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Vaping and Anesthesia

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ANE630 Research Practicum II

Abstract

Electronic cigarettes (ECs) are a fast-growing class of Electronic Nicotine Delivery Systems (ENDS) which were first put on the market 15 years ago. These devices have been advertised as safer alternatives to conventional cigarettes and a tool for smoking cessation by their manufacturers regardless of inadequate safety data (Kalkhoran, 2016). Since ECs have only been on the market for one and half decades, data on short-term health effects from inhaling EC aerosols are inadequate, and data regarding long-term health effects are very limited.

Despite insufficient safety data, the use of ECs has increased exponentially since they were put on the market, especially among adolescents and young adults. ECs now are the most commonly used tobacco product in this population (Jenssen, 2019).

Current research data suggests that EC usage can cause damage to the respiratory system, cardiovascular system, immune system, and musculoskeletal system in ways both similar to and different from conventional cigarette smoking. ECs also contain more toxic chemicals in the e-liquids and more heavy metals than those listed in conventional cigarettes. New generations of ECs can deliver much higher concentration of nicotine than conventional cigarettes. In addition, EC usage in adolescents is associated with higher rate of drug and alcohol addiction, and long-term cognitive and behavioral impairment compared to teens who never used ECs (Jenssen, 2019). Use of ECs as a perioperative smoking cessation aid is not supported at this time (Lee, 2018). The United States Food and Drug Administration (FDA) recently released a report on potential seizure risk associated with ECs usage among teens and young adults (Boyles, 2019). Further studies are needed to help us better understand the effects of vaping on the practice of anesthesia.

Vaping and Anesthesia

Introduction

While the concept of battery-powered nicotine delivery devices dates to 1963, it took four decades for such devices to come alive. ECs were first designed, developed, patented and introduced by a Chinese pharmacist, Hon Lik in 2003 (Kaur, 2018). They became commercially available and launched in Europe and the United States three years later. Since its first sales in the 2000s, the EC market has grown so quickly that it is estimated to be over $47 billion by 2025 (Chaumont, 2018).

In 2014, the US National Health Interview Survey (NHIS) reported that among the 146 million working adults, 3.8% (5.5 million) used ECs. In 2016, 3.2% of adults aged 18 years and older regularly used ECs. 15.3% adults aged 18 years and older have used an EC sometime in their lifetime. Current data shows there are 13 million users of ECs all over the world (Franzen, 2018). The highest rate of ECs use was seen among the young adult population between 18 and 24 years of age (Khan, 2018).

Multiple studies on the rapid rise of EC popularity showed that among active smokers, the reasons for using ECs were to try something new, try to quit or reduce traditional cigarette smoking, and to replace other tobacco products. The top reasons for EC usage among youths were curiosity, appealing flavors, and peer influences (Cooke, 2015). The usage of ECs was highest among male, non-Hispanic whites, aged 18-24 years, with an annual household income of less than $35,000 (Gaur, 2018).

ECs have been reported to contain fewer carcinogens than traditional cigarettes, cause fewer acute lung damages in healthy individuals, and to help with smoking cessation (Cooke,

2015). It has also been viewed as a potentially safer alternative for asthmatic smokers, but its effects on lung functions are unclear. Although ECs are said to be safe, the FDA has reported that the cartridges and solutions contain nitrosamine, diethylene glycol, heavy metals, and other contaminants potentially harmful to humans (Gaur, 2018). ECs have been under FDA regulation as tobacco products since 2016.

Researchers Kandel and Kandel (2014) discovered an enhanced effect of cocaine seen in mice primed with nicotine. This was likely caused by histone deacetylase inhibition in the striatum and activation of dopaminergic neurons in the ventral tegmental area. Additionally, there were reports of marijuana and cocaine uses with EC devices which made it potentially more dangerous and concerning (Qasim, 2018). There were also reported incidences of relapsed ulcerative colitis and enterocolitis in developing infants from EC aerosol exposure (Kaur, 2018).

Market research projections indicate that within the next 30 years, rates of EC use may exceed those of tobacco cigarettes (Ratajczak, 2018). Given their increased popularity, variability among different devices, lack of consistency among e-liquid product and product label, lack of regulation, permission to be used in public, sale to the minors, and potential gateway to combustible cigarettes, there is an urgent need to address the safety of these products and the implication of vaping to anesthesia practice.

Literature Review

Since its emergence on the market in 2007, ECs have quickly gained popularity especially in the adolescence and young adult population. Vaping has become a public health “epidemic” in a short period of time (Jenssen, 2019). Originally designed as a smoking cessation tool, ECs have

been commercialized into a gateway to nicotine and drug addiction (Jenssen, 2019). Studies have shown that ECs have harmful effects on the respiratory system, the cardiovascular system, the immune system, and the skeletal system, among others. The use of ECs might induce seizure in teens and young adults (Boyles, 2019). Exposure of ECs during pregnancy affects fetal development (Kaur, 2018). The flavoring agents in the e-liquids and heavy metal contained in the EC device are cytotoxic. Whether ECs are a valuable tool to aid smoking cessation is still being debated. EC use among adolescents is associated with increased incidence of mental and behavior disturbances (Jenssen, 2019).

Overall, very limited and conflicting data on ECs have been generated in the past decade. Most research on ECs were in vitro studies on cultured cells or in vivo experiments in animal models. The sample sizes of some of the studies were small. The large variety of commercially available EC device and e-liquid also affect the generalizability of the studies. The fact that most EC users in some studies were also conventional cigarette smokers made it difficult to separate the effect of vaping from that of conventional cigarette smoking. The currently available clinical data do not associate serious health risks with EC use, but it should be noted that data on mid- and long-term effects of EC usage are still lacking. Further studies are required to gather conclusive outcomes. Whether or not ECs are a valuable smoking cessation tool during the perioperative period and the implication of vaping on anesthesia practice are to be determined.

EC Device

ECs are also called “e-cigs”, “electronic vaping devices”, or “personal vaporizers”. They are essentially ENDS proposed for long-term smokers or individuals who wish to quit smoking. They

were marketed as “cheaper and safer smokeless alternatives” to traditional cigarettes (Gaur, 2018).

ECs are battery operated devices that produce aerosol (or vapor) by heating a solution typically made up of nicotine, propylene glycol (PG), vegetable glycerin (VG), and flavoring agents. PG and VG are humectants that keep flavorings and nicotine in suspension and facilitate vaporization when heated. ECs are composed of a battery part (usually a lithium battery), a reservoir that contains the liquid, and an atomizer with a heating element. Electronic current from the battery heats the metallic coil, aerosolizing the liquid conducted from the reservoir to the coil by a wick generally made up of cotton or silica (Khan, 2018).

Most EC devices look like cigarettes, pens, hookah tips, or screw drivers. The liquid may be packaged in replaceable cartridges, refilled, or contained in disposable EC themselves. The EC device is activated by inhalation at the tip or by pressing a button, depending on the model. The microprocessor controls the power Light-Emitting Diode (LED) tip and the heating element once the EC is activated. The LED tip glows when the vaporizer is in use and the heating element produces the vapor mist that carries the nicotine vapor (Cooke, 2015). ECs do not produce combustion or tar compared to traditional cigarettes, however ECs are not emission-free devices. Potential respiratory health risks resulting from secondhand EC aerosol exposure have not been sufficiently evaluated.

VG in the e-liquid is a sweet-tasting, colorless and odorless polyol that is extracted from palm, soy or coconut oil triglycerides by hydrolysis; when heated, it is responsible in part for the visible “smoke” element of the vapor.

The structure of ECs has undergone tremendous changes since their introduction in 2003. This includes changes in their size, nicotine concentrations, e-liquid composition, the atomizer, and the type of batteries. ECs have been made throughout four generations (Protano, 2018). The newer generation devices allow the users to adjust aerosol production and nicotine delivery. It was reported that plasma nicotine levels of healthy EC users increased by 35-72% due to the use of new generation EC devices, compared to first generation devices (Bowler, 2017).

ECs and Smoking Cessation

Smoking has devastating effects on human health. Combustible cigarettes are estimated to cause more than 480,000 deaths annually (Cooke, 2015). Smokers who quit before the age of 40 reduce the risk of dying from tobacco-related diseases by up to 90% (Cooke, 2015). The large health burden related to combustible cigarette use has led to efforts to identify healthier alternatives and means to quit smoking, including the use of ECs.

Recently, Public Health England (PHE) estimated that ECs are 95% less harmful than tobacco cigarettes, and when supported by a smoking cessation service, are effective at helping most people quit smoking (Clapp, 2017). EC use may potentially contribute to a modest tobacco cessation effect through mimicry of conventional smoking behaviors in theory. EC use decreased airway hyper-responsiveness and had little to no effect on pulmonary functions in comparison to combustible cigarettes in mild to moderate asthmatic smokers. Research showed that an increase in expired carbon monoxide (CO) levels is found in conventional cigarette users but not in EC users, and an increase in white blood cell, lymphocyte, and granulocyte count is seen acutely in conventional smokers but not in EC users. However, recent

population level data suggest that increased EC use in the USA correlates with smoking cessation (Clapp, 2017).

On the other hand, Bullen et al (2013) conducted one of the largest studies investigating the efficacy of ECs versus nicotine patches in achieving smoking cessation. This study enrolled 657 smokers interested in quitting. Subjects were randomized in a 4:4:1 ratio to either 16 mg of nicotine EC, 21 mg of nicotine patch, or placebo EC, respectively. They were followed for a 6-month period, with assessments at one and three months. At six months, tobacco cessation was evident in 7.3% with nicotine ECs, 5.3% with nicotine patches, and 4.1% with placebo ECs. Nicotine EC use did not demonstrate any advantage in tobacco cessation when compared with nicotine patches or placebo ECs. A recent Cochrane review analyzed studies evaluating the use of ECs in tobacco cessation and concluded that the role of EC is limited by the small number of trials, low event rates, and wide confidence intervals around the estimate mean (Bowler, 2017).

ECs and Nicotine

Nicotine is a botanically derived parasympathomimetic alkaloid. It can be easily absorbed by the body through contact, ingestion, and inhalation. It is one of the most addictive substances for the human body. It also lowers the threshold for addiction to other substances as a gateway drug. It can easily cross biological membranes including the blood brain barrier and placenta. Nicotine directly activates nicotinic acetylcholine receptors (nAChRs) and stimulates cellular responses including increased expression of heat shock proteins, induction of chromosome aberration, reduced cell proliferation, and suppression of apoptosis. Nicotine can also activate muscarinic acetylcholine receptors (mAChRs) and cause bronchoconstriction (Clapp, 2017).

Nicotine can also increase blood pressure and heart rate, elevate free fatty acid and blood glucose levels in the plasma, and induce peripheral and coronary vasoconstriction through catecholamine release and endothelial dysfunction (Benowitz, 2016). The sympathomimetic effects of nicotine are activated when nicotine binds to cholinergic receptors. This activates the peripheral and intrapulmonary chemoreceptors, stimulates the brain stem, and causes catecholamine release from the adrenals and vascular nerve endings. Nicotine affects the body through the release and metabolism of numerous neurotransmitters. Among these neurotransmitters epinephrine, norepinephrine, dopamine, acetylcholine, serotonin and vasopressin could contribute to effects of nicotine on blood vessels (Benowitz, 2017).

Nicotine is added to PG in concentrations up to 70mg/ml in ECs (Gaur, 2018). The risk of nicotine toxicity is increased in EC user due to its high concentrations in the cartridges. In experiments where mice were exposed to aerosolized nicotine-free and nicotine-containing e-liquid, increased airway hyper-reactivity, distal airspace enlargement, mucin production, and cytokine and protease expression were found in nicotine-containing group. These lung parameters were not changed in mice from the nicotine-free group (Ratajczak, 2018). Furthermore, recent nicotine studies in rodents suggest that prenatal nicotine exposures lead to epigenetic reprogramming in the offspring, abnormal lung development, and multigenerational transmission of asthmatic-like symptoms (Clapp, 2017). Despite the results, these were animal studies that used different EC devices, pumps, solutions, and exposures to examine the effects of ECs on respiratory outcomes (Cooke, 2015). The high variability in study designs on ECs have made it difficult to compare results to each other.

ECs and the Respiratory System

Compared to other associated health risks, it is more apparent that there are considerable pulmonary health risks associated with continued EC usage. Effects of EC use on pulmonary function have been studied and yielded variable results. While some of the studies found that EC users experience increased airway resistance and pulmonary function compromise upon exposure to EC vapor (Marini, 2014), others reported that short term use of ECs have no significant changes in lung function (Ferari, 2015).

A short term in vitro studies using cultured cells have shown that exposure to EC liquid or aerosols reduces cell viability, induces cytokine production, and causes oxidative stress (Chun, 2017). Further, two studies reported immediate reduction in exhaled nitric oxide similar to what is seen in tobacco smoking (Marini, 2014). Another study found an increase in inflammatory signaling molecules upon inhalation in resemblance to what is seen in tobacco smoking (Shields, 2017). Regular exposure to EC aerosols was seen associated with impaired respiratory function in these studies.

Safety and harm reduction are cited as rationales for EC use. In adults, the highest prevalence of EC use is in current conventional cigarette smokers, of which 31% report having tried ECs (Bowler, 2017). Bowler et al (2017) surveyed 10,294 people aged 45-80 from 2008 to 2011 with a history of at least 10 pack-years of conventional cigarette smoking (N=10,192) or no conventional cigarette smoking (≤1 pack-year lifetime; N=102) to determine whether EC use was associated with Chronic Obstructive Pulmonary Disease (COPD) progression or changes in smoking habits. They found that EC use was associated with an increased incidence of chronic bronchitis and COPD exacerbations and some evidence of more rapid decline in lung function in

EC users. They suggested that nicotine dependence appeared to be the cause of the dual usage of conventional and ECs and the failure to quit smoking. People who used ECs were more likely to have progression of lung disease after five years and a more rapid decline in lung function than non-users. Although this was an observation study, they found no evidence supporting the use of ECs as a harm reduction strategy among current smokers with or at risk for COPD.

It is well known that inhalation of tobacco smoke over a prolonged period causes respiratory complications including asthma and COPD. Chemical analyses reveal that EC aerosols contain numerous respiratory irritants and toxicants. There are documented cytotoxic effects of EC constituents on lung tissue. Knowledge of the long-term toxicological and immunological effects of EC aerosols remains elusive due to the relatively short existence of vaping. Recent data from the FDA have shown that the vapors from ECs contains some of the same toxic chemicals found in traditional cigarettes. Furthermore, the vapors derived from ECs accumulate in the airway epithelium in a similar fashion as the smoke from traditional cigarettes.

Wu et al (2014) studied the role of e-liquids in inducing inflammatory responses and regulating innate defense in human primary airway epithelial cells from nonsmokers. They found that nicotine amplified the effects including IL-6 production and Human RhinoVirus (HRV) infection triggered by nicotine-free e-liquid. This study suggested that exposure to e-liquids could induce an immune-compromised state and an increase in susceptibility to microbial infection of human airway. In addition, Susan et al (Kaur, 2018) reported that two weeks' exposure of C57BL/6 mice to EC vapors led to impairment of viral and bacterial clearance in the

lungs. These studies suggested that increased use of ECs might be associated with increased pulmonary infections and drug resistance.

Furthermore, researchers from Boston University found that exposure to e-vapors might increase the risk of lung cancer (Kaur, 2018). Vardavas et al reported an increase in total respiratory impedance and flow respiratory resistance and a significant decline in exhaled nitric oxide fraction (FeNO) levels — a marker for eosinophilic inflammation on 30 healthy individuals aged 19-56 years after short-term exposure to EC vapors (Kaur, 2018).

The lower airways are an important site of pathology for many diseases including asthma, chronic bronchitis, and cystic fibrosis. Ghosh et al (2018) performed research bronchoscopies on healthy nonsmokers, cigarette smokers, and EC users (vapers) and obtained bronchial brush biopsies and lavage samples from these subjects for proteomic investigation. Their study was the first to look for proteomic changes in the lower airways of vapers. They discovered that vaper airways appeared friable and erythematous upon visual inspection by bronchoscopy. Approximately 300 proteins were differently expressed in smoker and vapor airways epithelial cells from biopsy samples. 78 proteins were commonly altered in both groups and 113 were uniquely altered in vapers. They further employed in vitro and murine exposure models to support their human findings and concluded that chronic vaping could cause marked biological effects on the lung. They suspected that these effects might in part be mediated by the PG/VG base. They revealed that these changes were likely not harmless and might have clinical implications for the development of chronic lung diseases. Further studies will be required to determine the full extent of vaping on the lung.

Airways are highly sensitive to damage from inhaled pathogens, reactive chemicals, and foreign debris. Pulmonary reflex responses, such as sneezing and coughing, protect the airways from the potentially harmful substances we inhale each day. Previous studies investigating ciliated respiratory epithelium indicate that smoking shortens cilia length, reduces cilia beat frequency and disrupts respiratory epithelium, which most likely contributes to the inhibition of mucocilliary clearance (MCC). Studies examining the short-term effects of ECs indicate that nicotine-containing ECs, but not nicotine-free ECs, can have short-term adverse effects on lung defense mechanisms including MCC, urge to cough, and cough sensitivity (Ratajczak, 2018).

Palazzolo et al (2017) used peristaltic pumps to transport EC-generated aerosol and conventional cigarette smoke into custom-made chambers containing excised bullfrog palates. Mucous Transport Velocity (MTV) was determined before exposure, immediately after exposure, and approximately one day following exposure. MTVs were also determined at the same time points for palates exposed to air as the control. Surface and cross-sectional SEM images of palates from all three groups were obtained to support MTV data. Their results indicate that EC generated aerosol has a modest inhibitory effect on MTV one day post-exposure compared to the control group. In contrast, smoke completely inhibited MTV immediately after exposure and the MTV was unable to recover one day later. SEM images of some areas of palates exposed to smoke were completely devoid of cilia compared to the control palates. The epithelial thickness of aerosol-exposed palates appeared thicker than control palates while smoke-exposed palates appear to be thinner due to epithelial disruption. These results indicate that EC generated aerosol has only a modest effect on MCC of bullfrog

palates and aerosol sedimentation accounts for epithelial thickening. Cigarette smoke affects the MCC of the frog palate more severely than EC generated aerosol.

However, this investigation used amphibian and not mammalian tissue. Furthermore, the frog palate is not strictly considered respiratory tissue. The effect EC generated aerosol or smoke have on MCC in this study is not exactly comparable to humans.

Studies among ex-smokers who switched to ECs note reduced exposure to numerous respiratory toxicants, reduced asthma exacerbations, and COPD symptoms. Ferari et al (2015) compared the effects of ECs and traditional cigarettes on pulmonary function and nitric oxide release in exhaled air of smokers versus nonsmokers. They found that short term use of ECs did not lead to any adverse health effects in nonsmokers. They argued that although ECs are not without risk, these products seemingly pose fewer respiratory health harms issues compared to tobacco cigarettes, thus suggested the potential benefits of ECs on reducing respiratory-related health harms. Several observational studies measuring widespread early generation EC use have shown that, to date, most users of ECs continue to smoke tobacco cigarettes (Ghosh, 2016).

ECs and Asthma

Patients with asthma experience many health benefits from smoking cessation such as reduced symptoms and improvement in lung function. Many researchers and clinicians have strongly advocated for transitioning asthmatic smokers to ECs to reduce the healthcare burden of smoking-induced asthma exacerbations. However, EC aerosols are poorly characterized complex mixtures of inert and reactive chemicals, and it is unclear whether long-term inhalation will improve or worsen asthma.

Animal studies have reported beneficial effects of nicotine in the context of asthma, which are, at least partially, mediated by its anti-inflammatory properties and activation of the alpha7-nAChR. But nicotine-induced anti-inflammatory responses in the lung have also been associated with increased susceptibility to respiratory viral infections due to reduced migration of immune cells to sites of infection. While nicotine may reduce inflammation in the lungs, it also enhances mucus production and reduces the beneficial inflammatory responses in the context of viral infections, which are major triggers of asthma exacerbation.

Propylene Glycol (PG) and Vegetable Glycerin (VG), the two compounds representing the greatest majority of e-liquid volume, keep nicotine and flavoring agents in suspension, enhance absorption of the wicking material, and generate plumes of aerosolized particles when heated to sufficient temperatures. Aerosolization of PG and VG at high temperatures often generated by users of more advanced third and fourth generation devices results in the formation and inhalation of reactive compounds known to exacerbate asthma. There is also data linking the flavoring agents in the e-liquid, including Eugenol, cinnamaldehyde, and Benzaldehyde (Mint et al) with asthma exacerbations.

TRPV1, the capsaicin receptor, and TRPA1, the allyl isothiocyanate (mustard oil) receptor, play key roles in noxious chemical detection and initiation of pulmonary reflex responses. There is an emerging link between TRPA1-mediated neurogenic inflammation and asthma. TRPA1 is believed to be the major reactive irritant receptor in the airways. Altered level of expression and mutations of TRPV1 and TRPA1 genes have been reported after exposure of EC aerosols. Using results from laboratory, observational, and clinical studies, Ratajczak et al (2018) suggested that respiratory dysfunction may result from inhalation of EC aerosols.

Polosa et al assessed the effects of smoking abstinence and reduction in asthmatic smokers who switched to ECs (Cooke, 2015). Results of the study demonstrated that at six months both single users (use of ECs alone) and dual users (use of ECs and five or less conventional cigarettes/day) exhibited significant improvements in forced respiratory flow 25%-75%. At 12 months, a substantial improvement was observed in all asthma parameters measured (except FVX in single users), including methacholine challenge. This trial was the first study to demonstrate improvement in airway hyper-responsiveness, pulmonary function, and asthma control in asthmatic smokers who switched to EC use either completely or by reducing daily combustible tobacco consumption.

The observation that EC use might be associated with both increased respiratory and asthma symptoms and increased asthma-related school absenteeism in adolescents is potentially concerning since diminished lung function in later years has been linked to asthma and chronic bronchitis in childhood and adolescence. There is no data on the potential long-term effects of EC use and incidence or exacerbation of asthma.

Case Studies Related to ECs

Khan et al (2018) reported a case of 40-year-old female patient who developed worsening dyspnea and intermittent chest pain after increased use of ECs to help her quit smoking. Patient developed acute hypoxemic respiratory failure and required intubation and mechanical ventilation due to organizing pneumonia. This marked two reported cases of organizing pneumonia and ten reported cases of pulmonary toxicity related to EC use.

Sommerfeld et al (2018) presented a case report of a previously healthy 18-year-old woman who presented with dyspnea, cough, and pleuritic chest pain after short period of EC

use. She developed rapid onset respiratory failure with hypoxia and was diagnosed acute respiratory distress syndrome on arrival to the hospital. After being ruled out for an infectious etiology, the patient was diagnosed with hypersensitivity pneumonitis. She improved rapidly after intravenous methylprednisolone therapy was initiated. This was the first reported case of hypersensitivity pneumonitis and acute respiratory distress syndrome as a risk of EC use in an adolescent.

Hypersensitivity pneumonitis is an inflammatory disease of the lung parenchyma that is the result of an immune response to inhaled antigens. Typically, hypersensitivity pneumonitis is associated with antigens from microbial agents, such as moldy hay or grains, or with animal proteins in avian droppings. In the acute setting, hypersensitivity pneumonitis can be secondary to chemical exposure, of which can be found in ECs. This case report suggests that hypersensitivity pneumonitis can be a life-threatening health risk of EC use in an adolescent patient.

In addition to organizing pneumonia and hypersensitivity pneumonitis, lipoid pneumonia is also linked to EC use. Lipoid pneumonia results from an inflammatory response to lipids present in alveolar space. It can be endogenous in etiology, resulting from bronchial lipid storage disorders, bronchial obstruction or hypercholesterolemia, or exogenous, caused by inhalation or aspiration of animal, vegetable or mineral oil. Lipoid pneumonia has been described in individuals who aspirate liquid hydrocarbon through fire-eating, consume oil-based laxatives or repeatedly use petroleum-based lubricants and decongestants. Clinical presentation comprises a spectrum from asymptomatic chronic disease with incidental detection on chest radiograph to severe acute cases requiring ventilator support. Wiswam et al (2018) reported a young

female vaper presented with insidious onset cough, progressive dyspnea on exertion, fever, night sweats and was in respiratory failure when admitted to hospital. A video-assisted thoracoscopic surgery was suggestive of lipoid pneumonia. The only source of lipid was the vegetable glycerin found in ECs. Their data suggests that lipoid pneumonia should be considered as a diagnosis for presentations of interstitial disease in vapers.

ECs and the Cardiac System

Cardiovascular disease is the main cause of death in the United States, with smoking being the primary preventable cause of premature death and thrombosis being the main mechanism of cardiovascular mortality in smokers (Qasim, 2018). Smoking causes a prothrombotic state through altering fibrinolytic and thrombotic factors (Barua, 2013); smokers' isolated platelets exhibited increased aggregation (Ambrose, 2004); and exposure to cigarette smoke alters the dynamics of clot formation, making them more resistant to thrombolysis as compared with clots on nonsmokers (Barua, 2010). Smoking is responsible for one of every three deaths linked to cardiovascular disease (Qasim, 2018). Due to the perception that ECs are "safer" and "less harmful" than conventional cigarettes, their usage-among a variety of ages has increased tremendously during the past decade. Notably, there are limited studies regarding the negative effects of ECs on the cardiovascular system.

Qasim et al (2018) employed a passive e-Vape vapor inhalation system and developed an in vivo, whole-body EC mouse exposure protocol that mimics real-life human exposure scenarios/conditions and investigated the effects of ECs and clean air on platelet function and thrombogenesis. Their results show that platelets from EC-exposed mice are hyperactive, with enhanced aggregation and adhesion. ECs exposure enhances agonist-induced platelet

secretion, integrin $\alpha_{IIb}\beta_3$ activation, phosphatidylserine expression, AKT, and ERK phosphorylation. They were also found to be resistant to inhibition by prostacyclin. The EC-exposed mice exhibited shortened thrombosis occlusion and bleeding times. Their data demonstrated for the first time that ECs alter physiological hemostasis and increase the risk of thrombogenic events. Thus, the negative health consequences of EC exposure should not be underestimated and warrant further investigation.

Several studies have demonstrated endothelial dysfunction, oxidative stress imbalance, and arterial stiffness increase after vaping EC with nicotine (Benowitz, 2017). The pharmacological actions of nicotine make it difficult to distinguish the endothelial dysfunction, oxidative stress, and increased arterial stiffness were mediated by the carriers PG and glycerol (GLY) (Benowitz, 2017). PG and GLY can undergo combustion when vaporized at high wattage and thereby produce carbonyls, which are known cardiovascular toxicants (Benowitz, 2017). Although the carbonyls produced in realistic vaping conditions are likely far less than during tobacco combustion, a potential toxic effect on the cardiovascular system cannot be excluded (Benowitz, 2017).

Chaumont et al (2018) assessed the differential effects of vehicles (PG and GLY) and nicotine on microcirculatory function, arterial stiffness, hemodynamic parameters, and oxidative stress using a randomized, single blind, 3-period crossover design study. They found that neither sham-vaping nor vaping in the absence of nicotine resulted in modifications of cardiovascular parameters or oxidative stress. In contrast, impaired acetylcholine mediated vasodilation; increased indices of arterial stiffness; increased systolic, diastolic blood pressure, and heart rate; and finally, raised plasma myeloperoxidase were seen in vaping with nicotine.

Their findings demonstrated that high temperature EC vehicle vaporization does not alter micro- and macro- vascular function, and oxidative stress, and that these effects are solely attributable to nicotine.

Franzen et al (2018) conducted a randomized cross-over study of the acute use of three tobacco products, including a control group using a nicotine-free liquid. Fifteen active smokers were studied during and after smoking either a cigarette or an EC with or without nicotine (ego-T CE4 vaporizer). Subjects were blinded to the nicotine content of the EC and were followed up for two hours after smoking a cigarette or vaping an EC. Peripheral and central blood pressures as well as parameters of arterial stiffness were measured by a Mobil-O-Graph device. The peripheral blood pressure rose significantly for approximately 45 minutes after vaping nicotine-containing liquid ($p<0.05$) and for approximately 15 minutes after a conventional cigarette ($p<0.01$), whereas nicotine-free liquids did not lead to significant changes during the first hour of follow-up. Likewise, heart rate remained elevated approximately 45 minutes after vaping an EC with nicotine-containing liquid and over the first 30 minutes after smoking a cigarette in contrast to controls. Elevation of pulse wave velocity was independent from mean arterial pressure as well as heart rate in the EC and cigarette groups. These mechanisms could be triggered by an increase in circulating and local catecholamine and by nicotine. As already published, nicotine stimulates sympathetic ganglia and therefore increases sympathetic neuronal discharge-impaired nitric oxide production in the central nervous system (Mahmud, 2003). These findings may be associated with an increased long-term cardiovascular risk.

A study conducted by Monroy et al suggests that the use of ECs containing nicotine may have a damaging effect on heart cells as acute EC use was found to affect left ventricular

function and cause a delay in myocardial relaxation in a 70-year-old female. In addition, there have been other reports of atrial fibrillation and acute myocardial infarction in EC users, suggesting that EC use might pose a risk to the cardiovascular system.

E-liquid and Bone Health

Conventional cigarette smoking has been linked to the disturbances of normal bone remodeling and development of osteoporosis. Studies have shown that nicotine can interfere with the expression of several osteoblast genes in a dose-dependent manner. Besides nicotine, flavoring agents in e-liquids also affect osteoblast proliferation, differentiation, and matrix deposition (Otero, 2019).

Unlike traditional cigarettes, ECs have more than 7700 different flavors available on the market. One of the major reasons of adolescents being attracted to ECs is the wide variety of flavors available. Many of these flavoring agents are categorized as safe for ingestion. That does not necessarily mean they are safe for inhalation.

Otero et al (2019) conducted an in vitro study of e-liquids with or without nicotine on the cell validity and gene expression of human MG-63 and Saos-2 osteoblast-like cells. They tested 23 commercially available e-liquids from four different brands. Their results showed that the degree of cytotoxicity caused by e-liquid to the osteoblast cells is independent of nicotine and is flavor-dependent. Flavorless e-liquid was the least toxic among all the e-liquids tested. The least toxic flavored e-liquids were coffee and fruity. The most cytotoxic e-liquids were cinnamon-flavored ones.

Cytotoxicity of ECs

One of the unique selling point of ECs is the wide variety of flavors. According to a 2014 report, e-liquid exist in 7764 unique flavors sold under 466 brands; however, these flavoring agents could also lead to toxicity (Kaur, 2018).

Studies using in vitro methods suggests that EC flavorings could lead to lung cell damage (mostly by releasing free radicals) and inflammation in lung tissue. A study based on determining the cytotoxicity of e-liquids in human embryonic stem cells and in mouse neural stem cells demonstrated its direct correlation with the concentration of flavoring additives. Diacetyl, an artificial butter flavoring found in some flavored e-liquids, has been associated with bronchiolitis obliterans, a rare and severe lung condition, commonly known as “popcorn lung” (Kaur, 2018). Another study done by Leigh et al (2016) revealed that menthol, strawberry, and coffee flavors are very cytotoxic to human bronchial epithelial cells. This suggests that the cytotoxic effect of the e-liquid flavoring agents might be tissue specific.

Another group of researchers tested 13 kinds of commercially available e-liquids and found the presence of acetaldehyde and formaldehyde in eight of the tested samples. Varlet et al analyzed 42 models of refill liquids for ECs from 14 different brands to assess their toxicity. High amounts of α-, and β-pinene, γ-terpinene and benzene 1-methyl-4-(1-methylethyl) (para-cymene), used to enhance their flavors, were detected in several products. In addition, 2,3-butanedione, a diketone associated with respiratory diseases, was detected in three samples (Kaur, 2018).

Regarding the cytotoxic effects of nicotine in ECs, normal human bronchial epithelial cells exposed to nicotine containing aerosol from ECs showed impaired ciliary beat frequency, as

well as aberrancies in airway surface liquid volume as well as cystic fibrosis transmembrane regulator channel malfunction. Such defects are usually seen in chronic COPD tissue, leading to increased cytokine expression, airway hyper-reactivity, and eventually lung tissue destruction.

In experiments conducted by Yu et al (Kaur, 2018), ECs aerosol, both with and without nicotine, has demonstrated cytotoxic effects on epithelial cell lines and acts as a DNA-breaking agent. Exposure to EC aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage. In many of these studies, potential confounding factors such as aerosol temperature and particle size have not been taken into account.

Heavy Metals in ECs

The ECs are made of a large number of metal components in conjunction with cyclic temperature changes. Due to the structure and design of the ECs, some metallic compounds may be delivered to the aerosol from the atomizer, batteries, or e-liquids. Studies have reported the presence of metals in EC aerosol at levels higher than that in conventional cigarette smoke. These heavy metals could be released by the heating element and could pose serious health implications in users.

In a study conducted by Williams et al (Kaur, 2018), the aerosols of ECs were demonstrated to have high concentrations of silver, nickel, aluminum, and silicate as well as nanoparticles (<100nm) of tin, chromium, and nickel. Moreover, it was shown that titanium dioxide nanoparticles released in EC aerosols impair DNA repair by causing single-strand breaks and oxidative lesions to DNA in A549 cells.

Literature reveals that the EC aerosols and e-liquids are a potential source of elements that induce and promote development of chronic conditions. These include trace metals which are

leached from their core assembly. Some of these metals like nickel (Ni), chromium (Cr), cadmium (Cd), tin (Sn), aluminum (Al), and lead (Pb) are potential carcinogens. They have been associated with fatal conditions like lung and sinonasal cancer. Besides that, they may have adverse effects on oral tissues like periodontal ligament and mucosa where they may trigger chronic periodontitis and oral cancer (Gaur, 2018).

The nicotine in e-liquids is derived from Nicotinana tabacum (cultivated tobacco), a potent bio accumulator. It absorbs pollutants including the heavy metals from the immediate growing environment. Some of these metals (Ni, Cr, Cd, Pb, Al, Sn, Cu, and Mn) have numerous negative influences on human health. They produce direct effects on vital organs like the lungs, liver, kidney, and brain and indirectly lead to immunologic, neurologic, reproductive, developmental, and carcinogenic effects (Gaur, 2018). These may be acute or chronic, depending upon the duration of exposure.

Several trace metals including Al, arsenic (As), Cd, Cr, copper (Cu), iron (Fe), manganese (Mn), Ni, Pb, and zinc (Zn) are released from the ECs. Their concentration is higher in the aerosolized e-liquids as compared to the non-aerosolized forms. For instance, the levels of Ni and Cr have been found to be very high in aerosols due to their leaching from the core assembly (Gaur,2018).

As the manufacturing process for e-liquids is not standardized, there is a heightened risk that carcinogenic substances may be included. A recent study showed that about 2.1 to 15.1 mg of the nicotine from the cartridges was vaporized (Gaur, 2018). Although precise data regarding EC induced carcinomas is not available, the elevated levels of nicotine and heavy metals heighten the risk of cancer.

The inhalation of Ni causes chronic active inflammation in the lungs leading to alveolar epithelium hyperplasia, fibrosis, bronchiolization, alveolar proteinosis, and atrophy of the nasal olfactory epithelium. Cr (VI) is recognized by the International Agency for Research on Cancer (IARC) as a group 1 carcinogen. Pb is a major neurocogntitive and kidney toxicant for children at a relatively low concentration (10 ug/dL). Al accumulates in the kidneys, brain, lungs, liver, thyroid, and causes respiratory, neurological, and other smoking-related diseases. Inhaled Cu is a respiratory irritant which causes alveolar migration of macrophages, eosinophilia, and formation of histiocytic and non-caveating granulomas. Compounds of Mn may induce or exacerbate asthma (Gaur, 2018).

The results from the present review suggest that the concentration of metals in EC aerosols may be more than that in conventional cigarette smoke. This is related to the fact that ECs are an assembly of numerous metallic components which are highly susceptible to cyclic temperature changes. As EC aerosols are a major source of toxic heavy metals, marketing the ECs as a safe alternative to conventional cigarettes is questionable.

EC and the Adolescent

The rise in EC usage is one of the many concerning aspects regarding to ECs. The greatest increase was amongst current cigarette smokers, rising from 4.9% in 2010 to 9.4% in 2013 (King, 2015). The 2012-2013 National Adult Tobacco Survey found that the highest prevalence of EC use was in young adults aged 18-24 at 8.3%, nearly double that of the overall adult population prevalence (Agaku, 2014). Tobacco survey revealed a threefold increase in EC use between the years 2011 and 2013 in adolescents without a previous history of smoking. It was reported that 11.7% of the high school students in the United States used ECs in 2017. In 2018,

this number was increased to 20.8% (Jenssen, 2019). This could be attributable to their curiosity, the appealing nature of e-liquids, and the aggressive advertisement. Some publications postulate that vaping is less harmful than smoking (Franzen, 2018). ECs were thought to generate less noxious materials/toxicant than conventional cigarettes (Qasim, 2017).

Recent survey data indicate that adolescents with asthma had a higher prevalence of current EC use (12.4%) compared to their non-asthmatics peers (10.2%). Similarly, a study conducted among high school students from Ontario, Canada indicated a greater likelihood of EC use in asthmatics as compared to their non-asthmatic peers (Clapp, 2017).

While ECs may decrease the use of conventional cigarettes in adults with an existing smoking history, the prevalence of EC usage is greater in adolescent asthmatics relative to non-asthmatics which is of concern.

Recent data has shown that adolescents and young adults between 14-30 years of age who use ECs are 3.6 times more likely to use traditional cigarettes compared to those who don't use ECs. EC usage in adolescents has also been associated with development of anxiety, depression, long-term cognitive and behavioral impairments, and drug and alcohol abuse (Jenssen, 2019).

ECs vs. Conventional Cigarette Smoking

The adverse health effects of chronically inhaling combusted tobacco on the lung have been well described and include autophagy, DNA damage, goblet cell metaplasia, increased inflammation, and increased proteolysis in the lung (Ghosh, 2018). All of these changes can lead to increased incidences of COPD and lung cancer as well as significant extra-pulmonary effects including cardiovascular disease. Whether or not vaping is safe has remained highly

controversial. Proponents of vaping believe that it is safer than smoking. Opponents of vaping have emphasized that vaped e-liquids contain toxic chemicals including formaldehyde and heavy metals, which is harmful (Ghosh, 2018).

Combustible cigarette smoke contains at least 70 carcinogens including formaldehyde, free radicals, toxic gases, heavy metals, and tobacco-specific nitrosamines. These toxins have been measured at 9-fold to 450-fold greater than those found in EC aerosol (Drummond, 2014). Another form of toxin exposure, termed third-hand smoke, results from the particulate matter (PM) depositing on surfaces and can linger for months. It was reported that the PM emissions from EC aerosol were 15 times lower than emissions found in combustible cigarette smoke, though the levels still exceeded the World Health Organization (WHO) air quality guidelines (Cooke, 2015).

The greatest fear for the majority of health care professionals is that EC might pose unforeseen health problems either in the short term or long term. These harms stem from the toxic or carcinogenic constituents of the vapor, deleterious effects on lung function, or some unexpected consequence. Recent findings suggest that ECs may cause respiratory harm in ways that are both similar to and different from traditional cigarettes. Transcriptome sequencing of immortalized human bronchial epithelial cells following exposure to EC vapors and traditional cigarette smoke demonstrated the induction of similar distinct gene expression profiles (Ghosh, 2018). EC have side effects that can acutely affect users, including nausea, vomiting, dizziness, burn injuries, and upper respiratory tract irritation. The e-liquid contains chemicals that directly cause airway irritation when aerosolized, including nicotine and PG. Additionally, the glycol component found in e-liquid is commonly used as theatrical smoke, which has been reported to

decrease lung function after both acute and chronic exposure (Cooke, 2015). Another potential harmful aspect of EC is the direct cytotoxicity of e-liquids. The cytotoxicity was mainly related to the concentration and number of flavorings used and not the nicotine. Other studies examined the cytotoxicity of e-liquids and confirmed their potential cytotoxicity with certain flavors of e-liquids and different cell types (Ratajczak, 2018).

Cotinine is a metabolite of tobacco and a biomarker for tobacco exposure in humans. Flouris et al found that the serum cotinine levels generated by both active and passive EC smokers was comparable to those generated upon exposure to conventional cigarette smoke (Kaur, 2018). This means that ECs are no different to regular cigarettes as far as the health risks are concerned.

ECs have secondhand and thirdhand effects. The chemical components of aerosol can be different from those found in liquids due to the heating effect. The labeled nicotine-free EC products may still contain nicotine. EC might increase airway inflammation and airway hyper-responsiveness in patients with asthma. The glycol component of EC has effects on lung function on short- and long-term exposure. EC aerosol contains various toxic substances in low levels. Depending on heating degree, the toxic products can exceed the levels of combustible cigarettes. There are concerns of EC effects on fetus during pregnancy. There is concern of suicidal and incidental poisoning due to EC liquids (Gaur, 2018).

Trtchounian et al compared the smoking properties of conventional cigarettes and ECs, such as the vacuum required to produce smoke or aerosol and smoke/aerosol density. It was observed that ECs require more suction to release aerosols compared to conventional cigarettes. The health implications of this property have not been explored completely, but it is

speculated that stronger puffs may cause the aerosols to reach deeper tissues of the lungs, which might have adverse health outcomes in the users (Kaur, 2018).

It is known that pneumococci adhere to the host airway cells mediated by Platelet-Activating Factor Receptor (PAFR). Epidemiological studies suggest that inhalation of toxins increases the risk of airway bacterial infection. Cigarette smoking is associated with a fourfold increased risk of invasive pneumococcal disease. Passive exposure to environmental tobacco smoke is associated with a 1.5-fold risk of pneumonia in children. Miyashita et al (2018) recruited adults who vaped at least once a week and healthy never-smoked adult controls. They did a randomized controlled study on the expression of PAFR on nasal epithelial cells in non-vaping controls, and in adults before and after five minutes of vaping. Their results showed that vaping increased nasal PAFR expression at one hour. Nicotine-containing and nicotine-free EC vapor increased pneumococcal adhesion to airway cells in a dose-dependent and time-dependent manner in vitro. Vapor-stimulated adhesion in vitro was attenuated by the PAFR blocker CV3988. Nicotine-containing EC vapor increased mouse nasal PAFR expression, and nasopharyngeal pneumococcal colonization. Vapor contained redox-active metals, had considerable oxidative activity, and adhesion was attenuated by the antioxidant N-acetyl cysteine. This study suggests that EC vapor has the potential to increase susceptibility to pneumococcal infection.

Although it is speculated that some adverse health effects of inhaling EC vapor (ECV) are reduced compared with tobacco smoke, there is emerging evidence of toxic effects including the capacity to impair pulmonary bacterial host defenses. For example, EC vapor depletes lung antioxidants and delays the clearance of pneumococci from the lung in mice (Miyashita, 2018).

Because this was an animal study, it was unclear whether the concentration and duration of ECV used in vitro reflects exposure of airway cells in vivo. This study supports the hypothesis that ECV increases PAFR-dependent pneumococcal adhesion to upper and lower airway epithelial cells. The impact of regular vaping on the risk of pneumococcal airway infection remains to be determined.

It is crucial to understand that most of the chemicals present in tobacco smoke that are harmful to respiratory health are generated primarily during the combustion process. This is not a case for ECs. Evidence from laboratory studies comparing the chemical composition of aerosols emitted from ECs vs. tobacco cigarette smoke largely indicates that ECs contain far fewer potentially toxic chemicals, many of which are linked to adverse respiratory health effects (Cooke, 2015). What's more, concentrations of those toxicants identified in EC aerosols are in nearly all cases significantly lower than those measured in tobacco smoke with exception of some metals.

Results indicate that ECs may expose users to smaller particulates and lower amounts of particulate matter in general (Cooke, 2015). While inhalation of high levels of particulate matter has been linked to greater mortality risk from cardiopulmonary illnesses, the available data indicate that EC particulate emissions expose users at a level akin to the WHO guideline and are far lower than those of conventional cigarettes (Cooke, 2015). This suggests that ECs may be a less harmful source of particulate exposure in contrast to traditional cigarettes. However, further research is needed to reach a conclusion.

EC vs Nicotine Patch

Despite ECs not being approved by FDA for therapeutic use, ECs are advertised as a smoking cessation aid. Lee et al (2018) randomly divided preoperative patients who were smokers into two groups. One group (NRT group, N=10) received six weeks supply of nicotine transdermal patches in a tapering dose during perioperative period as a smoking cessation tool. The other group (END group, N=20) received six weeks supply of ECs in a tapering dose during perioperative period. There was no nicotine content in the sixth week supply for both groups. Rate of smoking cessation, smoking reduction, pulmonary function, adverse events, and satisfaction with the products were evaluated on the day of surgery, 30 days postoperatively, eight weeks postoperatively, and six months postoperatively. Their results showed that the patients from the END group significantly improved their forced expiratory volume in one second (FEV1) and FEV1 to forced vital capacity ratio (FEV1/FVC) compared to the patients from the NRT group postoperatively. There was not significant difference in the rate of smoking cessation, smoking reduction, adverse events, or patients' satisfaction with the products between these two groups at any time point during this study. They suggested that ECs are a feasible and acceptable smoking cessation aid in the perioperative setting compared to nicotine transdermal patches.

This was a very limited study with small sample size. Pulmonary function assessed by FEV1 and FEV1/FVC ratio can be effort-dependent and lack of reliability. Further study is needed to validate their work.

EC and Seizure

FDA just recently released a report on 35 cases of seizure potentially related to EC use in teens and young adults between 2010 and 2019 (Boyles, 2019). Even though the type of devices they use, the flavors of the e-liquid, and patient's baseline conditions were unknown, the high concentration of nicotine level which can be achieved in short period of time by using the third or fourth generation of ECs make it likely a potential risk factor for seizure activities (Boyles, 2019).

ECs and Safety

Multiple reports of injury caused by ECs have been made to the poison control department of the Center of Tobacco Products (Cooke, 2015). ECs have components of metals, plastics, fibers, ceramics, and lithium ion batteries which are known fire hazards. Multiple EC explosions have occurred resulting in severe burn injuries (Cooke, 2015). Lithium ion batteries have the tendency to explode when overheated, exposed to water, or in direct contact with metal objects (Selekman, 2019). In addition, there are increasing reports of accidental ingestion of e-liquids by smaller children due to the similar appearance of e-liquid packaging to juice boxes (Selekman, 2019). There are also increasing reports of infant deaths from choking on EC cartridges. E-liquids have even been used as means of suicidal attempts due to the lack of regulation (Selekman, 2019). ECs present many causes for concern outside of nicotine and heavy metal content.

Discussion

Tobacco use is considered to be one of the leading causes of preventable death and disease in Western Europe and the United States. ECs are a type of ENDS and carries significant

amount of nicotine, toxic chemicals, and heavy metals to its users. Use of ECs stimulates smoking behavior and is able to provide the sensation and satisfaction of traditional cigarette smoking. Other nicotine replacement therapies such as oral gums or patches do not have these features.

It is presently not possible to assess all the potential long-term harmful effects of EC use. Findings from clinical studies have demonstrated that ECs are likely less harmful compared to conventional tobacco cigarettes, and most harmful side effects are noticeably milder compared with conventional cigarettes. However, it is also clear that EC aerosols are not a “harmless water vapor”, as claimed by manufacturers and retailers, and potential respiratory health effects from vaping may emerge after long-term use. EC use has been linked to the incidences of organizing pneumonia, hypersensitivity pneumonitis, and lipoid pneumonitis. EC aerosols have been associated with damages to multiple vital organs and they are hazardous during pregnancy.

Clinical studies evaluating the safety and risk profile of EC use in humans are limited and most the current data is obtained from in vitro studies on cultured cells and in vivo experiments in animal models. Research regarding the acute health effects of EC is limited due to user variability, EC use experience, and differences between devices.

A major concern associated with the use of ECs is the lack of knowledge about their constituents. Although the amounts of harmful chemicals found in EC aerosols are far lower than conventional cigarettes, individual exposure depends on many factors such as device voltage, temperature, e-liquid flavor, nicotine content, and smoking behavior of the vaper. The diversity of the EC devices and e-liquids are also barriers to the studies on short- and long-term

health effect of ECs. Another barrier to these studies is the lack of control group because most of the EC users are also cigarette smokers.

In summary, there is some coherence across animal, laboratory, and human studies regarding the harmful effects of EC exposure. Current evidence indicates that although ECs are not without risk, these products seemingly pose fewer respiratory harms compared to tobacco cigarettes. There is significant research gap regarding potential respiratory health risks resulting from secondhand EC aerosol exposure and effects in humans, including children and other vulnerable populations. Many questions still remain regarding the possible harms and benefits of long-term EC versus combustible cigarette use. So far there is no clear evidence supporting the use of ECs.

EC use might predispose significant cardiovascular and pulmonary risks to the surgical patients. EC use appears to promote smoking behavior and drug and alcohol addiction. ECs are not an effective smoking cessation aid during perioperative period. EC usage might trigger seizure activities and might cause cancer. Explosions and severe burn injuries have been reported with ECs use. As ECs become more and more popular, it’s very important for anesthesia providers to know the harmful effects of vaping and its potential impact on the practice of anesthesia.

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