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VAPIng into ARDS: Acute Respiratory Distress Syndrome and Cardiopulmonary Failure

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ABSTRACT

"Modern" vaping involving battery-operated electronic devices began approximately one dozen years and has quickly evolved into a multibillion dollar industry providing products to an estimated 50 million users worldwide. Originally developed as an alternative to traditional cigarette smoking, vaping now appeals to a diverse demographic including substantial involvement of young people who often have never used cigarettes. The rapid rise of vaping fueled by multiple factors has understandably outpaced understanding of biological effects, made even more challenging due to wide ranging individual user habits and preferences. Consequently while vaping-related research gathers momentum, vaping-associated pathological injury (VAPI) has been established by clinical case reports with severe cases manifesting as acute respiratory distress syndrome (ARDS) with examples of right ventricular cardiac failure. Therefore, basic scientific studies are desperately needed to understand the impact of vaping upon the lungs as well as cardiopulmonary structure and function. Experimental models that capture fundamental characteristics of vaping-induced ARDS are essential to study pathogenesis and formulate recommendations to mitigate harmful effects attributable to ingredients or equipment. So too, treatment strategies to promote recovery from vaping-associated damage require development and testing at the preclinical level. This review summarizes the back story of vaping leading to present day conundrums with particular emphasis upon VAPI-associated ARDS and prioritization of research goals.

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Abbreviations: VAPI, Vaping-associated pulmonary injury; ARDS, Acute respiratory distress syndrome; EVALI, E-cigarette vaping-associated lung injury; DIY, Do it yourself; ENDS, Electronic nicotine delivery system; CASAA, Consumer Advocates for Smoke-Free Alternatives Association; PG, Propylene glycol; VG, Vegetable glycerin; THC, Tetrahydrocannabinol; COPD, Chronic obstructive pulmonary disease.

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1. Introduction

Vaping has grown from modest roots as an alternative to traditional cigarette use into a complex, controversial, and intractable societal problem. Vaping is a polarizing issue with strong arguments to be made on both sides of the debate. Fundamentally, the issue rests with a meteoric diversion of vaping into a recreational device for new users, particularly youthful ones, as opposed to an electronic nicotine delivery device for existing smokers. The impact of recreational vaping reverberates through the headlines, with added intensity resulting from high profile cases of "electronic cigarette or vaping-associated acute lung injury" (EVALI) in 2019 (Alexander, Bellinghausen, & Eakin, 2020; Amin, Haught, & Mousattat, 2020; Balmes, 2019; Cao et al., 2020; Casey, Muise, & Crotty Alexander, 2020; Doukas, Kavali, Menon, Izotov, & Bukhari, 2020; Fedt, Bhattarai, & Oelstrom, 2020; Gay et al., 2020). EVALI shows features of lipid pneumonia with lipid-laden alveolar macrophages.(Dicpinigaitis, Trachuk, Fakier, Teka, & Suhrland, 2020; Shields et al., 2020; Viswam, Trotter, Burge, & Walters, 2018) Lipid laden macrophages are often seen in bronchioloalveolar lavage of vaping subjects, but are not unique to vaping and cannot be used to make a conclusive diagnosis of VAPI.(Cecchini et al., 2020) Moreover, diagnosis of VAPI rests with imaging studies demonstrating pulmonary infiltrates in lungs of vape users and not with lipid laden macrophages which can be highly variable in presentation. (Pambuccian, 2020) Previous to the high profile EVALI outbreak, "vaping-associated pulmonary illness" (VAPI) had already been coined in recognition of pathological damage (Cecchini et al., 2020; Chen et al., 2020; Choi, Lin, Race, & Macmurdo, 2021; McCauley, Markin, & Hosmer, 2012). Reported cases include a subset of severe pulmonary failure categorized in clinical terms as acute respiratory distress syndrome (ARDS). Patients struggling with ARDS connected to mechanical ventilators in critical care have flooded into public consciousness because of the ongoing SARS-CoV-2 pandemic, but comparable examples of vaping-induced ARDS are well documented and there are overt similarities regardless of the inciting triggers. Awareness of potential lethality from the EVALI outbreak prompted rapid and intense research studies that identified the presumptive causal agent, but relatively little progress has been made in explaining how conventional vaping leads to ARDS with devastating consequences for afflicted individuals. There is a desperate and unfulfilled need for focused research into VAPI-ARDS, which would inform upon critical aspects of pulmonary sensitivity to vaping and offer insights for mitigation, treatment, and recovery interventions. Therefore, this review takes on the specific facet of VAPI-ARDS with the goal of highlighting fundamental biological problems, challenges, and areas to be targeted in current and future research.

Vaping-associated biological effects are far too diverse and multifaceted to be adequately covered in depth in a short article, so the focus of this review will be the pulmonary rather than systemic effects. Considerations will be framed primarily around individuals who engage in frequent and prolonged vaping using typical vape juice rather than other equally important concerns such as secondary exposure, indirect *in utero* exposure during pregnancy, "do it yourself" (DIY) vaping equipment (knows as "mods"), DIY juice recipes, and attendant complexities of cannabis and refined derivative compounds as vaped substances. Clearly there is ample and fertile ground for future research with so much to be studied juxtaposed against a paucity of universally established knowledge.

Undertaking a review of this nature, my intent is to avoid the pitfall of rendering judgment or condescension toward either side of the vaping debate. In preparation for this article, information was sourced from both pro-and anti-vaping groups as well as historical information on the origin story and subsequent transformation of 'modern' vaping. I offer background perspective on how vaping morphed from the original well-intended goal of providing tobacco smokers a healthier alternative that could serve as a bridge to cessation into being perceived as a public health crisis by attracting non-smokers, youthful users, and unregulated utilization. While some conclusions can be drawn from available information, the full scope of health effects will only begin to resolve in decades to come as current vapers diversify in age, patterns of use, individual preferences, lifestyle choices, and genetic backgrounds. We are entering a relatively new area of inhalation exposure investigation that will gather momentum as scientific research attempts to catch up with the inevitable and ever-changing personal, political, financial, and societal pressures that collectively influence the evolving world vaping and, in turn, VAPI.

2. Gathering clouds: the era of "modern vaping"

2.1. Rise of the vapers

Few influences upon human culture and behavior are more impactful than advances in electronic technology, with e-cigarettes and related devices as a prime example within the tobacco user community. (Villarroel, Cha, & Vahratian, 2020) Conceptually the e-cigarette was born decades ago but vaping as an alternative to tobacco cigarette smoking entered the so-called "modern" era approximately twenty years ago. Primarily, modern e-cigarettes as recognized today grew out of hardware innovations that allowed for battery operated aerosolization of a nicotine-containing solution creating a "vapor" that can be inhaled. The "Ruyan" (Chinese for "like smoke") was introduced by Hon Lik in 2004 with physical appearance similar to a Sharpie marker and became popular with smokers looking for a nicotine fix while still delivering behavioral customs of holding, puffing, and inhaling from a cigarette (Geller, 2015). Hon Lik picked up a chain smoking habit from his father, although being a pharmacist he was well aware of the terrible hazards associated with cigarettes. As a new take on longstanding problem, Hon Lik's Ruyan represented a "healthier" electronic nicotine delivery system (ENDS). The Ruyan was the first step, and soon thereafter a pair of Stanford graduate students hooked on cigarette smoking pitched the idea of a "superior product offering" as their masters thesis. Their ENDS device was intended to win over smokers by giving them what they loved about cigarettes while eliminating the worst characteristics of tobacco combustion. The initial ENDS concept of James Monsees and Adam Bowen would eventually spawn the JUUL vape pen and eponymously named company that would rise to dominate the ENDS market with a 72% share and $38 billion valuation in 2018 (Ducharme, 2021). The unprecedented popularity of "juuling" together with declining sales of traditional cigarettes incentivized a major stake investment by Altria Group (formerly known as the Phillip Morris Companies synonymous with Big Tobacco). Multiple concurrent events led powerful forces to unleash their collective wrath upon the JUUL company for it's undeniable popularity with young users who became addicted, although the principals maintain their intention was never to market to underage users or encourage use of their product as anything other than a preferable alternative to traditional cigarette use. Indeed, blood nicotine concentrations tested in a rat inhalation exposure model with JUUL pods showed serum levels (136.4 ng/ml) eight times higher relative to e-cigs group (17.1 ng/ml) and 5.2 times higher than traditional cigarettes (26.1 ng/ml).(Rao, Liu, & Springer, 2020) Notably, nicotine concentration in JUUL pods is high (59 mg/ml) compared to other studies that showed serum nicotine levels in the range produced by traditional combustible cigarettes using vape juice concentrations at or below 20 mg/ml.(Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013; Yingst et al., 2019) Mislabeling of nicotine concentrations in vape juice continues to be a problematic concern to the potential detriment of vapers who may be unaware of nicotine dosing. (Cameron et al., 2014; Davis, Dang, Kim, & Talbot, 2015; Jackson, Huskey, & Brown, 2020) Popularity of the JUUL device has waned somewhat since 2018 due to public fallout around EVALI, multiple public relations debacles, government regulations, and shifting preferences of end users toward other e-cigarette products such as Puff Bars. Nevertheless, JUUL still retains a significant share of annual sales for e-cigarettes

with continued growth expected to reach $48 billion by 2023 (Intelligence, 2020). Unfortunately, a substantial portion of that market is represented by 'lifestyle' ENDS users and recreational vapers as opposed smokers seeking healthier alternatives.(Tsai, Byun, Shin, & Crotty Alexander, 2020; Wang et al., 2020; Wang et al., 2021) Youthful demographics of vaping has become the rallying cry from anti-vapers for a product that was optimistically touted as the solution for putting Big Tobacco out of business. In 2020, 19.6% of high school students (3.02 million) and 4.7% of middle school students (550,000) reported current e-cigarette use. 3.6 million U.S. youths still currently used e-cigarettes in 2020. (Wang et al., 2020; Wang et al., 2021) Now that the proverbial "genie is out of the bottle", vaping is and will continue to be the focal point of societal, political, and business battles without any resolution in sight.

2.2. The substitute takes over the class

Undeniable health consequences and growing societal pressure for smokers remains a powerful motivation to develop innovative solution to replace traditional tobacco-burning cigarettes. At the center of the movement for smoking alternatives is the concept of "harm reduction", meaning that less harmful alternatives save lives and decrease the burden on healthcare systems for conditions arising from smoking such as lung cancer and emphysema. "Harm reduction" is a laudable goal capturing the zeitgeist that '*people smoke for nicotine but they die from the tar*'. Recognizing this fundamental basis of smoking as a nicotine addiction spawned various delivery approaches such as patches, gum, and e-cigarette variations, but none of these interventional strategies captured the physiologic feelings of a nicotine hit that smokers desire. Thus the limited efficacy and popularity of these nicotine replacement therapies was no match for JuulSalts, a patented chemical modification of nicotine with benzoic acid allowing for higher nicotine concentrations in vape juice, quicker bioavailability across the blood-brain barrier, and "satisfaction in an individual superior to that of freebase nicotine and more comparable to the satisfaction in an individual smoking a traditional cigarette" as written in the patent from Pax Labs (the parent company of JUUL) (Ducharme, 2021). In reality, JUUL was merely taking a page from Big Tobacco and the centuries old practice of "Flue-curing" that leads to accumulation of plant acids in the tobacco leaves during the curing process and nicotine protonation.(Duell, Pankow, & Peyton, 2020) Multiple types of acids (lactic, benzoic, levulinic, salicyclic, etc.) are suitable for nicotine protonation resulting in nicotine salts comparable to JuulSalts.(Harvanko, Havel, Jacob, & Benowitz, 2020) Development of JuulSalts was heralded as a game-changer for attracting smokers into vaping, but simultaneously presented the entirely new dilemma of non-smokers becoming nicotine addicts by "juuling" with the new tech of sleek discreet USB-style pens and flavored e-juices. The early advertising campaign launch for JUUL vaping included the now infamous hashtag #Vaporized social media phenomenon that bears the brunt of criticism as the quintessential example of marketing to underage users (Fadus, Smith, & Squeglia, 2019). Regardless of the original intent for the new generation of 'modern vaping' to curb smoking, appeal to underage users has become a lightning rod for attacking the vaping industry as a whole. Lack of clear regulatory oversight, the power of social media, and novel features of the JUUL experience created perfect conditions for a meteoric rise in sales, dominating market share, unimagined profits, and a new youthful user base. Flavored vape juices remain readily available despite interventions by the US government starting in 2019, which primarily specifically impacted JUUL pod sales and drove users to other sources for flavors. Consequently, debating vaping as a "harm reduction" is inextricably intertwined with controversies of youth vaping and nicotine addiction, proliferation of vape juices with names and flavors targeting underage users, and impassioned arguments from both sides over the validity and relevance of vaping research.

2.3. Over a decade of hits: consensus versus controversy

Asserting "harm reduction" by switching from smoking to vaping hinges upon demonstrable benefits to health and well-being of users as well as those subject to second hand exposure (Zhu, Zhuang, Wong, Cummins, & Tedeschi, 2017). Pathological damage, increased health risks, and decreases in quality of life as well as average lifespan resulting from of tobacco smoking are universally acknowledged. As such, making the case for superiority of vaping as an alternative would seem straightforward (Hartmann-Boyce et al., 2021). Indeed, pro-vaping advocacy organizations such as the Consumer Advocates for Smoke-Free Alternatives Association (CASAA; http://casaa.org) provide compelling rationales supported by substantial documentation to defend vaping for smoking cessation therapy (as well as an individual right to choose) (Association, 2021). CASAA also takes aim at undermining the basis of several contentious vaping-related topics including youth usage, the "gateway theory" of vaping leading to smoking, misappropriation of the EVALI outbreak of 2019 as representative of vaping in general (Leas et al., 2020), and the validity of many peer-reviewed vaping research studies (Fairchild, Healton, Curran, Abrams, & Bayer, 2019). Indeed, CASAA points to numerous studies concluding that vaping is a *relatively* safe and effective "off ramp" approach to smoking cessation with substantially decreased health risk (George et al., 2019; Wieczorek et al., 2020). Using CASAA logic, limiting access or denying smokers the option to use vaping products actually worsens societal and individual health and well-being (Board, 2019). Of course, CASAA finds vehement opposition from groups such as the Truth Initiative (https://truthinitiative.org), Still Blowing Smoke (https://stillblowingsmoke.org), and the American Heart Association (https://www.heart.org/en/healthy-living/healthy-lifestyle/quit-smoking-tobacco/the-ugly-truth-about-vaping). Arguments from the anti-vaping community focus upon increased health risks, insidious marketing practices that target adolescents, statistics showing a growing youth vaping "epidemic", highly addictive nicotine in vape juice posing unprecedented issues for addiction, suspect motivations and trustworthiness of Big Tobacco that essentially controls the vaping industry, and high profile stories of VAPI and EVALI (Bhatt, Ramphul, & Bush, 2020; Newton, 2019). The widely divergent positions, conflicting evidence, and accusations of bias presented by the camps of pro- *versus* anti-vaping likely leave the casual observer unable to reach any coherent conclusions (Kaisar, Prasad, Liles, & Cucullo, 2016). One inescapable conclusion persists: like society in general, scientific research was caught off guard by the breathtaking spread of vaping and has been trying to catch up in recent years (Fig. 1). This scramble to understand the biological effects of vaping has produced to a plethora of model systems, protocols, and interpretations. While diversity of approaches to assess vaping could be considered a strength, it is also a source of variability, confusion, and perplexity especially when results are inconsistent. Early research findings are typically characterized by wide ranging perspectives as data are gathered, analyzed, reported from multiple sources. While such investigative diversity is the natural order of scientific evolution and progress, any modest consensus is obfuscated by highly pitched and polarized positions of those who advocate for or against vaping.

The phenomenon of 'modern vaping' is a recent and growing trend with clinical information limited to the last decade. While the majority of vapers currently do not exhibit overt signs of significant damage, there is absolutely no way to predict the fate of chronic users in terms of symptoms and pathology in decades to come (Gotts, Jordt, McConnell, & Tarran, 2019). Scientific modeling of human exposure occurring over a lifetime of vaping simply does not exist, only hypothetical approximations. However, in the short term, case reports continue to accumulate of vaping-associated life-threatening illness or mortality. Surprisingly few research studies authentically recapitulate conditions and outcomes of severe VAPI or EVALI (Garcia-Arcos et al., 2016; Glynos et al., 2018; Madison et al., 2019), particularly with regard to how VAPI spirals downward into

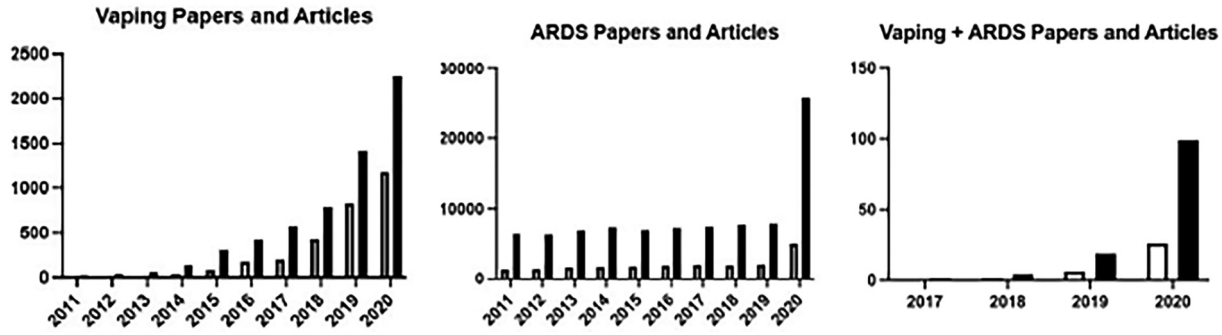

Fig. 1. Vaping, ARDS, and vaping & ARDS papers and articles published per year from 2011 to 2020. Prevalence of publications and articles related to vaping and ARDS as determined by searches using PubMed (open bar) and Google Scholar (black bar) focused on the time frame between 2011 and 2020 modern vaping became prevalent. Specific search terms used included "vape vaping" (left), "ARDS, acute respiratory distress syndrome" (center), and "vape, vaping, ARDS, acute respiratory distress syndrome" (right). The PubMed search consisted of primarily clinical results. An identical search on Google Scholar yielded primarily citations from popular culture.

ARDS. Research is desperately needed to understand the pathological damage observed in patients who succumb to pathological damage directly attributed to vaping. Fortunately, there is a rich cumulative literature on the pulmonary system, how inhalation-mediated damage occurs, and interventional approaches to treat ARDS as detailed in the following sections.

3. The pulmonary system gets vaporized

3.1. Pulmonary circuit: structure and function

From our first breath until the last exhalation, life sustaining blood flows from the right side of the heart to the lungs and back to the left side of the heart in the pulmonary circuit. Separation of pulmonary *versus* systemic circulation allows for highly efficient gas exchange as blood returned from the body is sent to the lungs through the incredibly fine network of capillary vessels intimately associated with alveolar air sacs. Dry air totaling a volume of 2000–3000 gal per day is inhaled and humidified on the journey from the nose through the trachea, into the bronchi, then the bronchioles, and ever smaller passageways until reaching alveolar sacs. Fluid is a critical part of proper lung function as each alveolus is protected with a surfactant-containing aqueous layer. Breathing also involves substantial fluid loss in the form of exhaled water vapor exhaled with every breath. Air passageways are maintained and cleansed by the constant movement of fluid along epithelial layers to wash inhaled particulates, contaminants, pathogens, and debris out of the respiratory system. Airway epithelium comprised of mucus-producing cells and ciliated cells comprises a critical defense that constantly traps and propels secretions up into the nose, mouth, or nasopharynx and out of the lungs. Importantly, maintenance of proper fluid levels within the respiratory system is essential to optimal function for both cleansing and gas exchange activities. In this context it is easy to envision how substantial vaping activity inevitably alters fluid homeostasis, ovewhelming the impressive ability of lungs and airways to expel liquids to maintain function. Indeed, mucociliary clearance activity is significantly impaired by nicotine (Chung et al., 2019) as well as cinnamaldehyde, a popular flavoring component of vape fluid. (Clapp et al., 2019) Aerosol readily mixes in with airway secretions as well as traveling deep into remote regions of bronchioles and alveoli. (Manigrasso, Buonanno, Fuoco, Stabile, & Avino, 2015; Sosnowski & Kramek-Romanowska, 2016) Thus, vaping impact throughout the respiratory tract depends upon a wide range of factors linked to the inhaled substances and their distribution as well as location within the respiratory system and cell types involved. This review will touch upon research topics involving specific lung regions and cell types, but detailed coverage of lung biology is beyond the scope that can be adequately addressed. Comprehensive understanding of the respiratory system and lung biology has been expertly summarized in excellent reviews and the reader should turn to these and other similar works for in-depth coverage (Franks et al., 2008; Luo et al., 2018).

3.2. Wet with juice: vape fluid aerosol inhalation into airways

The upper airway tract is the proximal site of entry for vape aerosols into the respiratory system, so it stands to reason that a significant amount of inhaled juice mixes into secretions of the formidable mucosal defense network intended to trap and remove airborne contaminants. Vape juice aerosol is comprised predominantly of propylene glycol (PG) and vegetable glycerin (VG) with the remainder consisting of water, food flavoring, and varying nicotine levels (Lechasseur & Morissette, 2020). Studies of cultured cells indicate that PG/VG mixtures can alter lipid metabolism and disrupt glucose uptake leading to speculation that vaping aerosols may compromise epithelial layer barrier function in the upper airway (Ganguly et al., 2020; Muthumalage, Lamb, Friedman, & Rahman, 2019; Woodall et al., 2020). A prescient study assessing nebulized PG inhalation (without heating) concluded there was no evidence for systemic toxicity but significant increases in mucin content of existing goblet cells as well as increased number of goblet cells in nasal turbinates.(Suber, Deskin, Nikiforov, Fouillet, & Coggins, 1989) Decades later, increased mucin levels consequential to PG/VG fluid exposure was noted in cell cultures of human nasal epithelia (Escobar et al., 2021), murine nasal epithelia, and human airway epithelia.(Ghosh et al., 2018) Disruption of lipid homeostasis in a murine inhalation model using a commercially sourced ENDS device prompted lipid accumulation in alveolar macrophages and type II pneumocytes. (Madison et al., 2019) Engagement of macrophages with xenobiotic agents of vape aerosol demonstrates their biological role as 'sentinel' cells of the lung. However, when tested using a rodent inhalation model, PG/VG mixtures PG/VG aerosols showed only very limited biological effects with no signs of toxicity (Phillips et al., 2017). As is often the case with vaping-related research, experimental model system design and exposure protocols are susceptible to criticism for relevance to real world conditions of human vaping. As such, extrapolation from the scientific literature to unequivocal effects of vaping in humans continues to spark debate and controversy. Evidence for genotoxicity and triggering of xenobiotic defense responses is stronger for the minor constituents of flavorings and nicotine (Abouassali et al., 2021; Akkanti et al., 2020; Al-Saleh et al., 2020; Barhdadi et al., 2021; Garcia-Arcos et al., 2016; Tellez et al., 2021). Epithelial cells lining the upper airway passages are on the front lines of interacting with inhaled particulates and droplets of vape aerosols and multiple studies suggest various biological effects including altered metabolic function (Madison et al., 2019), structural disturbances (Chaumont et al., 2019; Wehrli, Caporale, Langham, & Chatterjee, 2020), transcriptional reprogramming

(Szafran et al., 2020), and altered proteome (Ghosh et al., 2018). In addition to biological effects related to the components of the vape juice, additional concerns have been raised regarding the heating process including the type of element used, composition, and potential to form toxic by-products.(Marques, Piqueras, & Sanz, 2021) Aerosols from e-cigarettes contain numerous heavy metals derived from the heating filament and associated connections (nickel, chromium, copper, zinc, tin, lead) that can act as respiratory irritants or carcinogens.(Williams, Bozhilov, Ghai, & Talbot, 2017) Furthermore, abnormal heat conduction in the filament or increasing wattage settings can produce abnormally high temperatures that promote degradation and volatilization into aerosol.(Kleinman et al., 2020; Wagner, Chen, & Vrdoljak, 2020) Thus, VAPI can be exacerbated by xenogenic agents contributed directly from the heating element or by-products of heating element reaction with vape fluid. Of course, such pathological changes will inevitably depend upon multiple aspects of integrating exposure within the airway that include not only the vape aerosol but also individual vaping behaviors. Furthermore, inherent variability in genetics, preexisting conditions, and environmental confounding factors such as airborne pollution or respiratory allergens could certainly influence outcomes of vaping-induced biological responses.

3.3. Ripples into lung parenchyma (alveolar impact and vascular remodeling)

Tissue structures and interactions between inhaled agents and cells become much more delicate and intimate deep within the respiratory tract. Epithelial layers in alveoli are only a single cell that separates the air-filled lumen from capillary vasculature in order to facilitate gas and fluid exchange. Preservation of efficient exchange between the bloodstream and inhaled air is essential to maintaining oxygenation levels critical for homeostasis and ultimately survival. Access to the bloodstream is also fundamental for bioavailability of nicotine salts that are absorbed and transported throughout the body to satisfy physiologic addiction and the desired 'buzz'. Surface area of the collective alveoli within the human lung is truly phenomenal, covering over 100 square meters. With such a large area interfacing to the outside world the need for constant surveillance against foreign contaminants and agents is essential. Alveolar sacs lack the ciliated and secretory mechanisms of upper airways to wash away contaminants because of specialization for gas exchange, so alveolar macrophages act as guardians and sentinels. Macrophage activation or damage to alveolar integrity triggers inflammatory responses (Scott et al., 2018) that can accumulate withing the lung parenchyma within hours, causing substantial damage and secondary sequelae with potentially devastating consequences (Edmonds, Copeland, Conger, & Richmond, 2020; Puttur, Gregory, & Lloyd, 2019). In severe cases the progressive loss of alveolar structure and density, cell death, tissue structural deterioration, and fluid accumulation inevitably impacts upon intricate network of larger vessels and capillaries within the lung leading to adverse remodeling, increased vascular pressure, and pulmonary failure (Fathima & Zhang, 2020).

3.4. Cardiovascular responses: domino effects or separate concerns?

Cardiovascular effects of vaping are the subject of ongoing studies (Middlekauff, 2020; Vajdi & Tuktamyshov, 2020). Circulation of blood operates at substantially reduced vascular resistance in the pulmonary circuit (100–200 dynes/second/cm) relative to the systemic network (700–1500 dynes/second/cm). Low resistance is possible because the pulmonary circulatory network has the largest surface area of any vascular bed in the body, allowing efficient perfusion throughout lung parenchyma of blood pumped directly from the right ventricle. Adapted to relatively low normal pressures, the right ventricle does not cope well with chronic increases in afterload pressure with prolonged fluid accumulation in the lungs (pulmonary edema) provoking maladaptive remodeling that can transition into right side heart failure. Right ventricular dysfunction is a common feature of moderate to severe ARDS and a major determinant of mortality. Given these well documented clinical observations, it is certainly plausible that worst-case scenarios of VAPI involve pulmonary edema that, in turn, drive right ventricular dysfunction and a deadly spiral into ARDS. Correlative associations support a causal relationship between VAPI and ARDS, but this area of vaping-related research has been primarily focused upon the recent EVALI outbreak linked to vitamin E acetate (Matsumoto et al., 2020) and tetrahydrocannabinol (THC) (Fairchild et al., 2019). In comparison, chronic and/or frequent recurring vaping behavior of users addicted to nicotine or "cloud chasers" who view vaping as a hobby may also be at risk for VAPI-induced ARDS, but there remains a paucity of research in this specific area that could shed light on emerging clinical reports discussed below.

4. Swimming or drowning in vape juice?

4.1. Acute respiratory distress syndrome

The EVALI outbreak of 2019 demonstrated how quickly vaping toxic compounds can lead to life-threatening lung pathogenesis and dangerous vape juice experimentation by questionable suppliers without appreciation of fundamental biochemistry. Commercially available vape juices from reputable sources do not provoke EVALI (Farsalinos & Polosa, 2014; Marques et al., 2021), but the long term consequences of vaping upon bronchial airways, alveolar sacs, and neighboring capillaries remains largely unknown. Indeed, *in vivo* vaping studies showing subtle observed effects or absence of overt pathological changes remain a challenging conundrum for researchers (Shi et al., 2019). In contrast, vaping leading to inflammatory reactions, pneumonia, alveolar rarefaction, and adverse remodeling including scarring (Smith, Gotway, Crotty Alexander, & Hariri, 2021; Sood et al., 2021) has a clinical correlate in VAPI with various presentations of illness including severe syndromes such as ARDS (Akkanti et al., 2020; Al-Abdouh, Phillips, & Allison, 2020; Chapman, Tweed, & Moonsie, 2020; Sakla, Gattu, Singh, & Sadler, 2020; Vogel et al., 2021). High profile cases of VAPI with ARDS are a focal point of debate over the dangers of vaping, so replication of this condition with experimental models is fundamentally important to advancing understanding potential risks of vaping, identifying those at risk for serious illness, developing interventional approaches to mitigate injury, and understanding the recovery process.

ARDS can be provoked by various pathological processes both acute and chronic in nature. Inciting damage leading to ARDS can follow sepsis, severe pneumonia, COVID-19 infection, or inhalation of toxic substances, to name a few possibilities. Fluid accumulation in alveoli prevents efficient gas exchange and decreases blood oxygenation level. Severe shortness of breath is the main symptom of ARDS and the consequences can be fatal, with risk of death increasing with age and severity of illness. Survivors of ARDS may experience lasting damage to their lungs. The EVALI epidemic of 2019 demonstrated the rapid and sometimes lethal impact of acute inhalation injury and subsequent inflammatory damage, but it is important to clarify that EVALI is not a normal outcome of commercially purchased vaping juices, but rather from "street vapes" predominantly containing THC and vitamin E acetate (Ellington et al., 2020; Layden et al., 2020; Pajak, Bascoy, Li, Benninghoff, & Deitchman, 2020; Rodriguez, Roa, & Lemos-Ramirez, 2020). Indeed, conventional use of vape products is generally considered safe from provoking an EVALI-type crisis in the acute setting of hours to days after inhalation. However, a more insidious form of damage from chronic use over weeks to months does have the potential to provoke VAPI.(Marques et al., 2021; McDonough, Rahman, & Sundar, 2021; Miyashita & Foley, 2020) Presentation and severity of VAPI-induced illness shows marked variability and awareness has been raised in clinical settings to inquire about vaping use and history, as some patients (particularly adolescents vaping without parental knowledge) will be reluctant to disclose such information. Highly individualized

human behaviors and their protracted time course of vaping inhalation exposure makes broad generalizations impossible, but for those who engage in frequent heavy use for weeks to months there is certainly sufficient correlative evidence for increased risk of VAPI with the potential for complications of ARDS without early and aggressive intervention. In severe cases of VAPI with pulmonary edema, right ventricular enlargement of the heart leads to pulmonary failure and worsening prognosis for recovery.

4.2. Right ventricular remodeling and failure

The pulmonary circuit is responsible for delivering blood from the body to the lungs where life sustaining exchange of gases and moisture takes place. The physiology of pulmonary function is exquisitely attuned to maintaining optimal efficiency through processes of adaptation and remodeling. The lungs and heart exist in a dynamic balanced state of homeostasis that responds to changes, both rapidly for immediate effects as well as relatively slowly for chronic stresses. Pulmonary blood flow is a high flow low pressure system when healthy, but pathological conditions leading to increased vascular pressure have a domino effect upon right ventricular remodeling. The heart initially attempts to compensate for increased resistive pressure by increasing output, which can take the form of increased contractility and increased stroke volume output. Such cardiac adaptations may be useful as short term fixes, but chronic pulmonary hypertension eventually leads to maladaptive right ventricular enlargement and loss of contractile force. The net result is a dangerous downward spiral of pulmonary circuit failure that together with fluid accumulation in the lungs leads to life-threatening loss of function. The right ventricle cannot pump blood to the lungs as fast as it returns from the body. Blood then engorges the right side of the heart and associated veins with fluid forced out into tissues causing swelling (edema). Blood oxygenation drops, pH balance is dysregulated, and often extraordinary medical interventions with critical care are not enough to rescue afflicted individuals (Zochios, Parhar, Tunnicliffe, Roscoe, & Gao, 2017). For those who do survive, lingering long term aftereffects can be debilitating with life-changing consequences. Scenarios such as this represent the bleakest course of events for VAPI that have been documented in case reports (Diaban, & Z.; Vaziri, J.; Plisco, M., 2020; Sakla et al., 2020). The essential need to understand precipitating factors that contribute to VAPI with ARDS (including heart failure) will empower informed and trustworthy recommendations to discourage risky behaviors, advise vapers on best practices to avoid long term critical pulmonary damage, and accomplish the goal of all stakeholders in the vaping debate to eliminate morbidity and mortality as a possible outcome.

Long Term Consequences and the Great Unknowns

5. Road to recovery: stopping is a start to let the healing begin

5.1. Lung reparative capacity

Constant exposure of lung airways and alveolar spaces to the external world through respiration necessitates the capability to recover from insults and injuries in order to preserve function and maintain structural integrity. The air we breathe dynamically changes in composition and contaminants on an ongoing basis, and lung tissue possesses ability to flush out impurities and pollutants as well as recognize and actively remove invaders by phagocytic action of resident macrophages. Constant turnover of epithelial layers is also an important process to remove damaged and aged cells that are on the front lines of environmental exposure. Replacement of cells within the lung rests with specific subsets of progenitor populations giving rise to functionally specialized descendants dictated by structural organization within varied zones of the lung. The field of lung cellular replacement, repair, and regeneration research is complex and vast as captured in numerous articles and reviews that the reader should consult for detailed information beyond the scope of vaping-related investigation (Barkauskas, 2020; Basil et al., 2020; Bertoncello & McQualter, 2010; Fernanda de Mello Costa, Weiner, & Vaughan, 2020; Hogan et al., 2014; Lee & Rawlins, 2018; Navarro & Driscoll, 2017; Olajuyin, Zhang, & Ji, 2019; Schilders et al., 2016; Tsuchiya, Doi, Obata, Hatachi, & Nagayasu, 2020; Vaughan et al., 2015; Weiner et al., 2019; Yuan et al., 2019; Zepp et al., 2017; Zuo et al., 2015). Notably, recency of modern vaping has left little time for investigating impact of vape aerosol inhalation upon select lung cell types and potential impairment of repair processes. However, research studies have documented remarkable reparative capacity of the lungs as exemplified by the repopulation of the lung with healthy cells in samples from individuals who had quit smoking tobacco when compared to cells from lungs of smokers (Yoshida et al., 2020). Of course, lung recovery potential is not immutable and can be lost if severe chronic damage has compromised structural integrity of the lung tissue, such as in emphysema or chronic obstructive pulmonary disease (COPD). Thus, the consensus recommendation is that quitting smoking immediately offers beneficial effects that persist regardless of how long an individual has been smoking. Analogous advice applies for inhalation of any xenobiotic agent including vape juice that provokes defensive responses with increases severity from prolonged recurrent exposure. Although genotoxic effects of combustible tobacco smoking are established, the research on vaping products predominantly rests upon *in vitro* studies (Gay et al., 2020; Lee et al., 2018) that are criticized for relevance to *in vivo* conditions. Two recurrent areas of concerns for genotoxicity of vaping are 1) unknown consequences of flavoring inhalation and 2) toxic by-products created from heating chemical agents in vaping devices. Additional research focused upon these specific issues should be a priority for near-term studies to establish risk area and recommendations for safest vaping practices. So too, severe VAPI and ARDS likely provoke irreparable damage within the lungs and pulmonary circuit and the potential pathological impact of vaping remains a high priority area of future research.(González-López & Albaiceta, 2012; Noone & Reddy, 2021; Young, DiSilvio, Rao, Velliyattikuzhi, & Balaan, 2019) Such studies are urgently needed to establish trustworthy accounting of vaping-induced damage, realistic expectations for treatment, and development of innovative strategies to augment recovery.

5.2. Vascular remodeling

The pathologic impact of ARDS upon pulmonary structure and function have been extensively documented and studied over decades of basic and clinical research (Mikolka et al., 2020; Oliveira et al., 2017; Snow, Davies, Pontoppidan, Zapol, & Reid, 1982; Vieillard-Baron, Price, & Matthay, 2013). Findings indicate that degree of vascular remodeling and damage correlates with the duration of illness, specifically with respect to peripheral extension of vascular smooth muscle and increased medial thickness of muscular arteries. Additional injury occurs in the form of endothelial layer disruption and fibrocellular intimal obliteration of arteries and veins. Partial or complete disruption and even disappearance of much of the pulmonary vascular bed can occur. Long-term survivors exhibit tortuous arteries and irregularly dilated capillaries. Structural vascular damage from ARDS impairs pulmonary function and accelerates deterioration of alveolar spaces. Effects of vaping upon vascular tissue may be both direct and indirect (Olfert et al., 2018; Tsai et al., 2020) meaning there may be 1) direct biological impact of compounds from vape juice exposure upon vascular cells as well as 2) consequential vascular remodeling pursuant to lung damage and tissue edema. The latter scenario reflecting highly dynamic and reactive vascular tissue remodeling is extensively detailed in reviews of pulmonary hypertension (Thompson & Lawrie, 2017; Tuder, 2017). Utilizing current approaches for slowing or reversal of vascular pathology in pulmonary hypertension (Ali, Ichimura, & Spiekerkoetter, 2021) could also benefit VAPI patients prior to onset of ARDS. Unfortunately once lost, restoration of the vascular bed is limited and some loss of functional capacity is inevitable. Thus, early engagement of vapers will be essential to

mitigate risks of permanent damage in the vascular as well as myocardial context.

5.3. Myocardial repair

The transition of ARDS into pulmonary circuit failure with loss of right ventricular function represents a dangerous escalation of disease progression. Cardiac contractile impairment promotes tissue edema and compromises organ function. Preservation of cardiac output is essential for slowing deterioration of systemic homeostasis and promotion of recovery. Restoration of myocardial contractile performance remains the Holy Grail of cardiovascular research but has remained elusive for decades (Broughton et al., 2018). Currently, interventional approaches to restore or regenerate myocardial tissue offer only modest improvements at best and are predominantly relegated to experimental animal model settings with uncertain and untested relevance for treatment of human heart failure (Broughton & Sussman, 2019; Gude, Broughton, Firouzi, & Sussman, 2018; Liew, Ho, & Soh, 2020; Price, Vieira, & Riley, 2019). Substantial recovery from maladaptive chamber dilatation and wall thinning in right ventricular failure is unlikely, particularly in older patients. Therefore, as with vascular remodeling, intervention prior to myocardial decompensation is currently the only tractable solution to prevent remodeling, long term damage, and loss of functional performance in the pulmonary circulation.

6. Time for an intervention?

6.1. Standard therapeutic strategies

VAPI-associated ARDS is a relatively recent phenomenon, but ARDS resulting from other inciting agents such as toxin inhalation, viral infection (including COVID-19) (Kaur, Lungarella, & Rahman, 2020; Lan, Liu, & Zhou, 2021), sepsis, severe pneumonia is routinely treated in the clinical setting. ARDS accounts for 10% of intensive care unit admissions and 25% of mechanical ventilations. Mortality for severe ARDS patients in hospital care ranges from 46% to 60% (Saguil & Fargo, 2020). Although there is currently no cure for ARDS, multiple interventional approaches are typically initiated to mitigate symptoms, promote survival, and foster recovery (Bein et al., 2016; Gattinoni & Quintel, 2016a, 2016b). Blood oxygenation is increased using supplemental oxygen and mechanical ventilation. Fluid management therapy helps to decrease tissue edema and pressure. Additional measures such as neuromuscular blockade, prone body positioning, and anti-inflammatory regimens may also be beneficial. However, development of pharmacologic treatments remains frustratingly unsuccessful with many of the pathways thought to be involved in ARDS having been targeted without demonstrable benefit (Meyer, Gattinoni, & Calfee, 2021; Reddy, Calfee, & McAuley, 2021).

ARDS arises from multiple origins that collectively run toward shared phenotypic endpoints. Standard interventions will undoubtedly be of some benefit in clinical treatment of VAPI-associated ARDS. However, VAPI-associated ARDS may also exhibit unique or accentuated features owing to the distinct nature of chronic vape aerosol exposure. In all ARDS cases including VAPI, identifying underlying causes and understanding of primary cellular and molecular mechanisms are essential for treatment as well as development of new interventional strategies.

6.2. Next generation approaches

ARDS has been notoriously refractory to pharmacotherapeutics, prompting exploration of cutting edge approaches as treatment strategies (Nanchal & Truwit, 2018). Therapeutic interventions using adoptively transferred cells, exogenously introduced genes, and signaling molecules are all being tested and developed (Florian et al., 2021; Han, Liu, Liu, & Li, 2019; He et al., 2021; van Haasteren, Hyde, & Gill, 2018). Cutting edge concepts such as gene editing or modified RNAs could be incorporated into the arsenal of potential tools to modify the course of ARDS. Importantly, the legacy of failed approaches can also be viewed as an important resource to guide future studies and narrow in upon novel candidates, The onslaught of ARDS cases from the EVALI outbreak as well as the COVID-19 pandemic highlighted the dire need to novel treatment options. Assessment of past trends provides strong evidence for increasing frequency of VAPI as a clinical challenge, and research into treatment of VAPI-associated ARDS has broad-based applicability to the wider spectrum of ARDS cases regardless of underlying etiology. Therefore, VAPI research that unravels progression to ARDS represents a new opportunity to advance development of novel, safe, and efficacious interventional strategies.

7. Where do we go from here?

7.1. Present considerations

Vaping is here to stay and, if past is prologue, will continue to expand in both market share as well as invention of new products and devices. As with the beginning of commercialized tobacco smoking when detrimental health effects were not established, early adopters of vaping will be serving as test subjects in a worldwide experiment to determine the long term consequences to health and well-being. From a research standpoint, there are numerous challenges ahead in the quest to understand health risks of vaping and delineate biological effects on organismal, cellular, and molecular levels. First, the diversity of vaped substances in terms of commercial products, "Dank Vapes" and counterfeits, and "DIY" home mixing options is an overwhelming number of possibilities to consider, let alone test. Second, there is a dizzying array of vaping devices including disposables, cartridge-type units, tank filled e-cigarettes, "mods", and more. Variable voltage or current through the heating element in some devices adds another layer of complexity because constituent by-products of vape juice heated aerosolization will be affected by multiple considerations of device components and settings (Gotts, 2019; Wagner et al., 2020). Third, nicotine salt concentration selected from none to very high and addiction intensity influence biological responses as well as frequency of use by addicted individuals. Fourth, personal variation in user vaping topography including (but not limited to) volume, frequency, flow rate, and inhalation style will influence exposure (Robinson et al., 2016). Fifth, individual characteristics such as age, gender, genetics, pre-existing conditions, lifestyle (diet and exercise), and duration of vaping over lifespan will undoubtedly be factors in VAPI. This relatively brief accounting of the possibilities exemplifies why defining a 'typical' scenario for vaping in terms of exposure and user profile is impossible. Thus, researchers must carefully consider their experimental model and exposure protocol when designing a study intended to reveal the biological effects of vaping.

From the standpoint of applicability to the real world setting there is no substitute for animal model testing (Fig. 2). Mammalian models of inhalation exposure represent the closest approximation of vaping interaction with a biological system (Shao et al., 2019). The ability to use commercially available vaping juices and equipment that recapitulates the marketplace furthers relevance of animal model testing.(Cooper, Akers, & Henderson, 2021; Lefever et al., 2017) So too, exposure parameters can be selected with attention toward the type of vaping habit under investigation, whether a light social user or addicted lifestyle user (Kleinman et al., 2020; Mikheev et al., 2020). Assessment of effects using mammals provides the closest analogous view to human biology, although inhalation modeling using rodents depends upon animals that are obligate nose breathers unlike humans.(Nyunoya, March, Tesfaigzi, & Seagrave, 2011) Reductionist systems such as *in vitro* culture models do have value and relevance for narrowing variables and investigating select 'cause and effect' relationships between vaping agents and specific cell types. Researchers must always be mindful of strengths and limitations for model systems to provide trustworthy and realistic representations regarding relevance of findings for human users

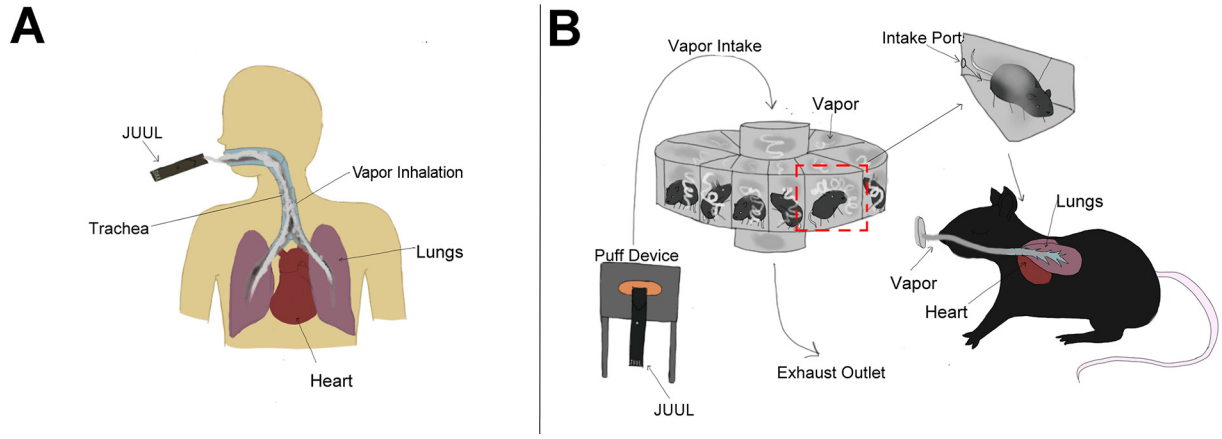

Fig. 2. Schematic representation of inhalation exposure in humans and experimental rodent model. (A). Direct to lung human exposure following inhalation from JUUL device containing vape juice. Aerosol is inhaled into airway space and lung from the device. (B) Indirect inhalation *via* chamber exposure in a rodent model using identical JUUL device. Puff topography for aerosolization into the chamber designed to mimic human vaping topography based upon published studies. (Dautzenberg & Bricard, 2015; Farsalinos et al., 2013).

(Moshensky et al., 2021). Failure to acknowledge the limits of translational applicability or offering hyperbolic conclusions diminishes credibility for vaping-related research, leaving the door open for skeptics and critics to attack the validity of findings and recommendations.

At present, there is an ongoing and essential need to identify and track pathological and functional changes in vapers from initial responses to progressive cumulative effects (Tackett et al., 2020; Xie et al., 2020). Assessing impact in the human population provides the most credible information regarding risk and recommendations (Giovanni, Keller, Bryant, Weiss, & Littman, 2020; Tzortzi, Kapetanstrataki, Evangelopoulou, & Beghrakis, 2020). Harm reduction remains a strong point for vaping advocates, but the validity of that assertion remains controversial. Only through assessments of impact upon humans will we be positioned to achieve consensus on the value of harm reduction for smokers transitioning to vaping (Lee, Gawron, & Goniewicz, 2015). Furthermore as vaping permeates the market of 'never smokers', particularly adolescents, the importance of understanding primary biological consequences of vaping for young users is obvious and essential. Unfortunately, rationalization of vaping risk, procrastination to seek help, or overt denial of vaping-associated effects can have life-threatening consequences as seen in a growing number of VAPI-associated ARDS clinical reports (Fig. 1) (Diaban, & Z.; Vaziri, J.; Plisco, M., 2020; Edmonds et al., 2020; Lilly, Khan, Waksmundzki-Silva, & Irwin, 2020; Smith et al., 2021; Sood et al., 2021). Defining how and why individuals succumb to VAPI-associated ARDS with rigorous research studies is essential for identifying risk factors, understanding disease progression, and developing effective treatments.

7.2. Future concerns

The relatively short history of modern vaping and undeniable escalation of VAPI-associated ARDS (Fig. 1) reveals the conundrum of how to deal with vaping in society and unknowable future effects upon current users. Clearly there are inherent risks to vaping, but possible benefits to society as well. While all parties should agree on never vaping for 'never smokers' is preferable, some individuals will start vaping either unaware of or indifferent to potential risks. Anti-vaping groups rightfully observe that certain aspects of vaping marketing campaigns targeting 'never smokers' is antithetical to the concept of harm reduction. Pervasive dissemination of skewed perspectives makes ferreting out reliable and trustworthy information challenging, thus discouraging important dialog and leaving vapers or those considering vaping desensitized to important information. Rigorous, relevant, and conservatively reported research in the laboratory, the clinic, and in population-based analyses is the antidote for our current stalemate by providing desperately needed answers.

Walking back from devolving tissue structure and function under advanced end-stage ARDS pathology, progressive alterations prompted by vaping could take years or decades to manifest in humans as VAPI. Initial subtle alterations indicative of early pathological deterioration would be valuable for understanding the progression of vaping injury, even for those who do not progress along into ARDS. Early warning signs of vaping-induced injury would be important to inform users of increased risk, even if asymptomatic. Also, the robust reparative capabilities of respiratory system are much more likely to fully recover from modest damage and minimize deleterious impact. Again, experimental animal models designed to assess VAPI with longitudinal analyses to investigate the temporal progression of injury from initial exposure until overt pathogenesis will be extremely valuable in this regard. Findings could then be applied toward development of testing on molecular levels, perhaps using readily obtainable bronchial lavage samples to detect initial alterations of epithelial or immune cell populations.

Taking a cue from aging studies (Angelidis et al., 2019; Burgstaller et al., 2017), the risk of damage and functional impairment from VAPI likely increases with age and decreased reparative capacity (Priemer, Gravenmier, Batouli, & Hooper, 2020). For older individuals choosing 'the lesser of two evils' by switching from smoking to vaping for harm reduction, aging-related loss of regenerative potential is a moot point compared to the damage caused by tobacco. In contrast, a substantial proportion of 'never smokers' start vaping at a relatively youthful age when lung reparative capacity is robust. As this population of early adopters ages into middle life the potential for VAPI likely increases with continued inhalation exposure. Tracking these individuals and, as always, encouraging cessation as soon as possible will play an increasingly important role in preventing respiratory and/or pulmonary complications later in life. Another area worthy of circumspection is the relationship between aging and cancer (Campisi, 2005; Hornsby, 2007), noting that individuals predisposed to oncogenic transformation develop cancer early in life, whereas those resistant to oncogenesis may have heightened early onset for degenerative diseases. In the context of lung biology, vapers with greater regenerative capacity may avoid degenerative conditions such as ARDS with the tradeoff of heightened cancer risk. Conversely, individuals resistant to oncogenic transformation from DNA damage and oxidative stress pursuant to vaping may eschew cancer but undergo deterioration leading to progressive VAPI that devolves into ARDS in advanced cases. At this point not enough time has passed to allow for an evaluation of the relationship between aging, VAPI, and cancer, but speculation on adverse consequences for present

day vapers as they grow older is justified given what is known from gerontology and oncology research (Tang et al., 2019).

In conclusion, the situation with respect to vaping and VAPI are captured by the quote: "Live in the present. The past is gone; the future is unknown – but the present is real, and your opportunities are now" (Maxwell Maltz). The proverbial 'genie is out of the bottle' as far as vaping is concerned, so the best we can do is strive for greater understanding and enlightened discussion made possible by careful research. Society needs to capitalize upon this moment by investigating the biological impact of vaping and pathogenesis of VAPI in anticipation of and preparation for consequences destined to emerge in the decades ahead.

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Declaration of Competing Interest

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