system. The absence of a presynaptic terminal defines these channels in immune cells as extrasynaptic-like channels[100]. $GABA_A$ receptors are present on immune cells, and are a potential site of drug action[101]. Studies have shown that, in asthmatic mice, the anti-inflammatory effect of propofol on Th2 inflammation is mediated by inhibition of Th2 cell differentiation, a mechanism attributed to induction of apoptosis *via* the GABA receptor during Th2 development[102].

In contrast, impairment of immune function by anesthetics may play a role in immunocompromised patients. In this line, Wheeler *et al*[103] demonstrated that, through their actions on the $GABA_A$ receptor, propofol and thiopental inhibited monocyte chemotaxis and phagocytosis. The implications clinical proposed reflect this dichotomous sense: If a patient's primary pathology is inflammatory, the immunomodulatory effects of propofol or thiopental could be therapeutic, but if the immune response is ineffective, these agents may increase the risk of infection[103].

Opioids

Although the main role of opioid peptides is the modulation of pain by binding to the opioid receptors widely distributed in the central nervous system, there is evidence of immunomodulatory effects exerted by endogenous and synthetic peptides, which activate opioid receptors. Different opioids show different effects on the immune system; immunosuppressive, immunostimulatory, or dual. Proposed mechanisms and sites of action of opioid-mediated immune modulation include: (1) direct action on the immune cells to modulate immune response, with the mu opioid receptor as the main molecular target; (2) the hypothalamic-pituitary-adrenal axis (HPA); and (3) modulation of the sympathetic activity, either in isolation or a combination thereof[104]. The interaction of opioids with each of these sites is complex and both species- and time-dependent. Regarding T helper cell balance, some opioids (fentanyl, methadone) have been shown to induce IL-4 and exert an anti-inflammatory effect on human T lymphocytes. Conversely, morphine and buprenorphine have not been shown to increase IL-4 mRNA or protein levels[105]. The proposed mechanism of this effect is that different agonists at opioid receptors in T cells may induce different signaling pathways or activate certain pathways with differential intensity.

Chronic morphine administration can suppress the innate immune system by inhibiting cytokine secretion, decreasing bacterial clearance by inhibiting macrophage phagocytosis, and altering leukocyte recruitment[106,107]. On the adaptive immune system, morphine interferes with antigen presentation, prevents activation and proliferation of T lymphocytes, and decreases T cell responses, contributing to lymphocyte apoptosis and B cell differentiation into antibody-secreting plasma cells[106,108]. Therefore, morphine use may be advantageous early in the inflammatory process, but after the initial inflammatory stage, its administration might be associated with an increase rate of infection[106].

While many experimental studies have highlighted the significant immunosuppression caused by opioids or their withdrawal[109], the results from clinical studies are still vague. No conclusive evidence exists that opioids contribute to or prevent infections perioperatively, in the

Table 1 Clinical studies of effects of anesthesia on immune cells and outcomes in obese patients

Ref.	Population	Interventions	Comparison	Outcome
Abramo *et al*[120]	Morbidly obese patients undergoing laparoscopic gastric bypass (n = 30)	TIVA Sevoflurane anesthesia Xenon anesthesia	Serum levels of IL-6, IL-10, TNF-α, and NO before anesthesia, at the end of surgery, and 12 h after the end of surgery	At the end of surgery, IL-10 and TNF-α levels were lower in patients anesthetized with xenon than in those given sevoflurane or TIVA
Roussabrov *et al*[121]	Obese patients undergoing short-duration gastric or uterine surgery (n = 36)	Ketamine (IV) pre-induction compared with no ketamine before general anesthesia	Serum levels of IL-1β, IL-2, IL-6, TNF-α, lymphocyte proliferation, and NK cell cytotoxicity	Results to those of previous studies in lean patients: No change in inflammation or immune response (11 studies), suppressed immune response (9 studies), or enhanced immune responses (1 study)

Summary of results from clinical studies comparing inhalational and intravenous anesthetics according to population, intervention, comparison, and outcomes. IV: Intravenous; IL: Interleukin; TNF: Tumor necrosis factor; NK: Natural killer cells; NO: Nitric oxide; TIVA: Total intravenous anesthesia.

ICU, or when used in the treatment of acute or chronic pain. Moreover, coexisting or underlying diseases such as cancer, diabetes mellitus, sepsis, and even obesity can all induce significant alterations in immune status. These comorbidities and some medications often used concomitantly in the perioperative period, such as corticosteroids, might modify the potential role of opioid-induced immunosuppression[110].

IAs and IVAs have diverse immunomodulatory effects that may yield positive or negative consequences on different disease processes (such as endotoxemia, generalized sepsis, tumor growth and metastasis, and ischemia-reperfusion injury). Therefore, anesthesiologists should consider the immunomodulatory effects of anesthetic drugs when designing anesthetic protocols for their patients. Considering the influence of obesity and anesthetic agents on lung immune cells, it is important to investigate the possible joint role of these factors, *e.g.*, during anesthesia induction in the obese population.

IMMUNOMODULATORY EFFECTS OF ANESTHETICS IN OBESITY

Obesity is a heterogenous condition. Inter-individual variability in AT distribution, presence of the metabolic syndrome, and other associated comorbidities confer several degrees of risk and require different levels of care, thus creating potential confounders that may affect outcomes in research studies. Therefore, perioperative care and anesthesia in obese patients are a great challenge. To date, several studies has proposed to answer the question of which anesthetic agent is best for the obese patient[111-114]. Most of these investigations have evaluated primary outcomes during and after anesthesia[115,116]. Although efforts have been made to develop standardized guidelines or protocols for the anesthetic care of the obese patient[117], there is no known ideal anesthesia technique or drug combination. However, the introduction of enhanced recovery after surgery (ERAS) protocols after obesity-related and bariatric procedures has gained great acceptance[118,119].

Despite the growing body of evidence supporting significant immunomodulatory effects for several anesthetic agents, there is a paucity of data on anesthetic-mediated immunomodulation in obesity. In this line, two small randomized controlled trials enrolling obese surgical patients evaluated the effects of different anesthetic approaches (Table 1). Abramo *et al*[120] investigated the effects of total intravenous anesthesia (TIVA), inhalation anesthesia (sevoflurane), or xenon anesthesia on serum levels of proinflammatory cytokines (IL-6, IL-10, TNF-α) and NO. The authors observed that xenon anesthesia was superior to the other two strategies in inhibiting postoperative serum TNF-α concentrations, but found no differences in other mediators[120]. The effects of ketamine on inflammatory and immune responses after short-duration procedures were similar to those previously reported in non-obese patients[121].

Inhaled anesthetics exert multiple protective effects that enhance perioperative organ function preservation in humans[122] and small animals[2]. Preclinical data have investigated the effects of anesthetic agents on the low-grade chronic inflammation of obesity[123-128]. These studies focused on the interaction of obesity and the metabolic syndrome with the expected protective effects of IAs, but did not evaluate immune system interactions.

In one study, sevoflurane preconditioning failed to induce cardioprotection in obese animals, in contrast to the effect observed in lean animals[123]. This negative effect can be explained by reduced activation of the ROS-mediated AMPK signaling pathway[123]. In another study, van den Brom *et al*[124] showed that sevoflurane has a stronger depressant effect on myocardial function than other agents, thus possibly increasing cardiac vulnerability to limited oxygen supply and increasing risk of ischemia during surgery.

Concerning the role of adrenergic receptors, the long-term metabolic stress seen in obesity and diabetes type 2 alters type α and β adrenoceptor (AR) function and their interaction with isoflurane anesthesia. Bussey *et al*[125] showed that isoflurane anesthesia enhanced α-AR sensitivity, normalized β-AR response, and impaired cardiovascular function by reducing hemodynamic compensation during acute stress in experimental obesity and type 2 diabetes. Finally, Zhang

Table 2 Animal studies of effects of inhalational anesthesia in obese or MetS animals

Ref.	Population	Interventions	Comparison	Outcome in obese animals	Outcome in lean animals
Song *et al*[123]	Animals fed high-fat *vs* low-fat diet	Myocardial ischemia and reperfusion	Ctrl x Sevoflurane preconditioning	No sevoflurane cardioprotection	Sevoflurane: ↓ infarct size; ↑endothelial nitric oxide synthase, myocardial nitrite and nitrate
van den Brom *et al*[124]	Animals fed western *vs* control diet	Sevoflurane 2% *vs* baseline on echocardiographic myocardial perfusion and function	Myocardial perfusion and systolic function	Sevoflurane: No additional effect on myocardial perfusion but impaired systolic function	Sevoflurane: ↑ microvascular filling velocity, no change in myocardial perfusion
Bussey *et al*[125]	Zucker type 2 diabetic Zucker obese *vs* lean counterpart animals	Conscious *vs* 2% isoflurane anesthesia	Hemodynamic effects (mean arterial pressure, heart rate) of α or β adrenoreceptor (AR) stimulation	Isoflurane exacerbated and prolonged α-AR sensitivity and normalized chronotropic β-AR responses	Maintenance of ↑ α-AR sensitivity, ↑ chronotropic β-AR heart rate and mean arterial pressure responses
Zhang *et al*[126]	Animals with hypercholesterolemia *vs* normocholesterolemic animals	60 min sevoflurane pre-treatment, 12 h before myocardial IR surgery	Expression of myocardial iNOS and eNOS	No cardioprotectant effects of sevoflurane, downregulation of eNOS. Interference with iNOS signaling pathway	Delayed sevoflurane cardioprotection: decreased infarct size and improved ventricular function
Yang *et al*[127]	Animals fed high-fat *vs* low-fat diet	60 min focal cerebral ischemia followed by 24 h of reperfusion 15 min sevoflurane postconditioning	Cerebral infarct volume, neurological score, motor coordination 24 h after reperfusion	Sevoflurane post-conditioning failed to confer neuroprotection; no neuroprotective effect of mitoKATP channel opener	Sevoflurane ↓ infarct size, improved neurological deficit scores; neuroprotective effect of mitoKATP channel opener
Yu *et al*[128]	Animals fed high-fat *vs* low-fat diet	Middle cerebral artery occlusion; Isoflurane post-treatment after 20 min *in vitro* ischemia or transient middle cerebral artery occlusion	Cell injury in hippocampal slices, brain infarct volume, neurological deficit	Attenuated isoflurane-induced neuroprotection; ↓ Akt signaling pathway	Isoflurane post-treatment ↓ injury

Summary of the results of experimental studies comparing inhalational anesthetics according to population, intervention, comparison, and outcomes. AR: Adrenergic receptor; eNOS: Endothelial nitric oxide; IR: Ischemia-reperfusion.

et al[126] showed that the expected cardioprotective effect of sevoflurane against reperfusion injury through interference on myocardial iNOS signaling was absent in hypercholesterolemic rats.

Obesity has been implicated in altering the protective postconditioning effect of sevoflurane anesthesia against cerebral ischemic injury. Molecular analyses demonstrated reduced expression of Kir6.2, a significant mitoKATP channel component in the brain. This reduced Kir6.2 expression may diminish mitoKATP channel activity, contributing to an inability to postcondition the brain against ischemia reperfusion-injury[127]. Furthermore, in a study of mice fed a high-fat diet, attenuation of neuroprotection was observed after isoflurane exposure in hippocampal slices exposed to oxygen-glucose deprivation. Obese mice exhibited higher levels of carboxyl-terminal modulator protein (CTMP, an Akt inhibitor) and lower levels of phosphorylated Akt than age-matched animals fed a regular diet, suggesting an influence of high-fat diet in decreasing prosurvival Akt signaling in the brain. This may explain the higher isoflurane concentrations required to neuroprotect from oxygen-glucose deprivation in this study[128]. Table 2 lists recent preclinical studies that assessed the potential cardioprotective and neuroprotective effects of IAs in animals with obesity and the metabolic syndrome.

One study showed that, apart from cardioprotective effects, 1 h of propofol (but not dexmedetomidine) infusion increased airway resistance and pulmonary inflammation, in an effect mediated by expression of TNF-α and IL-6 in lung tissue[129]. These results raised questions about the proposed mechanisms of propofol or its lipid vehicles on obesity-associated metainflammation.

CONCLUSION

If the immunomodulatory properties of anesthetic agents are indeed demonstrated to have impacts on perioperative care and short-term or even long-term outcomes, this would provide clinicians and researchers with valuable evidence to rethink the use of these agents and improve their usage, particularly in the obese population. A better understanding of the complex relationships and detailed mechanisms whereby anesthetic agents modulate obesity-associated pulmonary inflammation and immune responses is a growing field of study in which additional basic-science and clinical observation data are necessary. Further studies are required to link important pharmacokinetic aspects of these drugs to relevant aspects of lung immune function in obesity-related inflammatory conditions, as well as to identify

the mechanisms of these interactions so that drugs with potential lung-specific immunosuppressive effects can be identified and their impact evaluated. In the very near future, the perioperative care of the obese patient may also be guided by different anesthetic strategies, with careful regard to immune status.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to Mrs. Moira Elizabeth Schöttler and Mr. Filippe Vasconcellos for their assistance in editing the manuscript.

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P- Reviewer: De Cosmo G **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.f6publishing.com

World J Crit Care Med 2017 August 4; 6(3): 153-163

DOI: 10.5492/wjccm.v6.i3.153

ISSN 2220-3141 (online)

MINIREVIEWS

Generalizable items and modular structure for computerised physician staffing calculation on intensive care units

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Author contributions: Weiss M, Marx G and Iber T wrote the paper on behalf of the "Forum quality management and economics" of the German Association of Anaesthesiologists (BDA) and the German Society of Anaesthesiology and Intensive Care Medicine (DGAI); Weiss M, Marx G and Iber T were leading in the previous versions and the update and publications in German language of the calculation base for the personnel requirement of physicians on ICUs including an Excel calculation sheet by the "Forum quality management and economics" focusing on quantitative and qualitative cornerstones for personnel requirement of physicians on ICUs.

Supported by the German Association of Anaesthesiologists (BDA) and the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), in that BDA and DGAI sponsored meetings of the working group "personnel management" to create the physician staffing tools 2008 and 2012. Weiss M, Marx G and Iber T are members of the working group "personnel management of BDA and DGAI".

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

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Received: November 13, 2016
Peer-review started: November 15, 2016
First decision: February 15, 2017
Revised: February 23, 2017
Accepted: April 24, 2017
Article in press: April 24, 2017
Published online: August 4, 2017

Abstract

Intensive care medicine remains one of the most cost-driving areas within hospitals with high personnel costs. Under the scope of limited budgets and reimbursement, realistic needs are essential to justify personnel staffing. Unfortunately, all existing staffing models are top-down calculations with a high variability in results. We present a workload-oriented model, integrating quality of care, efficiency of processes, legal, educational, controlling, local, organisational and economic aspects. In our model, the physician's workload solely related to the intensive care unit depends on three tasks: Patient-oriented tasks, divided in basic tasks (performed in every patient) and additional tasks (necessary in patients with specific diagnostic and therapeutic requirements depending on their specific illness, only), and non patient-oriented tasks. All three tasks have to be taken into account for calculating the required number of physicians. The calculation tool further allows to determine minimal personnel staffing, distribution of calculated personnel demand regarding type of employee due to working hours per year, shift work or standby duty. This model was introduced and described first by the German Board of Anesthesiologists and the German Society of

Anesthesiology and Intensive Care Medicine in 2008 and since has been implemented and updated 2012 in Germany. The modular, flexible nature of the Excel-based calculation tool should allow adaption to the respective legal and organizational demands of different countries. After 8 years of experience with this calculation, we report the generalizable key aspects which may help physicians all around the world to justify realistic workload-oriented personnel staffing needs.

Key words: Budgets; Critical care; Economics; Humans; Intensive care units; Personnel hospital; Personnel staffing and scheduling; Physicians; Workload; Quality of health care

Core tip: After 8 years of experience with the first calculation tool for physician staffing on intensive care units, generalizable key aspects are presented to help physicians all around the world to justify realistic personnel needs. A workload-oriented modular, flexible Excel-based calculation tool is presented, integrating quality of care, efficiency of processes, legal, educational, controlling, local, organisational and economic aspects. Staffing calculations reflect basic tasks (every patient), additional tasks (specific diagnostic and therapeutic requirements), non patient-oriented tasks, and, auxilliary calculations, such as minimal personnel staffing, distribution of personnel demand regarding type of employee due to working hours per year, shift work or standby duty.

Weiss M, Marx G, Iber T. Generalizable items and modular structure for computerised physician staffing calculation on intensive care units. *World J Crit Care Med* 2017; 6(3): 153-163 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i3/153.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i3.153

INTRODUCTION

Intensive care medicine is one of the most cost-driving areas within hospitals with high personnel costs[1,2]. Thus, realistic requirements for personnel staffing are highly needed. Several professional societies in Germany (DGAI, BDA, DIVI, DGCH, BDCH)[3], Europe (ESICM)[4,5] or the United States (SCCM)[6,7] made recommendations for the staffing and organisation of interdisciplinary intensive care units (ICUs). The presence of physicians on ICUs 24-h, 7 d a week, 365 d a year are justified by the physicians perspective[3,4,6,7], and, in Germany, economically relevant for reimbursement. Unfortunately, all existing staffing models are top-down calculations with a high variability in the calculated results. In turn, this variability often reflects the range between sufficient personnel resources and being underpowered, thereby leading to controversial discussions. Taking into account quality of care, it is necessary to calculate the need by a bottom-up method based on the performed procedures and actions. Furthermore, in the G-DRG-reimbursement system, costs for continuous medical education are insufficiently taken into consideration[8]. Bearing these aspects in mind, the working group "personnel management of BDA und DGAI" published a workload-oriented modular calculation model for personnel staffing of physicians in the ICU in 2008[9] and an update in 2012[10]. Thereby, the actual-state of personnel staffing on the ICU can be compared with the necessary target-state and allows physician staffing on a workload basis. The BDA and DGAI tool enables an individualised systematic analysis for every type of hospital[10]. The purpose of this paper is to present generalizable items and a modular structure for a computerised calculation tool for widespread use which may help physicians to justify realistic workload-oriented personnel staffing requirements on ICUs all around the world.

MODULAR CALCULATION OF STAFFING OF PHYSICIANS ON ICUS

Generalizable items of personnel staffing in the ICU are presented. The workload-oriented calculation[9,10] has been developed for every type of ICU, taking into account various magnitudes, premises and organisational structures of hospitals, and degrees of care. The basic consideration in this model is analysing the workload of physicians on ICUs, which has been divided in basic tasks, additional tasks, and non patient-oriented tasks (including management issues and teaching). The personnel demand for these tasks can be calculated using Excel-based "calculation tools" (Tables 1-4). In addition, "assistance tools" can be provided to calculate minimal personnel staffing, distribution of calculated personnel need regarding type of employee due to working hours per year, shift work or stand by duty (Tables 5-8).

First of all, reflections are inevitable regarding the local situation, performance of the hospital, subset of patients, premises and organisational structures. Standard times regarding workload tasks have to be defined, at best should have been measured in the distinct hospital, and consented by different stakeholders.

However, before calculating workload-related personnel staffing, some aspects have to be clarified: (1) in-house times for admission, daily routine, omission and handing over by physicians; (2) in-house number and times for tasks, procedures and examinations, and non-recurring tasks performed per year per patients; (3) number of ICU beds; (4) number of cases and patient days per year; (5) average drop-out times (holidays, illness); (6) holidays given to shift workers, gross annual working time in hours per work-fellow; (7) number of physicians in specialist training with, *e.g.*, less than 3 mo ICU experience; (8) time for non patient-oriented

Table 1 Basic patient-oriented tasks of physicians on the intensive care unit

		In-house	Standard	In-house time		Standard time		
		Time (min)	Time (min)	Physician/ patient	Time/ patient	Physician/ patient	Time/ patient	Physicians/ handing over
Admission (time per patient, including daily routine on day of admission)								
	Patient takeover	5	5					
	Clinical evaluation	5	5					
	Writing of admission documents	20	20					
	Writing of physician's instructions	10	10					
	Reimbursement documentation (DRGs)	10	10					
	Basic examination and controls	5	5					
	Handing over round	5	5					
	Senior physician round	5	5					
	Sum	65	65					
Daily routine (time per patient)								
	Transit time	5	5					
	Physical examination and status	5	5					
	Writing of physician's instructions	5	5					
	Documentation	2	2					
	Radiology round	2	2					
	Microbiology round	2	2					
	Physiotherapy round	10	10					
	Talking with relatives	5	5					
	Rounds with consultants	5	5					
	Sum	41	41					
Omission/demission (time per patient)								
	Final examination	3	3					
	Final documentation	15	15					
	Physician's letter	5	5					
	Handing over	2	2					
	Sum	25	25					
Handing over medical rounds (time per patient)								
Shift 1	Handing over 1 Mo - Fr			25	5	25	5	5
Shift 2	Handing over 2 Mo - Fr			25	5	25	5	5
Shift 3	Handing over 3 Mo - Fr			15	5	15	5	3
	Senior physician round Mo - Fr			10	10	5	5	1
	Sum Mo - Fr			75		70		
Shift 1	Handing over 1 Sa, Su, public holiday			15	5	15	5	3
Shift 2	Handing over 2 Sa, Su, public holiday			0	5	0	5	0
Shift 3	Handing over 3 Sa, Su, public holiday			15	5	15	5	3
	Senior physician round Sa, Su, public holiday			5	5	5	5	1
	Sum Sa, Su, public holidays			35		35		

tasks of the ICU physicians (*e.g.*, working groups, administration, teaching); (9) number of full-time and partial-time physicians and working hours per week and year; and (10) shift work and standby duty.

In respect to all these items, *e.g.*, with average drop-out time of 19.5% in a three-shift system and legal working regulations regarding handing over to other work-shifts, the workload results in 26.25 h for three physicians per day. In other words, 6.8 full-time physicians are necessary to run an ICU 24-h, 7 d a week, 365 d a year. This minimal staffing is independent of the number of beds and patients.

Thus, *e.g.*, with 12.75 h per day at maximum in shift work with at maximum 48 h per week and a standby duty of maximum 54 h per week, minimal staffing demand can be calculated (Table 6). Weekly working hours multiplied with 52.2 result in the potential gross working time of a physician. The real net working time of a physician is yielded by subtracting the drop-out times (holidays, average times of illness) from the gross working time.

In the following, a modular calculation model for personnel staffing of physicians is presented. For better understanding, we filled the tables with a sample of a virtual ICU (Tables 1-8). After gathering the relevant data for the calculation sheets, the respective data can be filled in the input fields (marked in white color in Tables 1-8). When all the relevant white fields in the Tables of a distinct ICU are filled with the respective data, staff requirements/year in hours are summed up,

Table 2 Additional patient-oriented tasks of physicians on the intensive care unit

		Inhouse time (min)	Standard time (min)	Numbers per yr	Total time
Examinations					
	Angiography (diagnostic/interventional)	120	120	45	5400
	CT scan	60	45	379	22740
	Examination	20	20		
	Preparation time for transit	20	20		
	Transit time	20	20		
	Magentic resonance tomography MRT	65	65	80	5200
	Examination	20	20		
	Preparation time for transit	30	30		
	Transit time	15	15		
	Diagnostic bronchoscopy	40	40	298	11920
	Twelve-lead ECG	10	10	0	0
	Haemodynamics (PAC/PiCCO)	15	15	114	1710
	Limon	30	30	0	0
	CVVHF (Heparin)/setup, change	30	30	2	60
	CVVHF (Citrate)/setup, change	40	40	398	15920
	MARS	120	120	0	0
	Thrombelastography (TEG)	20	20	0	0
	Setting up	5	5		
	Control	5	5		
	Finalization	10	10		
Tasks/procedures					
	Ascites puncture	20	20	0	0
	Installation of arterial line	10	10	254	2540
	ARDS - 135° position	20	20	280	5600
	Transfusion blood/coagulation products (per unit)	5	5	2732	13660
	Cardioversion	15	15	4	60
	Insertion of central lines (CVC, Sheldon, PiCCO)	40	40	374	14960
	Intracranial pressure measurement	15	15	16	240
	Intubation	15	15	100	1500
	Support of consultants	10	10	49	490
	Transportation to operating theatre (in/out)	20	20	2600	52000
	Installation of PAC/PiCCO	10	10	1	10
	Isolation of patients (f.e. MRSA)/d	15	15	45	675
	Installation of peridural catheters	30	30	6	180
	Percutaneous puncture of bladder	30	30	0	0
	Puncture of pleura (one-time)	20	20	0	0
	Transesophageal echocardiography	45	45	31	1395
	Chest tube	30	30	113	3390
	Tracheotomy (dilation/plastically)	60	60	93	5580
	Transvenous pacemaker	10	10	0	0
	Ultrasonography of bladder	10	10	238	2380
	Ultrasonography of pleura	10	10	200	2000
	Transfer of patient to external institutions	30	30	0	0
	Major wound care	15	15	50	750
Additional efforts (onetime/patient/stay)					
	Physician's letter (extensive, multi-page)	30	30	708	21240
	Final documentation in decease	30	30	113	3390
	Inquires by health insurance	15	15	35	525
	Preparation for rehabilitation	45	45	107	4815
Sum additional tasks					
	In min				200330
	In h				3339

CT: Computed tomography; MRI: Magnetic resonance imaging.

and automatically transferred to the following tables.

WORKLOAD-ORIENTED STAFFING CALCULATIONS

Basic effort includes all duties of physicians, which have to be done in each patient on admission, on a daily basis, handing over to other work-shifts, and on omission from the ICU, irrespective of severity of disease (Table 1). For calculation, different personnel staffing variations on working days, weekends and holidays have been taken into account.

The additional tasks, depending on severity of disease and organ dysfunctions, reflect all other tasks, procedures and examinations, as well as non-recurring tasks performed per year per patients (Table 2).

Table 3 Non patient-oriented tasks of physicians on the intensive care unit

		Time in h per year	FE net	
Working groups				Name working groups ... Projects
	Airway management	84	0.04	
	Haemostaseology	84	0.04	
	Regional anaesthesia	84	0.04	
	Working group A	84	0.04	Ultrasound
	Working group B	84	0.04	Quality management, SOPs
	Working group C	42	0.02	Hygiene standards
Administrative tasks				
	Waste management/recycling	42	0.02	
	Department homepage	42	0.02	
	Controlling	84	0.04	
	Duty rota/duty pay off	218	0.10	
	Inhouse continued education	42	0.02	
	Executive board meetings	104	0.05	
	Anual report	84	0.04	
	Documentation of effort	84	0.04	
	Computers and interconnection	84	0.04	
	Rotation	21	0.01	
	Emergency room management	21	0.01	
	Rota plan	42	0,02	
	Holiday plan	42	0.02	
	Certificates	42	0.02	
	Administrative task A	84	0.04	Strategy planning
	Administrative task B		0.00	
	Administrative task C		0.00	
Work in committees				
	Antibiotics	42	0.02	
	Drugs	42	0.02	
	Urban planning	84	0.04	
	Equipment	84	0.04	
	Materials management and control	42	0.02	
	Transfusions	42	0.02	
	Committee A	84	0.04	Patients's feedback
	Committee B		0.00	
	Committee C		0.00	
Students in practical year (PY)				
	Number of PY students per year			8
	Time demand of physicians for PY students (h)	2192	1.30	1 gross physician/8 PY-students
Work in projects				
	Project A	218	0.10	Antibiotic stewardship
	Project B		0.00	
	Project C		0.00	
	Project D		0.00	
	Project E		0.00	
Teaching				
	Nurses	500	0.23	
	Other matters		0.00	
Regulatory decrees/representatives			0.00	
	Worker protection	52	0.02	
	Data security	52	0.02	
	Diagnosis related groups	52	0.02	
	Hygiene	52	0.02	
	Devices	52	0.02	
	Hazardous material	52	0.02	
	Ordinance on medical devices	52	0.02	
	Quality management	52	0.02	
	Protection against X-rays	52	0.02	
	Transplantation	52	0.02	
Sum hours net per year (h)		5348.4	3.16	

Non patient-oriented-tasks reflect working groups, administrative tasks, collaboration in commissions, teaching of students or nurses, tasks in projects and regulatory decrees (*e.g.*, X-rays, hygiene, quality management, laws regarding medical products)[11], knowledge development and continuation requirements (Table 3).

Total calculation results from patient days and cases per year, time efforts for basic and additional tasks, and for non patient-oriented tasks, which are summed up (Table 4). To result in the net annual working time,

Table 4 Total calculation of physician staffing on the intensive care unit

		Time demand per patient (min)			
Patient days per year	5868				
Caes per year	705				
Public holidays/yr	11				
Total amount					
Numbers of "admissions"	705	Admission	65		
Numbers of "daily routine"	5163	Daily routine	41		
Numbers of "discharges/transferrals"	705	Discharge/transferral	25		
Numbers of "handing over rounds monday - friday"	4019	Handing over round monday - friday	75		
Numbers of "handing over rounds Sat, Sun, public hol."	1849	Handing over rounds Sat, Sun, public holidays	35		
Total times					
Time "takeover"	45825 min				
Time "daily routine"	211683 min				
Time "discharges/transferrals"	17625 min				
Time "handing over rounds monday - friday"	301438 min				
Numbers "handing over rounds Sat, Sun, public hol."	64709 min				
Total time BT	641280 min				
	10688 h				
Total time AT	3339 h				
Time demand (BT + AT)	14027 h				
Time for non patient-oriented tasks	5348 h				
Holidays for shift workers	205 h				
Total time expenditure	19580 h				
Rest allowance in %	19.5%				
Total time expenditure plus rest allowance	23398 h				
Working hours without break per day (h)	8.4				
Standard weekly hours of FE in h	42				
Annual net time per FE (h)	1691	Gross time per FE		2192	h
Number of FE	11.6	(net 1)			
Number of beds	16				
LS role	0.4	(0.15 FE/6 beds/net)			
Leadership role h/yr	676	(hours for 0.15 FE/6 beds/net)			
Number of physicians < 3 mo of ICU experience/yr	7				
PT	2.1	(0.3 FE/physician < 3 mo ICU experience/year/net)			
Postgraduate training hours per year	3550	(hours for 0.3 FE/physician < 3 mo ICU experience/yr/net)			
Total time + leader ship, PT	23806	h			
Number FE without continuing medical education	14.1	(net 2)			
CME/SA (h)	704		50	(h/yr/FE)	
Continuing medical education/staff appraisal in FE	0.4				
Total time + LS, PT, CME, SA (net total)	24511	h			
Number FE (net total)	14.5				

BT: Basic tasks; AT: Additional tasks; FE: Full-time employee; LS: Leader ship role; PT: Postgraduate training; CME: Continuing medical education; SA: Staff appraisal.

festive seasons and holiday seasons have to be taken into account. Additional times, *e.g.*, for holidays given to shift workers, should be added. Following, times for rest allowance for full-time work-fellows should be stated. Rest allowance reflects holidays and average illness, and have to be defined as percentage of gross annual working time (Table 4). Real annual personnel demand in hours can be converted to annual full-time equivalents in that the sum of annual hours is divided through the net annual working time hours of an employee. If management functions are associated with the number of beds (*e.g.*, 0.15 physicians per 6 beds), proportional personnel staff for management can be calculated *(e.g.*, 0.3 physicians per fellows with less than 3 mo of ICU experience). Moreover, given the number of work-fellows in training per year, additional staff for teaching can be stated. On top, additional time for work-fellow dialogue and knowledge continuation for each full-time work-fellow should be added. Taken together, all these items lead to the number of full-time physicians needed per year to fulfill the items named above.

AUXILIARY STAFFING CALCULATIONS

If the total workload and need of personnel staffing in full-time physicians per year is known, assistance tools can clarify how to distribute employees with differing average working time per week (Table 5). As shown in the example in Table 5, the mix with partial-time and full-time physicians results in sum in 17 work-fellows to fulfill the tasks which were calculated to be provided by 14.5 full-time employees.

Calculation of minimal physician staffing per year

Table 5 Calculation with work-fellows with different annual working times

Carryover of table total calculation, total time + rest allowance, leadership, postgraduate training							24511
CME, staff appraisal: AWT desired net value (h)							
	Standard weekly hours (h)	**Public holidays**	**Gross AWT (h)**	**Rest allowance plus LS, PT, CME, SA (%)**	**Net AWT (h)**	**Number of physicians**	**Net AWT real (h)**
Employee type 1	42.00	11	2192	19.5	1691	4.0	6762
Employee type 2	21.00	11	1096	19.5	808	2.0	1616
Employee type 3	48.00	11	2506	19.5	1943	1.0	1943
Employee type 4	54.00	11	2819	19.5	2195	3.0	6584
Employee type 5	10.50	11	548	19.5	367	1.0	367
Employee type 6	40.00	11	2088	19.5	1606	3.0	4819
Employee type 7	20.00	11	1044	19.5	766	3.0	2298
Employee type 8		11	0	19.5	-74		0
Employee type 9		11	0	19.5	-74		0
Employee type 10		11	0	19.5	-74		0
				Sum employees		17.0	
				Sum annual working time net (h)			24389
				Hours net demand (if negative values) (h)			-121

Gross AWT = [Standard weekly hours : 5 (d)] × (261 workdays - public holidays), underlying (365 running days - 102 saturdays; sundays = 261 workdays). Net AWT = gross AWT - [gross AWT × (Rest allowance plus LS, PT, CMA, SA)]. AWT: Annual working time; CME: Continuing medical education; LS: Leadership; PT: Postgraduate training; SA: Staff appraisal.

Table 6 Calculation of minimal physician staffing per year to run an intensive care unit

Shift model hours		Number of handing overs day	Sum handing over (min) per day	Sum handing over (h) per day		
Time handing over round (min)						
8 h	30	3	90	1.50		
12 h		2	60	1.00		
x h			0	0.00		
Standard weekly hours FE		42	(FE) in h	Gross per year	Net per year	
Working hours per day in h		8.4		2192	1691	
Rest allowance in %		19.5				
Minimal demand of physicians						
Minimal occupancy: 1 physician, 24 h/d, 7 d/wk, 365 d/yr						
Number of physicians per shift		Shift	Net hours per day plus handing over	Net hours per year plus handing over	Gross hours per year plus handing over	FE net 42 h/wk
1		8 h	25.50	9308	11122	6.6
1		12 h	25.00	9125	10904	6.5
1		x h	24.00	8760	10468	6.2

Not considered: times for CME, LS, PT, SA. Take care for legal working regulations: *e.g.*, at maximum 48 h/wk in shift work, as well as 54 h/wk with opt-out in standby duty! Take care for legal regulations: *e.g.*, at maximum 12 h shift + 45 min handing over!AWT: Annual working time; CME: Continuing medical education; FE: Full-time employee; LS: Leadership; PT: Postgraduate training; SA: Staff appraisal.

to run an ICU is presented in Table 6. How many work-fellows do I need at minimum to guarantee a 24-h, 7-d a week, 365-d a year coverage with physician personnel, and in some countries, depending on that to get reimbursed or fulfill quality standards? Calculating the hours needed per year to cover full-time physician coverage, reflecting average drop-out times (holidays, average time for illness, *e.g.*, 19.5% per year) and legal working regulations (*e.g.*, 12.75 h per day at maximum in shift work with at maximum 48 h per week with standby duty of 54 h at maximum per week), minimal staffing demand can be calculated (Table 6). In this calculation, times for non-patient-oriented tasks, continuing medical education, leadership tasks, postgraduate training and staff appraisal are not considered.

If the total workload and need of personnel staffing in full-time physicians is known, an assistance tool may help to calculate the personnel needed to run the ICU based on shift work (Table 7).

Also, with known total workload, with an assistance tool, calculation of the personnel needed to run the ICU based on standby duty is possible (Table 8).

Table 7 Calculation of physician staffing in shift work

Duty hours (shift)					**06:00-14:54**	**Time**						
Public holidays / year					**11**		**Carryover of table total calculation, total time plus RA, LS, PT, CME, SA =**				**Demand of physicians**	
Rest allowance in %					**19.5**							
Working hours without break per day (h)					**8.4**		**Sum net annual working time desired (h)**				**24511**	
Standard weekly hours of full-time employee (FE) in h					**42**		**Sum number full-time physicians (net total) desired**				**14.5**	
Gross annual time per full-time employee FE (h)					**2192**							
Net annual time per full-time employee FE (h)					**1691**		**(without public holidays, holidays, illness)**					
Shift	**Days**	**Shift model**	**Start**	**End**	**Break h**	**Working hours without break h**	**Physician/ shift**	**Demand/week**		**Physicians**	**Demand /year**	
								Workdays/ week (*n*)	**Workhours/ week**	**Workdays/ year (*n*)**	**Workhours/ year net (h)**	**Full-time employees/ year net**
a. m. shift	Weekday	8 h	6:00	14:54	0.5	8.4	5	5	210	250	10500	6.2
p. m. shift	Weekday	8 h	14:00	22:54	0.5	8.4	2	5	84	250	4200	2.5
night shift	Weekday	8 h	22:00	6:54	0.5	8.4	2	5	84	250	4200	2.5
a. m. shift	Weekday	8 h	6:00	14:54	0.5	8.4	2	2	33.6	104	1747.2	1
p. m. shift	Weekday	8 h	14:00	22:54	0.5	8.4	2	2	33.6	104	1747.2	1
night shift	Weekday	8 h	22:00	6:54	0.5	8.4	2	2	33.6	104	1747.2	1
a. m. shift	Public holiday	8 h	6:00	14:54	0.5	8.4	2			11	184.8	0.1
p. m. shift	Public holiday	8 h	14:00	22:54	0.5	8.4	2			11	184.8	0.1
night shift	Public holiday	8 h	22:00	6:54	0.5	8.4	2			11	184.8	0.1
Senior physician	weekend/ Public holiday		8:00	10:00	0	2	1	2	4	115	230	0.1
Inhouse special duty			0:00	0:00					0		0	0
								Sum	482.8		24926	14.7
								Net demand			-415.4	-0.2

Take care for legal regulations: *e.g.*, at maximum 12 h shift + 45 min handing over! Take care for legal working regulations: *e.g.*, at maximum 48 h/wk in shift work! CME: Continuing medical education; FE: Full-time employee; LS: Leadership, PT: Postgraduate training; SA: Staff appraisal.

DISCUSSION

One calculation tool cannot cover all aspects worldwide. However, modular tools, such as the BDA/DGAI tool[10], have the key advantage to systematically look at the own performance spectrum, structural and legal conditions, and to calculate the corresponding personnel need. It should be kept in mind that besides all the workload-based calculations, due to arrange for manpower, a minimal personnel staffing is necessary to run an ICU with full-time coverage by a physician 24-h, 7-d a week, 365-d a year. This minimal staffing demand is independent of the workload, number of beds and patients.

Regarding medicolegal aspects, professional societies in Germany (DIVI, DGAI) and in Europe (ESICM) agree on the demand of continuous presence of physicians on the ICU. Previous top-down staffing models resulted in a high variability between sufficient and underpowered personnel resources. For example, the top-down calculation of the European Society of Intensive Care Medicine suggested the need of 5 physicians per ICU comprising 6 to 8 beds per year[4,5]. Thus, calculation of a 24 bed unit leads to a demand of 15 to 20 physicians, and, thereby, to a difference in demand of 5 physicians or 25%. In Germany, 24-h coverage by a physician is an inalienable prerequisite for reimbursement within the G-DRG system in terms of quality management. The presented calculation instrument directly couples workload to the personnel demand. Irrespective of quantitative calculations of staff, in Germany, reflecting legal demands, it has to be assured that performance is delivered all the time economically and according to commonly accepted standards of care and knowledge[12] on the level of an experienced physician[13], with benefit for the patient. Thus, besides quantitative, qualitative cornerstones for personnel requirement of physicians on ICUs have to be taken into account. The modular basis of the BDA/DGAI tool allows subsets of patients treated, social and industrial law, medical quality standards, economic and reimbursement items of the respective countries to be taken into consideration and to adapt the tool for personnel staffing in various countries and types of hospitals. In former days, the ICU personnel staffing tool was allocated *via* disc in Germany. Currently, it is provided online for free to all BDA/DGAI members, and, at the owner's expense, to interested stakeholders by BDA/DGAI[10]. The tool is widespread all over Germany in university and non-university hospitals and has been fine-tuned through the years since 2008, reflecting and

Table 8 Calculation of physician staffing in standby duty

Duty hours (shift)					**07:15-16:09**		**Time**						
Public holidays/year					**11**			**Carryover of table total calculation, total time plus**				**Demand of physicians**	
Rest allowance in %					**19.5**			**RA, LS, PT, CME, SA =**					
Working hours without break per day (h)					**8.4**			**Sum net annual working time desired (h)**				**24511**	
Standard weekly hours of full-time employee (FE) in h					**42**			**Sum number full-time physicians (net total) desired**				**14.5**	
Gross annual time per full-time employee FE (h)					**2192**								
Net annual time per full-time employee FE (h)					**1691**			**(without public holidays, holidays, illness)**					
Shift	**Days**	**Type**	**Start**	**End**	**Break h**	**Working hours without break h**	**Physician/ shift**	**Demand physicians/wk**		**Demand physicians/yr**			
								Workdays/ wk (*n*)	**Workhours/ wk**	**Workdays/ yr (*n*)**	**Workhours/ yr net**	**Core time full-time employee/ yr net**	**Standby duty full-time employees/yr net**
a. m. shift	Weekday		7:15	16:09	0.5	8.4	3	5	126	250	6300	3.7	
p. m. shift	Weekday		13:30	22:24	0.5	8.4	2	5	84	250	4200	2.5	
x shift	Weekday		0:00	0:00				5	0	250	0	0	
a. m. shift	Weekday		7:15	16:09	0.5	8.4	0	2	0	104	0	0	
p. m. shift	Weekday		0:00	0:00				2	0	104	0	0	
x shift	Weekday		0:00	0:00				2	0	104	0	0	
a. m. shift	Public holiday		7:15	16:09	0.5	8.4	2			11	184.8	0.1	
p. m. shift	Public holiday		0:00	0:00			2			11	0	0	
x shift	Public holiday		0:00	0:00			2			11	0	0	
Standby duty	Weekday	1	0:00	0:00	0			5	0.0	250	0		0
Standby duty	Weekend	1	0:00	0:00	0			2	0.0	104	0		0
Standby duty	Public holiday	1	0:00	0:00	0					11	0		0
Standby duty	Weekday	2	16:09	8:00	0	15.85	2	5	158.5	250	7925		4.7
Standby duty	Weekend	2	7:15	8:00	0	24.75	2	2	99	104	5148		3
Standby duty	Public holiday	2	7:15	8:00	0	24.75	2			11	544.5		0.3
Senior physician	Weekend /public holiday		8:00	10:00	0	2	1	2	4	115	230		0.1
Inhouse special duty			0:00	0:00					0		0		0
Sum									261.5		24532.3	6.3	8.2
Sum core time, standby duty + special duties full-time employees net													14.5
Net demand											-21.7		0

CME: Continuing medical education; FE: Full-time employee; LS: Leadership; PT: Postgraduate training; SA: Staff appraisal.

integrating the feedback of the users. However, studies reflecting improved outcomes or better productivity have not been performed. Feedback to BDA/DGAI revealed that personnel calculations were effectuated in around 1/3 of the users, transposed partially in 1/3, and not accepted in 1/3. Unfortunately, there is no in total or representative scientific evaluation of personnel staffing in non-university and university hospitals all

over Germany which could reflect the gap between the calculations done by the tool and the actual personnel staffing of the ICUs. Moreover, whether staffing differences from basic and regular care up to maximal care hospitals result in better productivity or improved outcome in Germany is still a matter of debate. However, quality of care, length of stay and mortality in ICUs has been reported to be highly dependent on organisational structures, personnel staffing and qualification of physicians[9,14,15]. Reductions in personnel staffing are counterproductive if safety for patients and staff, and efficiency of processes decline[16-19], and/or the costs for materials increase[18,20]. Furthermore, it has to be taken into account that optimal reduction in errors is expected with a 85% average utilisation of an ICU with 100% of personnel staffing[19]. To achieve optimal quality, physician staffing has been claimed as follows[5,21]: The ICU has to be under a qualified, uniform, physician organised guidance, *e.g.*, by a physician of a specialty which has intensive care medicine as an integrated part, such as anaesthesia, surgery, internal medicine, and who has special certification in intensive care medicine. The leader of the ICU should not be in other duties in his hospital, devoted full-time or at least 75% of time to intensive care[5,21].

To find out whether timings for tasks are realistic, in the ICU personnel staffing tool, we proceeded as follows. To determine duration of tasks to be performed, estimations by experts' opinion (10 leaders of ICUs), a survey in 200 ICUs in Germany (practitioning ICU physicians), and real time measurements on a surgical and a medical university and a non-university interdisciplinary ICU of a basic and regular care hospital have been compared[22]. In 20%, expert opinion survey and measured times were consistent. Differences, such as higher values for daily routine in the basic care non-university hospital, may be explained by different process operations on the various wards. Thus, necessary time requirements depend on the comparability of basic prerequisites, process operations, structural and legal conditions. Therefore, cited timings for tasks can serve as an indication for time requirements, however, have to be verified, at best with real time measurements in the own structural conditions and process operations.

Tasks beyond the ICU, such as initial trauma care, care for in-hospital emergencies or engagement as external emergency physician, should not be incorporated in the staffing calculation of the ICU, but calculated separately. Quantitative and qualitative cornerstones for personnel requirement of physicians in anaesthesia reflecting recent legal rights of patients in Germany, meeting legal demands of therapeutic quality, and, thus, serving patient safety, have been published in 2015 by the German Society of Anesthesiologists (BDA) and the German Society of Anesthesiology and Intensive Care Medicine (DGAI)[23]. Subsequently, the current Excel-based calculation tool version (2015) regarding physician staffing in anaesthesia has been published, especially reflecting recent laws governing physician's working conditions and competence in the field of anaesthesia, as well as demands of strengthened legal rights of patients, patient care and safety[24].

CONCLUSION

Workload-oriented models of physician staffing with generalizable items taking into account quality, efficiency of processes, legal, educational, controlling, local, organisational and economic aspects, differentiating basic effort, additional effort, and non patient-oriented tasks, may help to justify realistic personnel staffing demands. Modular calculation models may serve to individualise generalizable aspects to various types of hospitals, process operations, structural and legal conditions, as well as funding and refunding systems, resulting in broadly use and acceptance by various stakeholders all around the world. In the future, it should be evaluated whether this model may lead to improvement of patient safety and quality of management.

ACKNOWLEDGMENTS

We thank Vagts DA, Schleppers A, Leidinger W, Sehn N and Klöss T of the working group "personnel management of BDA and DGAI" for their constructive contribution to develop and update the workmanship oriented modular calculation model for personnel staffing of physicians in the ICU in 2008 and in 2012. We thank Clair Hartmann, MD, working in our Department of Anesthesiology in Ulm, for checking the manuscript as a native speaker.

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P- Reviewer: Krishnan T, Lin JA **S- Editor**: Song XX **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

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World J Crit Care Med 2017 August 4; 6(3): 164-171

DOI: 10.5492/wjccm.v6.i3.164

ISSN 2220-3141 (online)

EVIDENCE-BASED MEDICINE

Effects of intrapulmonary percussive ventilation on airway mucus clearance: A bench model

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Author contributions: All authors contributed equally to the literature search, data collection, study design and analysis, manuscript preparation and final review.

Conflict-of-interest statement: None of the authors have any conflicts of interest.

Data sharing statement: There is no technical appendix for this manuscript because the study was extensively described within the manuscript itself. The statistical codes and the raw dataset were also included within the manuscript.

Manuscript source: Invited manuscript

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Received: May 7, 2017
Peer-review started: May 10, 2017
First decision: May 23, 2017
Revised: June 1, 2017
Accepted: June 30, 2017
Article in press: July 3, 2017
Published online: August 4, 2017

Abstract

AIM

To determine the ability of intrapulmonary percussive ventilation (IPV) to promote airway clearance in spontaneously breathing patients and those on mechanical ventilation.

METHODS

An artificial lung was used to simulate a spontaneously breathing patient (Group 1), and was then connected to a mechanical ventilator to simulate a patient on mechanical ventilation (Group 2). An 8.5 mm endotracheal tube (ETT) connected to the test lung, simulated the patient airway. Artificial mucus was instilled into the mid-portion of the ETT. A filter was attached at both ends of the ETT to collect the mucus displaced proximally (mouth-piece filter) and distally (lung filter). The IPV machine was attached to the proximal end of the ETT and was applied for 10-min each to Group 1 and 2. After each experiment, the weight of the various circuit components were determined and compared to their dry weights to calculate the weight of the displaced mucus.

RESULTS

In Group 1 (spontaneously breathing model), 26.8% ± 3.1% of the simulated mucus was displaced proximally, compared to 0% in Group 2 (the mechanically ventilated model) with a *P*-value of < 0.01. In fact, 17% ± 1.5% of the mucus in Group 2 remained in the mid-portion of the ETT where it was initially instilled and 80% ± 4.2% was displaced distally back towards the lung (*P* < 0.01). There was an overall statistically significant amount of mucus

movement proximally towards the mouth-piece in the spontaneously breathing (SB) patient. There was also an overall statistically significant amount of mucus movement distally back towards the lung in the mechanically ventilated (MV) model. In the mechanically ventilated model, no mucus was observed to move towards the proximal/mouth piece section of the ETT.

CONCLUSION

This bench model suggests that IPV is associated with displacement of mucus towards the proximal mouthpiece in the SB patient, and distally in the MV model.

Key words: Mucus; Sputum; Mechanical ventilators; Percussion; Respiratory drainage; Breathing exercises

Core tip: Many respiratory conditions result in increased respiratory secretions and poor clearance, and are associated with poor patient outcomes. Intrapulmonary percussive ventilation (IPV) is an airway clearance technique that has become increasingly used over the last few years, however there is a paucity of data to support its efficacy. Using a simulated bench model, we found that IPV is associated with movement of mucus towards the mouth in the spontaneously breathing patient and thus supporting airway clearance. Interestingly, in patients on mechanical ventilation, IPV mainly displaced mucus distally into the lungs and thus may be harmful in this patient population.

Fernandez-Restrepo L, Shaffer L, Amalakuhan B, Restrepo MI, Peters J, Restrepo R. Effects of intrapulmonary percussive ventilation on airway mucus clearance: A bench model. *World J Crit Care Med* 2017; 6(3): 164-171 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i3/164.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i3.164

INTRODUCTION

Many chronic conditions such as bronchiectasis, cystic fibrosis (CF), neuromuscular disease and chronic obstructive pulmonary disease (COPD) are associated with an increase in both the quantity and viscosity of respiratory secretions. Other conditions are associated with a decreased ability to clear secretions, such as those with impaired ciliary function or cough, with the latter being very common during mechanical ventilation, after strokes or surgical procedures, and in neuromuscular disorders[1]. Previous studies have shown that when these secretions are not adequately cleared, complications arise such as atelectasis, mucus plugging, and recurrent pneumonia[1]. Inadequate mucus clearance in patients in the intensive care unit (ICU) can lead to poor clinic outcomes such as prolonged time on mechanical ventilation, increase in need for tracheostomies, decreased quality of life, overall worsening lung function and an increase in mortality[2-6]. Administration of airway clearance therapies (ACTs) involve the use of manual techniques coupled with postural drainage, breathing exercises and mechanical devices to improve patient outcomes and optimize recovery after acute illnesses[7]. However, there are few studies on the optimal ACT and under which clinical settings they are most effective[8,9].

Intrapulmonary percussive ventilation (IPV) is one such ACT that has recently become increasingly utilized in hospitalized patients. During IPV treatments, the patient breathes through an accessory device called a Phasitron®, which delivers rapid, high flow, mini-bursts (percussions) of tidal volumes into the lungs while simultaneously delivering therapeutic aerosols. In the clinical setting, IPV can be administered by mouthpiece, mask or endotracheal tubes (ETTs). This technique is also thought to improve expiratory flow by opening collapsed airways, thus promoting mucus clearance.

Several reports have suggested that IPV facilitates airway clearance and improves ventilation in patients with conditions such as cystic fibrosis[10-14], neuromuscular disorders[15,16], atelectasis[17-19], inhalation injury[20-22], and COPD[23-26]. To our knowledge there has only been one study that has evaluated the efficacy of IPV as an ACT in spontaneously breathing patients, and it illustrated a positive benefit[27]. When oscillating devices such as IPV were compared to conventional physiotherapy for airway clearance in people with cystic fibrosis, the most recent Cochrane meta-analysis found little evidence to support the use of any particular oscillating device for airway clearance over any other ACT modality[28]. The handful of other studies that exist have compared IPV to conventional chest physical therapy and showed no additional benefit with IPV. These results raise the question of whether IPV indeed is able to act as an effective ACT or whether its benefit is simply theoretical[14,29]. Furthermore, to our knowledge only one study has evaluated the efficacy of IPV in mechanically ventilated patients, and although it showed some benefit, it was completed only in a specific population of eight patients with neuromuscular disease[15]. Despite IPV's widespread use as an ACT across numerous clinical settings, there are a paucity of data to document its benefit.

The objective of this study was to evaluate the ability of IPV to promote airway clearance in both spontaneously breathing patients and those on mechanical ventilation using a controlled simulated bench model.

MATERIALS AND METHODS

Artificial test lung

The artificial test lung was obtained from "Michigan Instruments" (Grand Rapids, MI) and utilized in both the spontaneously breathing (SB) group/model and the mechanically ventilated (MV) group/model. This artificial test lung has been validated and mimics the human lung in many ways. First, the artificial test lung

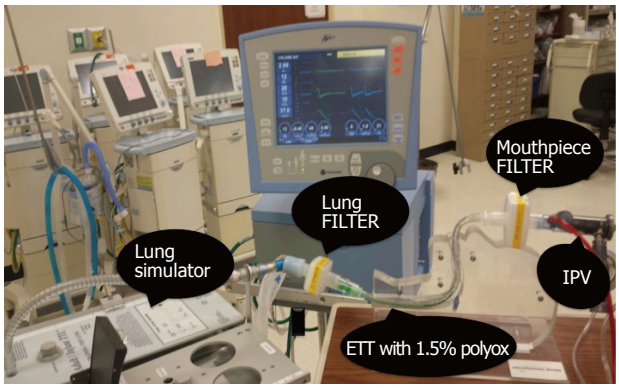

Figure 1 Experimental circuit utilized. The IPV2-C machine (Percussionaire Corporation; Sagle, ID, Figure 2) was attached to the proximal end of the ETT. The IPV device was given a constant setting with a frequency of 230 cycles/minute, an I/E ratio of 1: 4, and an airway pressure of 30 cmH_2O. The IPV was applied for 10-min each to group 1 and Group 2. IPV: Intrapulmonary percussive ventilation; ETT: Endotracheal tube.

Figure 2 Intrapulmonary percussive ventilation-C machine (Percussionaire Corporation; Sagle, ID).

has a total lung capacity that replicates a "normal" adult human lung, which is approximately 4-6 L. Thus the size of the artificial lung mimics that of a "normal" adult human lung. Second, the test lung also mimics the standard human lung's residual volume (1.84 L). Third, we used a standard compliance of 30 mL/cmH_2O in both groups which is equivalent to a patient with severe pneumonia, in order to mimic the actual scenario for which IPV would be utilized in clinical practice. Furthermore, we used a standard airway resistance of 5 cmH_2O/L per second which mimics the normal airway resistance of an actual patient. Fourth, this artificial test lung has also been shown to mimic the pressure-to-flow and pressure-to-volume relationships in normal human lungs[30].

Experimental model

An artificial test lung was used to simulate a spontaneously breathing patient (Group 1 or SB), and then connected to a mechanical ventilator (Avea, BD; Yorba Linda, CA) to simulate a mechanically ventilated patient (Group 2 or MV). An 8.5 mm ETT connected to the test lung was used to simulate the patient airway. The ventilator parameters selected for the study were a tidal volume of 400 mL, a respiratory rate of 12 breaths/min, an inspiratory time of 1 s, and a PEEP of 5 cmH_2O. These setting demonstrated little or no movement of mucus in the absence of IPV. Five milliliters of 1.5% of a water-soluble resin coagulant used as a mucus simulant (Polyox; Dow Chemical Company; Cary, NC, United States) were instilled into the mid-portion of the ETT. This percent viscosity is shown to be most consistent with that of mucus in a normal human airway[31]. An anesthesia filter was attached at both ends of the ETT to collect the artificial mucus displaced proximally (mouthpiece filter) and distally (lung filter) the proximal end was defined as the "Mouth Piece Filter", which was the "goal exit site" of the displaced mucus. The distal end was defined as the "Lung Filter", which was the site considered within the lungs. The experimental setup can be seen in Figures 1 and 2.

An Allosun portable oscillometer EM116 (Allosun, China) was used to document the rate on the IPV that generated a frequency of 240 cycles/min. This frequency was selected as it represents the highest frequency obtained by similar devices. An I/E ratio of 1:4 was selected and airway pressure was adjusted to 30 cmH_2O prior to connecting each device to the inspiratory limb of the ventilator circuit.

In Group 1 (SB), 10 trials were performed to document variability between experiments. Since experimental variability was less than 5%, only 3 trials were completed for Group 2 (MV). Each experiment was run for 10 min since this is the typical time the treatment is administered in the clinical setting.

Measurements

After each experiment, the weight of the following circuit components was determined and compared to their dry weights to calculate the weight of the displaced mucus: (1) "Mouth Piece Filter" (proximal filter); (2) Proximal ETT; (3) Mid-ETT (portion 23-27 cm); (4) Distal ETT; and (5) "Lung Filter" (distal filter).

Key variables

The concept of fluid dynamics as it relates to the movement of mucus within the airway is also important, and it is worthwhile to acknowledge that variables such as temperature/humidity, the density/concentration of the mucus and flow conditions were controlled in this experiment. Each experiment was conducted in a lab room strictly controlled at 32 ℃, which is the average temperature of the upper trachea in humans[32]. The humidity of the room was also strictly controlled at standard values (heated humidified air was not used). All experiments were completed with the same viscosity/density of artificial mucus which has been shown to be consistent with the mucus in a normal human airway as illustrated by Shah *et al*[31]. All experiments were conducted using the same flow as well. By keeping these variables constant, the effects

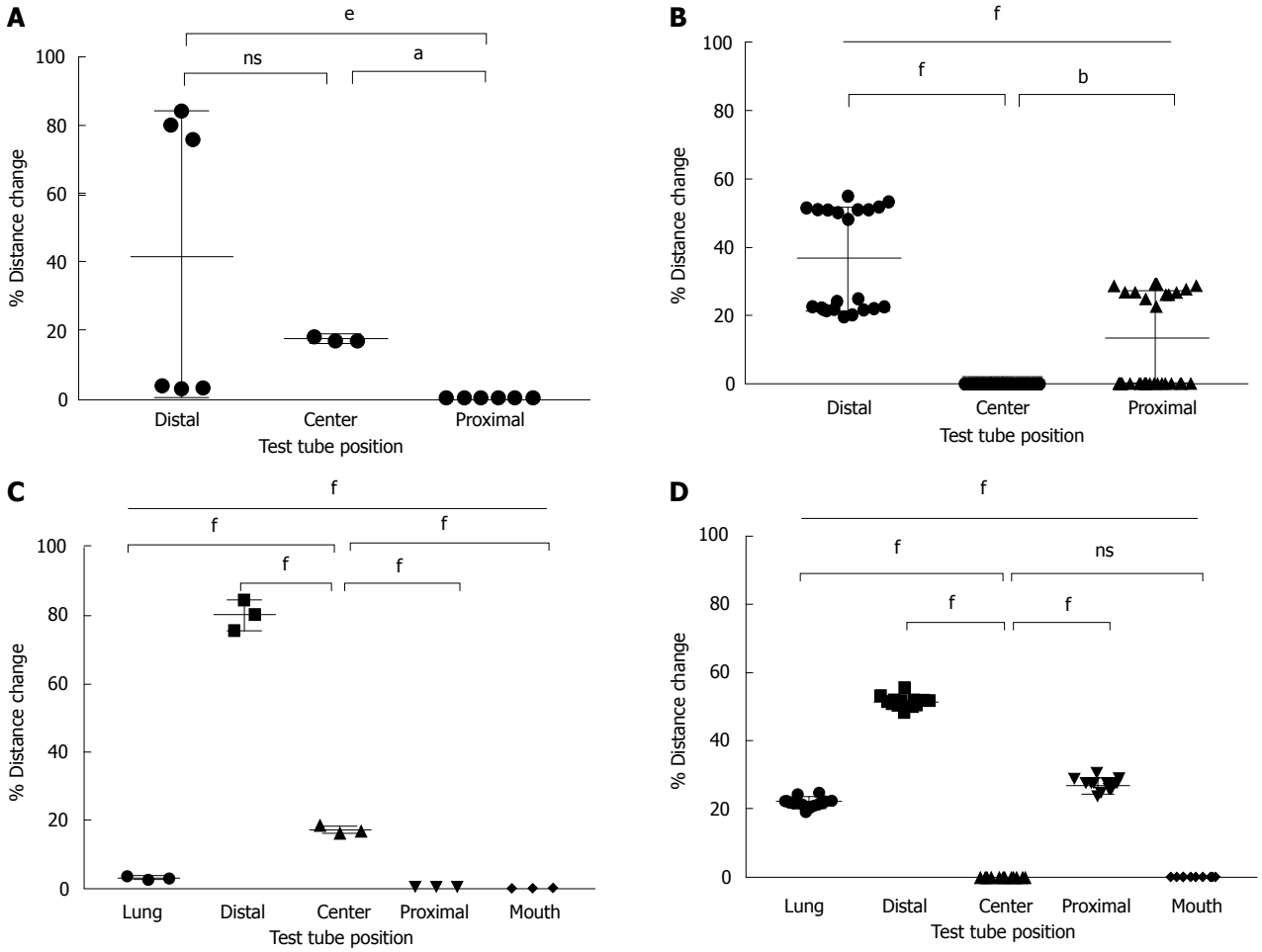

Figure 3 Percent of distance of mucus movement in the different portion of the endotracheal tube in both simulated intrapulmonary percussive ventilation models: mechanical ventilation (A and B) and spontaneous breathing (C and D). There was an overall statistically significant amount of mucus movement proximally towards the mouth-piece in the spontaneously breathing patient. There was also an overall statistically significant amount of mucus movement distally back towards the lung in the mechanically ventilated model. Statistical significant *P* values: $^{a}P < 0.05$, $^{b}P < 0.01$, $^{e}P < 0.001$, $^{f}P < 0.0001$. ns: No statistical significance.

of the intervention (use of IPV) in both groups could be evaluated within a constant/replicable environment/context.

Statistical analysis

Due to the limited sample size used in this study, the distribution of the data were not distributed normally, and for this reason only non-parametric tests were used[33]. All data are presented as medians with interquartile ranges (IQR), or means with standard deviations (SD) as appropriate. Paired nonparametric Mann-Whitney *U* test, Kruskal Wallis test or two-tailed Student's *t*-test were used to compare data at different tube distances. All statistical calculations were performed by a trained and expert biostatistician, using Prism 5 software (GraphPad) and SPSS 21.0. *P* values < 0.05 were considered statistically significant.

RESULTS

In Group 1 (spontaneously breathing model), 26.8% ± 3.1% of the simulated mucus was displaced proximally, compared to 0% in Group 2 (the mechanically ventilated model). In fact, 17% ± 1.5% of the mucus in Group 2 remained in the mid-portion of the ETT where it was initially instilled and 80% ± 4.2% was displaced distally back towards the lung. There was an overall statistically significant amount of mucus movement proximally towards the mouth-piece in the spontaneously breathing patient. There was also an overall statistically significant amount of mucus movement distally back towards the lung in the mechanically ventilated model. The amounts of mucus measured within each section of the circuit is shown in Table 1 and Figure 3.

DISCUSSION

The results from this study suggest that when IPV is used in a simulated model of a spontaneously breathing patient, it is associated with a statistically significant amount of mucus movement proximally, and thus supports airway clearance. In contrast, when IPV is used in the simulated model of a mechanically ventilated patient, it was found to be associated almost exclusively with the displacement of mucus distally back towards the lung, and thus did not support airway clearance.

Table 1 Amount of mucus within each section of the circuit

Location	Group 1 (%)	Group 2 (%)
Mouth piece/proximal filter	0	0
Proximal ETT	26.8 ± 0.63	0
Mid-ETT (portion 23-27cm)	0	17 ± 1.04
Distal ETT	51.2 ± 1.75	80 ± 4.2
Lung/distal filter	22 ± 0.55	3 ± 1.04

ETT: Endotracheal tube.

IPV utilizes tidal volumes delivered at high oscillatory frequencies to loosen mucus and help with expectoration. Previous bench models have shown that high-frequency oscillations not only dislodge bronchial secretions from the walls of the airway but also reduce its actual viscosity making it easier to clear[34]. In a way these oscillations act like a "physical mucolytic". One clinical study has shown that applying high-frequency oscillations directly to the airway opening of spontaneously breathing patients does indeed enhance secretion clearance compared to no therapeutic intervention[27]. Our study confirms the results from this study that IPV indeed improves mucus clearance in a simulated model of a spontaneously breathing patient. However, it is worth noting that when IPV has been compared to conventional chest physical therapy in spontaneously breathing patients, there appears to be no difference in efficacy of mucus clearance. In a study of 20 clinically stable CF patients, IPV was not associated with increased sputum clearance compared to conventional chest physical therapy[14]. Another study of 22 stable patients with bronchiectasis found similar results[29]. Taking the results from this current study and the study by George *et al*[27], IPV indeed improves sputum clearance; however, it may not provide added benefit compared to conventional chest physical therapy. However, the major value of IPV when compared to conventional chest physical therapy appears to be its increased tolerability, patient preference, replicability of its benefits and greater adherence to therapy, considering that conventional chest physical therapy is often uncomfortable and requires an experienced/trained individual to aid the patient for optimal results[29]. Since the benefit of chest physical therapy depends on the patient and the therapist, the benefits seen in the studies by Van Ginderdeuren *et al*[14] and Paneroni *et al*[29] may be difficult to replicate, making IPV more advantageous. Thus IPV may be a more effective clinical alternative for airway clearance in spontaneously breathing patients, although this requires further clinical studies to validate.

Similarly, there are few studies evaluating the efficacy of IPV as an ACT in mechanically ventilated patients. In one small observational study conducted in 8 patients with Duchenne Muscular Dystrophy who were ventilator dependent and had tracheostomies, IPV was shown to increase the quantity of mucus clearance[15]. Our study showed the opposite findings, and in fact showed that more than 80% of the mucus was displaced distally back towards the lung. The biologic plausibility of why IPV may be detrimental in patients on invasive MV is important to understand considering these negative consequences. It is possible that the interplay between the positive pressure from the MV and the percussive oscillatory pressure waves from the IPV machine created a flow that was directed distally rather than proximally towards the opening of the airway. While this finding was noted in our study, it is not clear if this occurs *in vivo*. But considering that the majority of the mucus (approximately 80%) was displaced distally in the MV group, and that our artificial test lung and bench model has been validated and extensively used by prior studies, it raises valid concerns about its safety that requires further testing[35-37]. IPV is currently being used in mechanically ventilated patients at variable driving pressures and oscillatory frequencies (our study chose the most common setting used clinically) and its use is growing exponentially. We hope the results of this bench study will result in additional future studies.

There are several limitations of this study. One of which is that *in vitro* models do not perfectly reflect the flow characteristics of a spontaneously breathing patient. Our *in-vitro* model did not measure the impact of the treatment effects within a chest cavity where recoil of the chest plays a significant role in increasing expiratory flows. If active expiration were to be simulated as happens in the spontaneously breathing patient, higher expiratory flows could have enhanced mucus transport to either the proximal end of the ETT or the filter representing the mouthpiece. However, there are many advantages to studying IPV in this simplified bench model that would be difficult to evaluate in an actual clinical setting. For example, using this simulated model, we can directly measure the amount of mucus in the airway and directly determine the amount displaced in either direction. In patients, we cannot control for the actual amount of mucus in the airway at time zero because this will vary from hour-to-hour and day-to-day. Furthermore, different patients will differ in their baseline amount of mucus production based on complex physiological mechanisms and differences in their disease processes. This simplified model allows control of many factors that cannot be controlled in an *in-vivo* model. One of the main reasons for performing this study is that many Health Care Professionals accept that IPV is beneficial in both spontaneously breathing and mechanically ventilated patients with almost no data to document or substantiate its actual benefit. Our goal was to raise awareness through a bench study and create interest in furthering clinical research in this area.

Another potential limitation worth mentioning is that our model of the human lung did not contain cilia. An important question is whether IPV may interact with human cilia and in a manner our model could

not account for. However, we were unable to find any literature to support the concept that IPV may indeed promote or suppress ciliary function. While we are not capable of predicting the effects of IPV on ciliary motion, it is possible that IPV may reduce or enhance ciliary function. This is clearly an area of research that needs to be investigated. Additionally, many acute and chronic disease processes cause dysfunction of the mucociliary system[38]. For example many chronic pulmonary diseases such as primary ciliary dyskinesis, COPD, asthma and cystic fibrosis have abnormal functioning and dysplastic cilia when examined under electron microscopy[38]. Furthermore, cigarette smokers and those with acute pneumonia also have been shown to have significant ciliary dyskinesia from direct effects of bacterial and viral pathogens[38,39]. No bench model can attempt to reproduce the complexity or variability of ciliary function, but its plausible that the lack of cilia in our model mimics in some capacity the actual human lung during many disease states.

A third potential limitation in our study was that although we controlled for humidification by conducting our experiments in a tightly controlled environment within a room at standard humidity, we did not attach a humidifier to our experimental circuit separately. Dellamonica *et al*[40] found that the optimal way to effectively humidify this circuit was to attach a humidifier down stream from the IPV machine. Dellamonica *et al*[40] recognized that when IPV is combined with invasive mechanical ventilation, the production of high inspiratory flow rates and gas decompression prevented optimal humidification and warming of the inspired gas. This combination often results in the drying of mucus and the risk for airway obstruction. The question arises whether this may have caused the lack of proximal movement of the mucus in our MV model. Although this is plausible, if this was indeed the reason for the negative impact of IPV in our MV model, we would have expected the majority of the mucus to remain in the middle of the circuit where it was initially instilled, and not be displaced distally (> 80% of the mucus in fact moved distally). Furthermore, because each experiment was conducted for a very short period of time (approximately 10 min) the potential desiccating properties of the IPV machine should not likely have made a large impact. But regardless, further studies are needed to confirm or refute this hypothesis.

A fourth limitation is that our study used only fixed settings on the IPV. Although an I:E ratio of 1:4 is consistently selected by most users when administering IPV, it may have explained a lower mucus displacement towards the proximal filter than expected. Movement of mucus is dependent not only on viscosity/elasticity but also adhesivity. This model also did not utilize either artificial epithelial lining fluid or surfactant that might have better reflected the adhesive properties of mucus within human airways.

Overall, although IPV may indeed be a beneficial means to induce airway mucus clearance, this study highlights that that optimal clinical settings in both spontaneously breathing and mechanically ventilated patient need to be further elucidated to determine who will benefit from this mode of therapy and under which circumstances. It is also reasonable to infer that during mechanical ventilation, IPV may not be beneficial and could result in forward movement of secretions into the lung. Future studies on its use and optimal settings in both MV and SB patients are clearly warranted.

COMMENTS

Background

Many respiratory conditions are associated with an increase in respiratory secretions. Retention of these secretions is associated with poor patient outcomes. Intrapulmonary percussive ventilation (IPV) is a type of airway clearance technique that helps to remove airway mucus. Despite its widespread use across numerous clinical settings, there is a paucity of data to support its efficacy.

Research frontiers

There is little research in the area of air way clearance therapies (ACT's), and those that do exist have small sample sizes with a lack of effective control subjects. As the prevalence of cystic fibrosis increases due to patients living longer and the increased identification of previously undiagnosed patients with non-cystic fibrosis bronchiectasis, the need for more effective and validated airway clearance therapies is becoming more important.

Innovations and breakthroughs

There are few studies that have evaluated the effectiveness of IPV in both spontaneously breathing patients, and even fewer in those requiring mechanical ventilation. Furthermore, the study of ACTs in actual patients is complex due to patient-to-patient variabilities in their underlying disease states and variabilities in mucus production hour-to-hour and day-to-day. This study is one of the few bench studies that exist evaluating the effectiveness of IPV in two important clinical states, using an effective control group.

Applications

One of the main reasons for performing this study is that many Health Care Professionals accept that IPV is beneficial in both spontaneously breathing and mechanically ventilated patients with almost no data to document or substantiate its actual benefit. The results from this study suggest that when IPV is used in a simulated model of a spontaneously breathing patient, it is indeed associated with a statistically significant amount of mucus movement proximally, and thus supports airway clearance. In contrast, when IPV is used in the simulated model of a mechanically ventilated patient, it was found to be associated almost exclusively with the displacement of mucus distally back towards the lung, and thus did not support airway clearance. This study raises valid concerns about the safety of IPV in mechanically ventilated patients that requires further testing. Overall, although IPV may indeed be a beneficial means to induce airway mucus clearance, this study highlights that that optimal clinical settings in both spontaneously breathing and mechanically ventilated patient need to be further elucidated to determine who will benefit from this mode of therapy and under which circumstances.

Terminology

IPV: This term stands for "intrapulmonary percussive ventilation", which is a mechanical device that is widely used in the United States to help patients clear their secretions. It is especially used in those with bronchiectasis and those on mechanical ventilation who have particularly thick secretions and have poor cough reflexes due to sedations and acute-on-chronic disease states. This device delivers tidal volumes of air at varying frequencies into the airways of patients to help vibrate/percuss the airway and loosen impacted mucus.

Peer-review

This is an interesting and well-conducted bench study.

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P- Reviewer: Inchauspe AA, Shen HN **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.f6publishing.com

World J Crit Care Med 2017 August 4; 6(3): 172-178

DOI: 10.5492/wjccm.v6.i3.172

ISSN 2220-3141 (online)

EVIDENCE-BASED MEDICINE

Algorithm-based arterial blood sampling recognition increasing safety in point-of-care diagnostics

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Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: There are no conflicts of interest arising from this work.

Data sharing statement: No further data are available.

Manuscript source: Invited manuscript

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Received: February 16, 2017
Peer-review started: February 17, 2017
First decision: April 14, 2017
Revised: May 2, 2017
Accepted: May 12, 2017
Article in press: May 15, 2017

Published online: August 4, 2017

Abstract

AIM

To detect blood withdrawal for patients with arterial blood pressure monitoring to increase patient safety and provide better sample dating.

METHODS

Blood pressure information obtained from a patient monitor was fed as a real-time data stream to an experimental medical framework. This framework was connected to an analytical application which observes changes in systolic, diastolic and mean pressure to determine anomalies in the continuous data stream. Detection was based on an increased mean blood pressure caused by the closing of the withdrawal three-way tap and an absence of systolic and diastolic measurements during this manipulation. For evaluation of the proposed algorithm, measured data from animal studies in healthy pigs were used.

RESULTS

Using this novel approach for processing real-time measurement data of arterial pressure monitoring, the exact time of blood withdrawal could be successfully detected retrospectively and in real-time. The algorithm was able to detect 422 of 434 (97%) blood withdrawals for blood gas analysis in the retrospective analysis of 7 study trials. Additionally, 64 sampling events for other procedures like laboratory and activated clotting time analyses were detected. The proposed algorithm achieved a sensitivity of 0.97, a precision of 0.96 and an F1 score of 0.97.

CONCLUSION

Arterial blood pressure monitoring data can be used to

perform an accurate identification of individual blood samplings in order to reduce sample mix-ups and thereby increase patient safety.

Key words: Blood withdrawal detection; Sample dating algorithm; Arterial blood gas analysis; Patient monitoring; Point-of-care diagnostics

Core tip: Blood samplings for point-of-care analysis are essential procedures performed in large quantities in hospital wards every day. Whereas many guidelines and good practices exist, human error may still occur and additional safeguards are needed to avoid mix-ups. Using data from arterial blood pressure monitoring, which regularly is present in critical patients for whom errors would be most severe, different features, even the absence of information, may be used for analysis. We developed a novel approach accounting for lack of data in arterial blood pressure monitoring to determine the exact time of blood withdrawal for better sample dating and patient identification.

Peter J, Klingert W, Klingert K, Thiel K, Wulff D, Königsrainer A, Rosenstiel W, Schenk M. Algorithm-based arterial blood sampling recognition increasing safety in point-of-care diagnostics. *World J Crit Care Med* 2017; 6(3): 172-178 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i3/172.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i3.172

INTRODUCTION

Pre-analytical procedures in point-of-care diagnostics are prone to different types of safety relevant errors. Most of them are caused by human failure the "often interrupted" and stressful surrounding of intensive care units. The most common error in the process of handling and analyzing venous blood samples is patient misidentification[1]. Critical patient identification errors are observed in up to 1 per 1000 procedures or specimens[2-4]. The correct dating and matching of blood samples is significant for an adequate patient care and helps to avoid life threatening situations caused by mix-ups[1,5,6].

Precise sample labeling (*e.g.*, barcode labels) is the most obvious way of prevention. Establishing guidelines for sample handling might be another. However, non-compliance with these guidelines, introducing additional effort of documentation and cross-checking, remains a major problem[1,7,8].

Technical safeguards against human failure would be a forward-looking strategy in this setting. The estimation of additional parameters for patient identification in the analytical phase may help to identify sampling mix-ups[9]. But those all face the limitations of post-analytical data analysis. Approaches to prevent mixed-up samples therefore have to be technical solutions becoming effective in the pre-analytical phase[10].

Arterial blood sampling from the arterial line leads to an unavoidable and characteristic pattern (*e.g.*, artificial blood pressure, no pulsation) in blood pressure monitoring[11,12]. With respect to vital sign monitoring, this pattern is useless and is often overlooked. But the missing of blood pressure data contains useful information. Monitoring data may be missing not at random (MNAR) or be missing at random (MAR)[13]. Data MAR like the missing of a single measurement in a defined sequence may reduce sample size or degree of freedom for analysis but probably will not bias the result. Data MNAR, like missing data in specific conditions, could add a strong bias to analyses[14]. Dealing with missing data can be performed in different ways: Missing data can just be excluded, the last value carried forward, related information can be used to estimate the missing value, imputation can be performed on logical rules or indicator variables can be used to represent the state of missing information. However, mean imputation is still the most common method to process missing data[15]. In the case of blood withdrawal, missing ABP information is NMAR caused by the specific procedure. Therefore, analyzing this pattern may help to identify the patient- and time-dependent blood sampling procedure and thus provide a valuable marker for pre-analytical safety approaches.

MATERIALS AND METHODS

Objective

The aim of this study was to use available and missing information from arterial pressure monitoring to detect the exact time of blood withdrawal. Those calculated points in time can be used as a reference for dating blood samples and improve patient safety by validating a blood sample with a performed blood withdrawal from the selected patient.

A proof-of-concept approach is implemented to demonstrate the capabilities of the developed algorithm in real-time.

Measurement setup and data acquisition

Test and validation data were obtained from studies performed at the Department of General, Visceral and Transplant Surgery at the University Hospital Tübingen, Germany, in an experimental ICU setting for animal studies.

The arterial blood pressure was measured with a *PiCCO*-catheter system (MAQUET Holding B.V. and Co. KG, Germany) placed in the femoral artery using Seldinger technique and connected to a medical three-way tap allowing for blockage of the blood flow and attaching a syringe or vacutainer for blood withdrawal. For ABP measurements, a pressurized saline infusion bag was used to provide a standing fluid pillar for the sensor.

The mean (ABPm), diastolic (ABPd) and systolic

(ABPs) arterial pressure were displayed with an IntelliVue MP50-Monitor (Koninklijke Philips Electronics N.V., Netherlands), exported *via* a serial connection and processed with the TICoMS monitoring and control framework and stored in a PostgreSQL database at 1 Hz[16].

Blood withdrawal process

The detection of blood withdrawals using pressure monitoring was tailored to a usual blood withdrawal process from an arterial access. During blood withdrawal, the three-way tap was rotated and pressure measurement *via* the standing fluid pillar was blocked off. Then the sample was collected. Afterwards the three-way tap was returned to its measurement position and the catheter was flushed. Blood withdrawals were performed by physicians, scientists, medical students and lab technicians. The blood sample was measured in a blood gas analysis device (ABL800 FLEX, Radiometer Medical ApS, Denmark).

Detection algorithm

By rotating the three-way tap to obtain a blood sample, the pressure measurement was decoupled from the physiological state and set to an artificial level. Therefore, a static mean pressure *ABPm* with no physiological pulsation was observed on the patient monitor, leading to an absence of measurements for ABPs and ABPd.

Using this observation, the detection algorithm was designed and implemented with Matlab 2016a (The MathWorks, Inc., United States). The direct connection to the database and integration into the processing pipeline allowed real-time application.

In a first step, raw data from the patient monitor were processed and analyzed to detect deviations from the current state and to calculate indicator tags for each parameter at 1 Hz. If multiple observations were detected within this timeframe, the most recent measurement was used for further processing.

The detection was based on a scoring function that was normalized between 0 and 1. To calculate the scoring function all used parameters (ABPm, ABPs, ABPd) can be weighted individually, thus adapting their influence to the total score. To obtain the normalized score the sum of all parameters weights used (w↓i) (must be 1. For detection of blood withdrawals, the weight of all parameters was chosen to be the same and the scoring was therefore based on the normalized sum of the individual scores for each parameter:

$S = (S_{ABPm} + S_{ABPs} + S_{ABPd})/3$.

The scoring function therefore represents a score between 0 and 1, whereas 1 means that all indicators for a blood withdrawal are present and 0 that no indication for such an event was given. This allows an easy adaption of the algorithm and including additional parameters.

When the scoring function was calculated, a simple threshold was used to determine if a blood withdrawal event was present. The threshold for the scoring function was set to $S_{Th} = 0.7$, and if $S > S_{Th}$ a manipulation was assumed.

To obtain a more robust result and avoid false detections for cases where only a single measurement exceeds the threshold, a series of 10 successive points in time must reach the threshold S_{Th} to be accounted for as a blood withdrawal event.

For *ABPm*, the score S_{ABPm} was based on a deviation from the mean observation of the last 10 min, ignoring missing data. If the deviation was more than 10 mmHg from the mean the individual score was 1 otherwise 0.

For *ABPs* and *ABPd* the availability of the values was used for the scores S_{ABPs} and S_{ABPd}, respectively. Therefore, the tags from the first algorithmic step can be used and accounted for in the score as 1 if the measurement currently was missing or 0 if the measurement was present.

Due to multiple points in time where the threshold may be reached, a consensus time was calculated. The first point in a successive order of 10 scores exceeding the threshold was used.

Validation

First, existing data sets from previous study trials were used to calculate the exact times of blood withdrawals retrospectively. The arterial pressure measurements from the trials were read from the database and processed in successive order for each stored point in time. Each detected event was automatically plotted with a *Matlab* script as a graphic chart of a 10-min window to perform a visual inspection and validation of the variables and the scoring function.

Because the used blood gas analyzer was connected to the *TICoMS* infrastructure as the used medical framework as well, the analysis results and their dates were also processed and stored during the performed trials and thus available for retrospective analysis. The exact times of blood gas analyses were extracted and used as a reference for the blood withdrawal times. For each known analysis point the event was processed in the same way as the events detected by the algorithm: Plotting the corresponding pressure measurements and calculating a detection score. The resulting points in time and plots where then used to determine correct hits by the algorithm and match the detections correctly to the blood gas analysis and other events.

Second, a real-time version of the algorithm was tested alongside two study trials performed with the experimental setup described above. This gave the opportunity to observe the blood withdrawal events and the analytic algorithm concurrently without delay. The integration and real-time processing capabilities of the proposed method within the used medical software framework was evaluated.

For evaluation of the algorithm's performance, all known blood gas measurements are matched to the

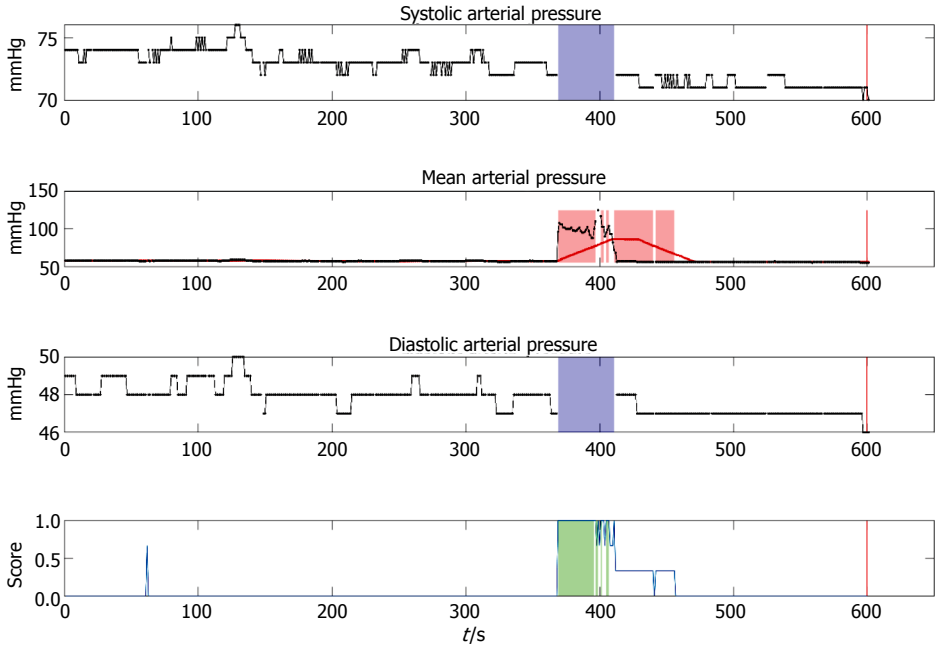

Figure 1 Example plot of the estimation process from a single detection during trial 2. A ten minute window for the measured blood pressures and the calculated score (bottom) is shown. Absence of data for ABPs and ABPd is shown as blue boxes, exceeding ABPm and scoring threshold are shown with red and green boxes, respectively.

detected events and counted as *hits*, missed blood gas analysis events are counted as *misses*. Additional detections were visually inspected and compared to other performed procedures to determine if an actual manipulation is present. Such events are additional blood withdrawals for laboratory and activated clotting time analysis. These events are accounted for as additional hits by the algorithm and denoted as *other*, whereas all other disturbances erroneously detected by the proposed algorithm are classified as false positives (FP) and denoted as errors. The performance of the detection is evaluated in terms of sensitivity or true positive rate, which represents the fraction of detected events of the total number of events:

TPR = (hits + other)/(hits + other + misses).

Precision or positive predictive value:

PPV = (hits + other)/(hits + other + errors).

And the F1 score as the harmonic mean of sensitivity and precision:

F1 = [2 × (hits + other)]/[2 × (hits + other + misses + errors)]

RESULTS

The retrospective analysis was performed by calculating the scoring function and thus the exact times of blood withdrawal events from the numerical values stored in the database. Independently, the timestamps in the database for the results of the blood gas analysis were exported.

Each event detected by the algorithm was processed to store the exact times in a text file, containing all dates and times of the events and as an image where the *ABPm*, *ABPs*, *ABPd* measurements and the calculating scoring function are plotted below each other. An example for such a detection event plot is shown in Figure 1. In this figure 10 min windows of the three measured parameters ABPs, ABPm, ABPd and the calculated scoring function are displayed. For *ABPs* and ABPd time frames with missing data are highlighted with a blue box in their respective graphs. For *ABPm* the calculated moving average pressure is plotted with a red line. Exceeding the defined deviation from the mean pressure is highlighted with a red box in the graph. Scoring function threshold exceedance for a consecutive order of 10 measurements is highlighted with green boxes.

Additionally, after processing all data from a single trial, a summarized plot for all events was generated to provide an overview of the performed blood gas analyses in comparison to the detected events. Such an overview is shown in Figure 2 for trial number 3. The plot displays the detected events and the performed blood gas analyses along the time axis of the study trial. In the upper row, red bars are used to show the points of blood withdrawal detections. The lower row represents the time of known blood gas analysis measurements. The blood gas analyses were performed regularly and except for one analysis at the beginning, all events were successfully detected by the algorithm. An additional detection is shown around hour 51 of the trial. Furthermore, the delay between blood withdrawal and the storing of the analysis results can be observed, as the red bars precede the black bars slightly.

The results of the retrospective analyses for all trials and the algorithmic performance for each individual trial and in total are shown in Table 1. Each column represents a single trial with the number of performed

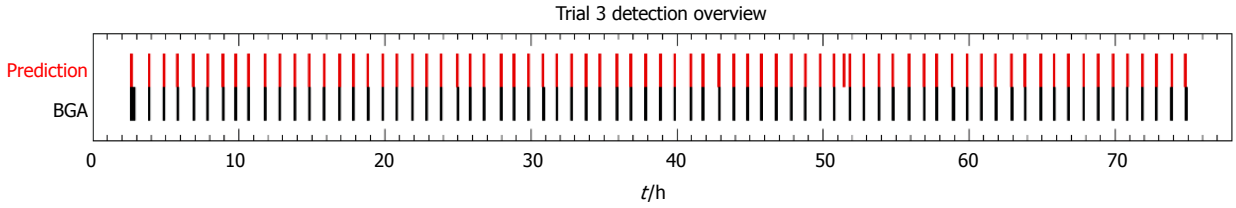

Figure 2 Example time-series for the predicted blood withdrawal time (upper red bars) and the time of measurements in the blood gas analysis device (lower black bars) during a 72 h trial.

Table 1 Detection results of the proposed algorithm applied retrospectively to the data acquired in seven trials

Trial	1	2	3	4	5	6	7	Total
Number of BGAs	72	34	75	73	66	40	74	434
Detected Manipulations	77	36	74	73	78	57	109	514
Detected BGAs (hits)	69	33	73	70	66	38	73	422
Missed BGAs (misses)	3	1	2	3	0	2	1	12
Other events (other)	5	2	1	1	8	15	32	64
False detections (errors)	3	1	0	2	4	4	4	18
Sensitivity	0.96	0.97	0.97	0.96	1.00	0.95	0.99	0.97
Precision	0.96	0.97	1.00	0.97	0.94	0.91	0.95	0.96
F1 Score	0.96	0.97	0.99	0.97	0.97	0.93	0.97	0.97

BGAs, the number of manipulations detected by the algorithm, the hits and misses for the BGAs, other events and false positive detections. The statistical measures for each trial, sensitivity, precision and F1 score are shown below. The rightmost column shows the combined result of all analyzed trials. A total number of 434 BGAs was present in the observed data. The algorithm detected 514 events, of which 422 were BGAs. Thus, BGAs could be successfully detected in 422 of 434 cases (97.23%). Sixty-four other observed events like blood withdrawal for laboratory and activated clotting time analysis were detected. In 18 cases, the algorithm performed a wrongful detection of an event, whereas only fluctuations in the pressure curve were present. Overall, a sensitivity of 0.97, a precision of 0.96 and an F1 score of 0.97 were achieved. The algorithm proved to successfully detect blood withdrawals by a broad variety of caregivers at different levels of professional experience.

The real-time version of the algorithm was successfully integrated in the medical software framework for two additional trials and could successfully detect blood withdrawals and manipulations from the arterial catheter in real-time, thus showing the fundamental feasibility of the proposed method for clinical application as a precaution measure against mix-ups.

DISCUSSION

A highly accurate algorithm was developed to detect blood withdrawals and other manipulation events in patients with established arterial blood pressure monitoring. This algorithm identified more than 97 percent of the performed samplings for blood gas analyses.

Using a 10-min sliding window for mean calculation of the measured *ABPm* allowed for dynamic adaption to the current patient state and changing blood pressures. Therefore, the detection capabilities were maintained stable for long observation times (96 h in this study). In all trials a total number of only 18 false positive detections occurred. Even if the algorithm detected such additional events, there was a strong bias between false positive and false negative rates for the task of withdrawal detections. Successful detection of all real events was the uppermost important goal, as it was required for a correct sample dating a matching for the patient. False negative rate was therefore the critical statistical size as an undetected blood sample cannot be dated and processed. On the other hand, false positives, hence detections without indication did occur but caused no significant harm due to their low frequency of occurrence. However, an increased frequency of false positive detections yields the risk of selecting wrong events. But this error was limited to a definable timeframe. Only the last 10 min were evaluated for detection of blood withdrawal events, so only events within this time frame are relevant.

Characteristic pattern of blood withdrawals occurring on arterial blood pressure were used for algorithmic detection of the events. Neither data imputation for missing measurements nor ignoring missing values was performed. Instead, by using tags indicating when information was missing this knowledge of systolic and diastolic pressure was preserved. In the context of arterial blood withdrawal this data was NMAR but absent due to the artificial pressure level provided by the pressurized infusion bag. The combination of present information with tags derived from the missing systolic and diastolic measurements yields this useful

detection algorithm.

Due to general anesthetics, patient movement was not present in study conditions but should be evaluated for a general clinical application. However, explicitly using the information obtained from the absence of the systolic and diastolic pressures, random events like movements should not lead to such a loss of data, thus not exceeding the threshold for the scoring function.

With a known exact time of blood withdrawal, the blood sample can automatically be dated back to the moment of withdrawal if the measurement was processed by a hospital information system. As shown in the analysis, for the chosen 10 min window the event can be dated back from the exact measurement times to obtain the withdrawal point. If longer times for handling the blood samples are needed, the observed timeframe should be enlarged or even shifted, for example ignoring the most recent minutes for the analysis at all, as processing and transporting time of the blood sample provides a lower boundary.

Additional parameters can easily be included in the detection algorithm with an individual scoring weight to adapt for specific procedures or additional detection performance. If for example an arterial temperature was measured as well, the temperature change resulting from flushing the catheter with saline solution, can be detected as a characteristic event as well and be included in the scoring function.

For improved versions of the detection algorithm and additional studies there are several directions further research might be headed to. Instead of using the observed numerical values for *ABPm*, *ABPs* and *ABPd*, the pressure curve itself may be analyzed. Using such high resolution raw data, calculation of the numerical values for systolic, diastolic and mean pressure may be specifically tailored to process the state of missing data, therefore refining the detection by improving the decision when a systolic and diastolic measurement can be calculated. This might be further extended by integrating models for heart beat detection and to establish a better estimate for deviations from the expected heart rate and variations in to decide if a physiological measurement was present.

The application of the provided solution to a hospital ward with multiple patients could be performed by integration in point-of-care devices like a blood gas analyzer. As suggested by Huijsmans *et al*[9], usage of additional parameters in the analytical phase should be considered for better sample identification and reducing mix-ups. Using the novel information of automatically calculated times for blood withdrawals, a list of admitted patients can be limited to those, where such an event was detected. This would reduce the error potential of wrong data entries or mix-ups in patient identification from the entire patient database. A full list of all patients should still be available in a second menu, providing an override if detection was not possible. However, this additional step would force attention of the caregiver, being aware of currently performing an override and focusing on the correct patient selection in this no longer standard procedure. This can significantly improve patient identification as the most commonly observed problem in different studies by Wallin, Wagar and Vallenstein *et al*[1-3].

Additionally, after successful patient identification, a selection of the detected points of blood withdrawal could be performed and directly be stored with the analysis result, allowing for a more accurate timing of the blood sample. The time between blood withdrawal and analysis is known when automated detection is performed. A warning could then be shown if a predefined time between sampling and measurement is exceeded.

In this paper, we provide a sample application and a first step on the way to automated systems in clinical care settings interacting with point-of-care devices. Detection of blood withdrawal is just an example for the broad range of possibilities that may lead to solutions which will help caregivers and reduce their workload or provide additional safeguards in stressful situations addressing the major problem of noncompliance with guidelines observed by Iboje *et al*[7].

Major challenges are still to be faced in terms of data access, interconnection of medical devices and dealing with consequently overwhelming big data of patient information. These tasks need to be solved in cooperation with established knowledge from computer science, tailored to the specific needs of the medical sector. By unleashing such great potential, many repetitive or standardized tasks can be automated or computer-assisted checks and protection systems against mistakes could be implemented to increase patient safety and reduce the risk of potential errors for caregivers in stressful situations caused by high workload.

COMMENTS

Background

Monitoring of arterial blood pressure with arterial catheters is commonly performed in critical patients. Regular arterial blood withdrawals are performed to assess the patient state.

Research frontiers

Interconnection of medical devices and automated systems in the medical sector are still experimental. Combining computer science and medicine is still a challenge. Whereas automation and guidance and advanced safeguards are common in other fields of application.

Innovations and breakthroughs

A novel approach for the detection of blood withdrawal in patients with an arterial catheter for arterial blood pressure monitoring is described. By interconnecting a patient monitor to a point-of-care diagnostic device, the selection of patient data can be narrowed to patients with plausible sampling events.

Applications

Detection of blood withdrawal may be a useful feature integrated in medical monitors and blood gas analysis devices to increase patient safety by allowing a better, automated sample dating and the reduction of the risk for sample

mix-ups in hospital wards. However, for a practical implementation additional validation steps are required and medical devices like the blood gas analyzer must be adapted by the manufacturer to allow a pre-selection for patients with recently detected blood withdrawals.

Terminology

Arterial blood pressure (ABP), Mean Arterial blood pressure (MAP or ABPm), systolic ABPs, diastolic ABPd, blood gas analysis BGA, arterial blood gas (ABG).

Peer-review

The authors prepared and evaluated the algorithm of automatic detection of blood withdrawals by using data from continuous direct blood pressure monitoring. The algorithm may be useful to recognize and eliminate errors in recording blood withdrawal events from the specific patients. The algorithm provides reasonable precision and prediction rates. The methods used were adequate. The manuscript is well-written and will be interesting for intensive care specialists.

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P- Reviewer: Beltowski J **S- Editor**: Song XX **L- Editor**: A
E- Editor: Lu YJ

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