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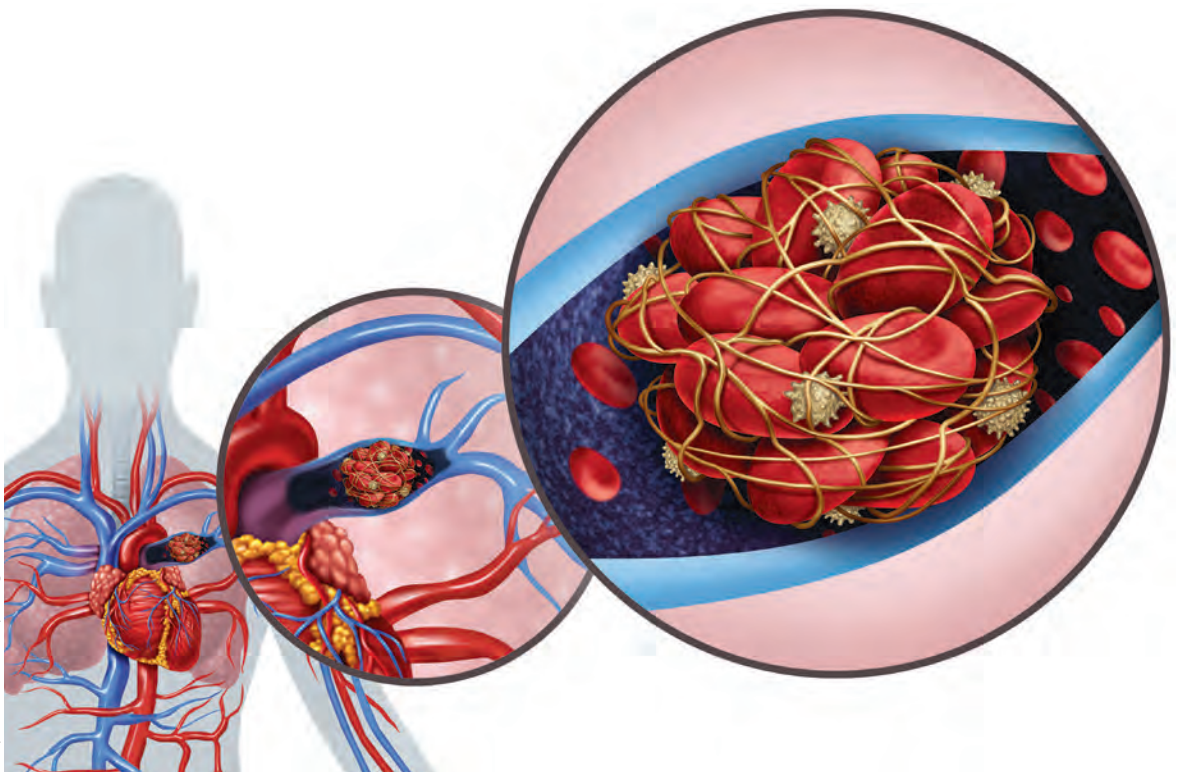

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‘Door-to-thrombectomy’ time linked to better acute PE outcomes

BY NEIL OSTERWEIL

FROM CHEST 2024 ▪ BOSTON — The sooner that patients with acute pulmonary embolism (PE) get treated with mechanical thrombectomy, the greater the likelihood that they will have favorable short- and long-term outcomes, regardless of their degree of initial risk, a study of registry data showed.

Among nearly 800 patients with acute PE whose data are recorded in the FlowTriever All-Comer Registry for Patient Safety and Hemodynamics (FLASH), a prospective multicenter registry of individuals treated with mechanical thrombectomy using the FlowTriever system (Inari Medical), shorter time from admission to mechanical thrombectomy was associated with significantly greater reductions in intraprocedural mean and systolic pulmonary artery pressures (PAP), greater reductions in the right ventricular/left ventricular (RV/LV) ratio, and longer 6-minute walk times at 6 months, reported Krunal H. Patel, MD, a pulmonary and critical care fellow at the Lewis Katz School of Medicine at Temple University Hospital in Philadelphia.

“Mechanical thrombectomy in the FLASH registry showed a mortality benefit. I think as time progresses and mechanical thrombectomy becomes more popular, we’re just going to need to figure out what is the ideal time for

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Use of SGLT2 inhibitors associated with better survival in PAH

BY JIM KLING

FROM CHEST 2024 ▪ BOSTON — The use of sodium-glucose cotransporter-2 (SGLT2) inhibitors is associated with reduced short- and long-term mortality among patients with pulmonary arterial hypertension (PAH), according to results from a new propensity score–matched analysis.

“There are a lot of new studies that show benefits [of SGLT2 inhibitors] in heart failure, in [chronic kidney disease], and of course, in diabetes. Group one pulmonary hypertension includes not only the inflammatory cascades but also fibrotic and neurovascularization, and all these different parts of the pathophysiology are linked to each other,” said Irakli Lemonjava, MD, who presented the study at the CHEST Annual Meeting.

“There are studies that show that SGLT2 inhibitors can have an impact on inflammatory cascades, fibrosis, and vascular remodeling in general. Together, all this data triggered this idea for me, and that’s when I decided to conduct further studies.”

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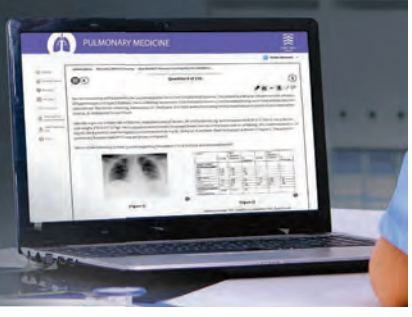

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intervention," he said during an oral abstract session at the CHEST Annual Meeting.

"There's mortality benefit in any case whether the patient is high risk or intermediate-high. This is a thought-provoking retrospective analysis that says that early intervention is probably better than doing it late, but regardless, the FLASH registry trial showed that early thrombectomy or thrombectomy in general shows positive mortality benefit," Dr. Patel said.

He likened the challenge for pulmonary and critical care specialists to that of interventional cardiologists, who have determined that the ideal window for starting percutaneous coronary interventions is within 90 minutes of the patient's arrival at the facility.

"I think we have to get our 'door-to-balloon' time for PE care," he said.

Study details

Dr. Patel and colleague Parth M. Rali, MD, FCCP, associate professor of thoracic medicine at Temple, conducted a retrospective review of data on 787 US patients in the FLASH registry for whom time to mechanical thrombectomy data were available.

They stratified the patients into short and long time to mechanical thrombectomy groups, with "short" defined as ≤ 12 hours of presentation and "long" as > 12 hours.

They found that the median time to thrombectomy was 19.68 hours. In all, 242 patients (31%) were treated within the short window, and the remaining 545 patients (69%) were treated after at least 12 hours had passed.

Comparing clinical characteristics between the groups, the investigators noted that significantly more patients in the short time group vs long time group were categorized as high risk (11.2% vs 6.2%; $P = .0026$). This difference is likely due to the need for greater urgency among high-risk patients, Dr. Patel said.

Patients in the short time group also had significantly higher baseline RV/LV ratios and lactate levels, but baseline dyspnea scores and pre-procedure median and systolic PAP were similar between the groups.

The mean time to thrombectomy was 6.08 hours in the short time group vs 34.04 hours in the long time group. Their respective median times were 6.01 and 24.73 hours.

The procedural time was similar between the groups, at 45 and 42 minutes, respectively.

The location of the treated thrombus was central only in 35.1% and 26.5% patients in the short and long time groups, respectively.

Lobar-only thrombi were treated in 7.9% and 14.3%, respectively, and both central and lobar thrombi were treated in 57.0% and 59.2%, respectively.

Both 48-hour and 30-day all-cause mortality rates were similar between the groups (0.4%/0.2% and 0.5%/1.0%).

Patients in the short time group had slightly but significantly longer post-procedure hospital and intensive care unit stays, but 30-day readmission rates — whether for PE- or non-PE–related causes — were similar.

Where the differences between the groups really showed, however, were PAP reductions over baseline, with decline in median pressures of -8.7 mm Hg in the short group vs -7.2 mm Hg in the long group ($P = .0008$), and drops in systolic PAP of -14.4 vs -12.1 mm Hg, respectively ($P = .0011$).

In addition, reductions in RV/LV ratios from baseline were also significantly greater among patients whose thrombectomies had been expedited at the 48-hour, 30-day, and 6-month follow-up periods.

At 6 months, patients who had received mechanical thrombectomy within 12 hours also had significantly longer 6-minute walk distances (442.2 vs 390.5 m; $P = .0032$).

Low thrombolysis rate

Following his presentation, session co-moderator Galina Glazman-Kuczaj, MD, from the Division of Pulmonary and Critical Care Medicine at Albany Med Health System, Albany, New York, asked Dr. Patel what percentage of patients, if any, had received thrombolytic therapy before the thrombectomy procedure.

He noted that only 1% or 2% of patients in the FLASH registry received thrombolysis. Dr. Glazman-Kuczaj said that "it was reassuring for [Dr. Patel] to report that it was only a small population of patients who got thrombolysis beforehand in either group because you would expect that maybe people in the group that took longer to have a thrombectomy got some thrombolysis beforehand and that perhaps they were more stable, but it seems like thrombectomy was the first-line treatment in both groups."

The FLASH Registry is funded by Inari Medical. Drs. Patel and Glazman-Kuczaj reported no relevant financial relationships. ■

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Higher mortality trend in patients with CF and CVD

BY NEIL OSTERWEIL

FROM CHEST 2024 ▪ BOSTON — With the remarkable advances made in therapy over the past decade, many patients with cystic fibrosis (CF) can expect to survive into their 50s and even well beyond. But as patients with CF live longer, they are increasingly likely to develop complications such as cardiovascular diseases (CVDs) that beset many older adults. And as evidence from a new study suggests, there is an increasing need for cardiovascular screening and specialized cardiac care for these patients.

Among more than 83,000 patients with CF hospitalized for any reason from 2016 through 2021, less than 1% of patients had a cardiac cause listed, but in unadjusted analyses, these patients had a more than two-fold risk for in-hospital death than those with CF hospitalized for other causes, reported Adnan Bhat, MD, assistant professor of hospital medicine at the University of Florida, Gainesville.

Although the excess mortality was no longer statistically significant in analyses adjusted for potential confounding factors, the data highlight a trend that requires further exploration, he said during an oral abstract session at the CHEST Annual Meeting.

"There's a trend for people with cystic fibrosis admitted for cardiac causes to have a higher in-hospital mortality and increased rate of discharge to nursing facilities, especially for patients admitted for heart failure. The clinical implication is that there is an increased need to start screening for cardiovascular risk factors," he said.

National database sample

Dr. Bhat and colleagues conducted a retrospective study using the National Inpatient Sample database to identify all hospitalizations among patients with CF in the United States from 2016 through 2021.

They included all hospitalizations with a principal diagnosis code for atrial fibrillation, heart failure, or myocardial infarction.

Of 83,250 total hospitalizations during the study period, 415 (0.5%) were for primary cardiac causes. These included 170 hospitalizations for atrial fibrillation, 95 for heart failure, and 150 for myocardial infarction.

Patients hospitalized for cardiac causes had a higher mean age (59.5 vs 34.5 years) and more comorbidities than patients hospitalized for other causes. These comorbidities included hyperlipidemia, chronic kidney disease, obesity, and a family history of coronary artery disease.

In all, 5% of patients hospitalized for a cardiac cause died in hospital, compared with 2% of patients hospitalized for other reasons ($P = .044$).

"It's really an interesting area of research, and there's hope that this will bring more focus on how to better screen [for CVD risk]."
– Dr. Gao

However, in logistic regression analyses adjusting for age, sex, and race, this difference was no longer significant.

Similarly, an unadjusted analysis showed that patients with cardiac disease were twice as likely to be discharged to a nursing facility (8% vs 4%, respectively), but this difference too disappeared in adjusted analyses.

The risk for in-hospital mortality appeared to be highest among those patients with a primary diagnosis of heart failure, who had an 11% rate of in-hospital death, compared with 2% among patients with CF hospitalized for other causes.

The total number of deaths was too small, however, to allow for regression analysis, Dr. Bhat said.

Nonetheless, taken together, the data indicate a trend toward increased mortality from cardiovascular causes among older patients with CF, as well as the need for further research into the cardiovascular health of these patients, Dr. Bhat concluded.

Better nutrition, higher risk

In an interview, Yuqing A. Gao, MD, from the Santa Monica Pulmonary Sleep Clinic in California, who was not involved in the study, commented that with the advent of elexacaftor/tezacaftor/ivacaftor modulator therapy, patients with CF tend to have increases in body mass index and improved nutritional intake and absorption, which in turn could increase hyperlipidemia and other factors that might in turn contribute to increased CVD risk.

"It's really an interesting area of research, and there's hope that this will bring more focus on how to better screen [for CVD risk] because that's something that's very much not known at this time," she said.

Dr. Gao was co-moderator for the session where Dr. Bhat presented the data. Dr. Bhat did not report a study funding source. Drs. Bhat and Gao reported no relevant financial relationships. ■

SGLT2

// continued from page 1

The researchers drew data on 125,634 adult patients from the TriNetX database who were diagnosed with PAH after January 1, 2013.

They used propensity score matching to account for demographic characteristics and 10 organ system disorders to compare patients with exposure to SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin; n = 6238) with those without such exposure (n = 6243).

At 1 year, 8.1% of patients taking SGLT2 inhibitors had died, compared with 15.5% of patients not taking SGLT2 inhibitors (risk reduction [RR], 0.52; $P < .0001$).

The values were 13% and 22.5% (RR, 0.579; P < .0001) at 3 years and 14.6% and 25% at 5 years (RR, 0.583; $P < .0001$).

The study generated discussion during the Q&A period following the talk. One audience member asked if the group was able to access patients both inside and outside the US. "Because I wonder if access to [SGLT2] inhibitors is actually a surrogate marker for access to other medications," the attendee asked.

"The majority of the patients with pulmonary hypertension are much older and they have comorbidities, including cardiovascular risk factors..."
– Dr. Quadery

Although the finding is intriguing, it shouldn't change clinical practice, according to Dr. Lemonjava, a resident physician at Jefferson Einstein Philadelphia Hospital, Philadelphia. "I don't think we can make any changes based on what I shared today. Our purpose was to trigger the question. I think the numbers are so impressive that it will trigger more studies. I think if in the future it's demonstrated by clinical trials that [SGLT2 inhibitors are beneficial], it will not be a problem to prescribe for someone with pulmonary arterial hypertension because they do not have many side effects," he said.

Session co-moderator Syed Rehan Quadery, MD, praised the study but emphasized the remaining uncertainty.

"It's an excellent proof of concept study. More trials need to [be done] on it, and we don't understand the mechanism of action in which it improves survival in patients with pulmonary artery hypertension," said Dr. Quadery, a consultant respiratory physician at National Pulmonary Hypertension Unit, Dublin, Ireland.

"The majority of the patients with pulmonary hypertension are much older and they have comorbidities, including cardiovascular risk factors, and maybe that is one of the ways in which this drug helps. Plus, there are multiple mechanisms in which it may be working, including anti-inflammatory as well as antiproliferative mechanisms through inhibiting the Notch-3 signaling pathway."

Dr. Quadery and his co-moderator, Zeenat Safdar, MD, both noted that SGLT2 inhibitors have already been demonstrated to improve outcomes in heart failure. "[SGLT2 inhibition] improves survival, it decreases hospitalization, it improves morbidity and mortality.

There are a lot of things that can be shown in different [animal or in vitro] models. In humans, we actually don't know exactly how it works, but we know that it does. If it works in left heart failure, it also [could] work in right heart failure," said Dr. Safdar, who is the director of the Houston Methodist Lung Center, Houston Methodist Hospital, Houston.

The study was independently supported. Drs. Lemonjava, Quadery, and Safdar reported no relevant financial relationships. ■

AIR QUALITY

Is wildfire smoke more toxic than general air pollution?

BY MANUELA CALLARI

Wildfire-related air pollution in Europe kills more than non-wildfire air pollution. As climate change exacerbates the frequency and violence of wildfires, researchers are studying the health implications of mitigation methods such as prescribed fires.

Presenting at the annual congress of the European Respiratory Society, Cathryn Tonne, PhD, an environmental epidemiologist at the Instituto de Salud Global de Barcelona, Spain, said wildfire-related particulate matter sized 2.5 micrometers of less ($PM_{2.5}$) is more toxic than general $PM_{2.5}$, leading to significantly higher mortality rates.

Prescribed, controlled fires have been employed worldwide to reduce the chance of uncontrolled, catastrophic fires. However, researchers wonder whether the techniques reduce the overall fire-related $PM_{2.5}$ or add to it. "Prescribed fire increases ecosystem resilience and can reduce the risk of catastrophic wildfire," said Jason Sacks, MPH, an epidemiologist in the Center for Public Health and Environmental Assessment in the Office of Research and Development at the Environmental Protection Agency, at the congress. "But it also leads to poorer air quality and health impacts, and we still don't know what this means at a regional scale."

Wildfire pollution kills more than other air pollution

Researchers at the Instituto de Salud Global de Barcelona used a large dataset of daily mortality data from 32 European countries collected through the EARLY-ADAPT project. They utilized the SILAM model to derive daily average concentrations of wildfire-related $PM_{2.5}$, non-fire $PM_{2.5}$, and total $PM_{2.5}$ levels. They also employed GEOSTAT population grids at a 1-km resolution to calculate the attributable number of deaths across different regions, specifically focusing on data from 2006, 2011, and 2018.

The data analysis indicated that the relative risk per unit of $PM_{2.5}$ is substantially larger for wildfire-related $PM_{2.5}$, compared with non-fire $PM_{2.5}$. "We essentially assume that wildfire smoke $PM_{2.5}$ has the same toxicity as total $PM_{2.5}$, but it's increasingly clear that's likely not the case," Dr. Tonne said, presenting the study.

When employing exposure-response functions (ERFs) specific to wildfire smoke, researchers found that the attributable deaths from all causes of wildfire $PM_{2.5}$ were approximately 10 times larger than those calculated using total $PM_{2.5}$ exposure estimates. Dr. Tonne explained that this stark difference highlights the critical need for tailored ERFs that accurately reflect the unique health risks posed by wildfire smoke.

"Respiratory mortality usually has the strongest relative risks, and we're seeing that in this study as well," Dr. Tonne said. "Wildfire smoke seems to operate through quite immediate mechanisms, likely through inflammation and oxidative stress."

One significant challenge of the study was the lack of uniform spatial resolution across all countries involved in the analysis. This inconsistency may affect how accurately mortality estimates can be attributed to specific $PM_{2.5}$ sources. Additionally, the study had limited statistical power for generating age- and sex-specific mortality estimates, which could obscure important demographic differences in vulnerability to wildfire smoke exposure. The analysis was also constrained to data available only up to 2020, thereby excluding critical wildfire events from subsequent years, such as those in 2022 and 2023, which may have further elucidated the health impacts of wildfire smoke in Europe.

Fires prescription

Prescribed fires or controlled burns are intentional fires set by land managers under carefully managed conditions.

Historically, many forested areas have been subjected to fire suppression practices, which allow combustible materials like dry leaves, twigs, and shrubs to accumulate over time. This buildup leads to a higher likelihood of severe, uncontrollable wildfires. Prescribed fires can reduce these fuel loads and improve the health and resilience of ecosystems.

They release fewer pollutants and emissions than the large-scale, unmanageable wildfires they help prevent because they happen at lower temperatures. But they still

WILDFIRE *continued on following page*

High levels of indoor pollutants promote wheezing in preschoolers

BY HEIDI SPLETE

Higher concentrations of specific volatile organic compounds (VOCs) in daycare centers were significantly associated with an increased risk for wheezing in children who attended these centers, based on data from more than 500 children.

"There is an increasing concern about of the role of Indoor Air Quality (IAQ) in development of respiratory disorders like asthma, especially in children whose immune system is under development, and they are more vulnerable to the effects of poor air quality," said lead author Ioannis Sakellaris, PhD, of Université Paris-Saclay, Villejuif, France. However, the effects of specific pollutants on the health of young children in daycare settings has not been examined, he said.

In a presentation at the annual congress of the European Respiratory Society, Dr. Sakellaris reviewed data from the French CRESPI cohort study, an epidemiological study of the impact of exposures to disinfectants and cleaning products on workers and children in daycare centers in France.

The study population included 532 children (47.4% girls) with a mean age of 22.3 months (aged 3 months to 4 years) in 106 daycare centers. A total of 171 children reportedly experienced at least one episode of wheezing since birth. A total of 67 VOCs were measured during one day, and concentrations were studied in four categories based on quartiles. The researchers used parental questionnaires to evaluate three outcomes, which included wheezing since birth, recurrent wheezing (≥ 3 times since birth), and wheezing with inhaled corticosteroid use. The researchers adjusted for factors including child age and parental smoking status and education level.

Overall, ever wheezing was significantly associated with higher concentrations of 1,2,4-trimethylbenzene (odds ratio [OR] for Q4 vs Q1, 1.56; $P = .08$ for trend), 1-methoxy-2-propylacetate (OR, 1.62; $P = .01$), decamethylcyclopentasiloxane (OR, 2.12; $P = .004$), and methylisobutylcetone (OR, 1.85; $P < .001$).

The results emphasize the significant role of IAQ in respiratory health, Dr. Sakellaris said. "Further efforts to reduce pollutant concentrations and limit sources are needed," he said. In addition, more studies on the combined effect of multiple VOCs are necessary for a deeper understanding of the complex relations between IAQ and children's respiratory health, he said.

Pay attention to indoor pollutants

"Since the COVID-19 pandemic, the use of cleaning products and disinfectants has exploded," Alexander S. Rabin, MD, of the University of Michigan, Ann Arbor, said in an interview. Although many of these cleaning agents contain chemicals, including VOCs, that are known respiratory irritants, little is known about the relationship between VOCs and children's respiratory outcomes in daycare settings, said Dr. Rabin, who was not involved in the study.

"I was struck by the wide array of VOCs detected in daycare settings," Dr. Rabin said. However, the relationship to childhood wheeze was not entirely surprising as the VOCs included the known irritants benzene and toluene, he added. The results suggest that exposure to VOCs, in not only cleaning agents but also building materials and other consumer products in daycare settings, may be associated with an increased risk for wheeze in children, Dr. Rabin said. However, "it is important to know more about confounding variables, including concurrent rates of respiratory infection that are common among children," Dr. Rabin said. "As the authors highlight, further work on the compound effects of multiple pollutants would be of interest. Lastly, it would be helpful to clearly identify the most common sources of VOCs that place children at greatest risk for wheeze, so that appropriate steps can be taken to mitigate risk," he said.

The original CRESPI cohort study was supported by ANSES, ADEME, Fondation de France, and ARS Ile-de-France. Drs. Sakellaris and Rabin had no financial conflicts to disclose. ■

WILDFIRE *continued from previous page*

introduce pollutants in the air that can negatively affect nearby communities' health.

People with preexisting respiratory conditions, such as asthma or COPD, are particularly vulnerable to smoke, which can trigger health issues like breathing difficulties, coughing, and eye irritation.

The cumulative impact of increased burns raises concerns about long-term air quality, especially in densely populated areas. "We need to understand if we're actually tipping the scale to having less wildfire smoke or just increasing the total amount of smoke," Mr. Sacks said.

Mitigation strategies include accurately picking the right timing and weather conditions to determine when and where to conduct controlled burns and effective and timely communication to inform local communities about upcoming burns, the potential for smoke exposure, and how to protect themselves.

There is a growing need to improve public messaging around prescribed fires, Mr. Sacks said, because often the message communicated is oversimplified, such as "there will be smoke, but don't worry. But that's not the message we want to convey, especially for people with asthma or COPD."

GILITUKHA/THINKSTOCK

Instead, he said public health agencies should provide clearer, science-based guidance on the risks for smoke exposure and practical steps people can take to reduce their risk.

What can doctors do?

Chris Carlsten, MD, director of the Centre for Lung Health and professor and head of the Respiratory Medicine Division at the University of British Columbia, Vancouver, Canada, told this news organization that determining whether an exacerbation of a respiratory condition is caused by fire exposure or other factors, such as viral infections, is complex because both can trigger similar responses and may complement each other.

"It's very difficult for any individual to know whether, when they're having an exacerbation of asthma or COPD, that's due to the fire," he said. Fire smoke also increases infection risks, further complicating diagnosis.

Dr. Carlsten suggested that physicians could recommend preventative use of inhalers for at-risk patients when wildfires occur rather than waiting for symptoms to worsen. "That is a really interesting idea that could be practical." Still, he advised caution, stressing that patients should consult their providers because not all may react well to increased inhaler use.

He also highlighted a significant shift in the health care landscape, noting that traditionally, the focus has been on the cardiovascular impacts of pollution, particularly traffic-related pollution. However, as wildfire smoke becomes a growing issue, the focus is shifting back to respiratory problems, with profound implications for health care resources, budgets, and drug approvals based on the burden of respiratory disease.

"Fire smoke is becoming more of a problem," Dr. Carlsten said. "This swing back to respiratory has huge implications for healthcare systems and respiratory disease burden."

Mr. Sacks and Dr. Carlsten reported no relevant financial relationships. The study presented by Dr. Tonne received funding from the European Union's Horizon Europe research and innovation programme under Grant Agreement No. 101057131. ■

AI outperforms trainees in lung disease diagnosis

BY MANUELA CALLARI

Artificial intelligence (AI) can assist doctors in assessing and diagnosing respiratory illnesses in infants and children, according to two new studies presented at the annual congress of the European Respiratory Society. Researchers can train artificial neural networks (ANNs) to detect lung disease in premature babies by analyzing their breathing patterns while they sleep. "Our noninvasive test is less distressing for the baby and their parents, meaning they can access treatment more quickly, and may also be relevant for their long-term prognosis," said Edgar Delgado-Eckert, PhD, adjunct professor in the Department of Biomedical Engineering at the University of Basel, Switzerland, and a research group leader at the University Children's Hospital, Basel.

Manjith Narayanan, MD, a consultant in pediatric pulmonology at the Royal Hospital for Children and Young People, Edinburgh, Scotland, and honorary senior clinical lecturer at the University of Edinburgh, said chatbots such as ChatGPT, Bard, and Bing can perform as well as or better than trainee doctors when assessing children with respiratory issues. He said chatbots could triage patients more quickly and ease pressure on health services.

Researchers at the University of Edinburgh provided 10 trainee doctors with less than 4 months of clinical experience in pediatrics with clinical scenarios that covered cystic fibrosis, asthma, sleep-disordered breathing, breathlessness, chest infections, or no obvious diagnosis. The trainee doctors had 1 hour to use the internet, although they were not allowed to use chatbots to solve each scenario with a descriptive answer. Each scenario was also presented to the three large language models (LLMs): OpenAI's ChatGPT, Google's Bard, and Microsoft's Bing. Six pediatric respiratory experts assessed all responses, scoring correctness, comprehensiveness, usefulness, plausibility, and coherence on a scale of 0-9. They were also asked to say whether they thought a human or a chatbot generated each response.

ChatGPT scored an average of 7 out of 9 overall and was believed to be more human-like than responses from the other chatbots. Bard scored an average of 6 out of 9 and was more "coherent" than trainee doctors but similar in other respects. Bing and trainee doctors scored an average of 4 out of 9. The six pediatricians reliably identified Bing and Bard's responses as nonhuman.

"Our study is the first to test LLMs against trainee doctors in situations that reflect real-life clinical practice," Dr. Narayanan said. "We did this by allowing the trainee doctors to have full access to resources available on the internet, as they would in real life. This moves the focus away from testing memory, where LLMs have a clear advantage."

The researchers found no obvious hallucinations — seemingly made-up information — with any of

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the three LLMs. Still, Dr. Narayanan said, "We need to be aware of this possibility and build mitigations."

Identifying bronchopulmonary dysplasia (BPD) in premature babies remains a challenge. Lung function tests usually require blowing out on request, which is a task babies cannot perform. Current techniques require sophisticated equipment to measure an infant's lung ventilation characteristics, so doctors usually diagnose BPD by the presence of its leading causes, prematurity and the need for respiratory support.

Researchers at the University of Basel trained an ANN model to predict BPD in premature babies. The team studied 139 full-term and 190 premature infants who had been assessed for BPD, recording their breathing for 10 minutes during sleep. For each baby, 100 consecutive regular breaths, excluding sighs or other artefacts, were used to train, validate, and test an ANN called a Long Short-Term Memory model (LSTM). Researchers used 60% of the data to teach the network to recognize BPD, 20% to validate the model, and 20% to see if it could correctly identify BPD. The LSTM model classified flow values as BPD with 96% accuracy.

The study presented by Dr. Delgado-Eckert received funding from the Swiss National Science Foundation. Dr. Narayanan reported no relevant financial relationships. ■

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Modified sleep apnea index score linked to CV risk

BY HEIDI SPLETE

Use of a modified sleep apnea index can identify cardiovascular (CV) risk factors in adults with moderate to severe OSA, according to results from a study presented at the American Academy of Otolaryngology–Head and Neck Surgery 2024 Annual Meeting.

The modified sleep apnea severity index (mSASI) combines patient anatomy, weight, sleep study metrics, and symptoms, to provide a more nuanced measure of OSA than the standard apnea-hypopnea index (AHI), said Jennifer A. Goldfarb, MHS, a medical student at Thomas Jefferson University, Philadelphia, who presented the findings.

OSA has an association with many negative CV comorbidities. However, "the AHI provides only a single metric and does not provide a

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holistic assessment of the individual patient's disease severity," said senior author Colin T. Huntley, MD, also of Thomas Jefferson University.

Previous research has shown a correlation between mSASI and mean arterial pressure and serum C-reactive protein in OSA patients, but the connection with CV risk factors has not been well studied, Ms. Goldfarb noted.

In the retrospective cohort study, Ms. Goldfarb and colleagues looked at mSASI scores from 260 CPAP–intolerant patients with OSA who underwent upper airway stimulation, maxillomandibular advancement, or expansion sphincter pharyngoplasty at a single sleep surgery clinic between 2014 and 2021. The mSASI uses a score of 1-3, with 3 as the highest level of OSA severity.

CV risk factors were assessed at the patient's initial evaluation by the sleep surgery team. They included coronary artery disease, type 2 diabetes, atrial fibrillation, congestive heart failure, hypertension, and cerebrovascular accident.

A total of 142 patients (55%) had an mSASI of 1; 91 (35%) had an mSASI of 2; and 27 (10%) had an mSASI of 3. At least one CV risk factor was present in 58%, 68%, and 63% of these groups, respectively ($P = .3$).

Stratifying participants by mSASI scores, the researchers found that patients with an mSASI of 2 or 3 were significantly more likely than those with an mSASI of 1 to have more CV risk factors on initial presentation, and were significantly more likely to be diagnosed with hypertension ($P = .02$ for both.

With the AHI, however, patients with moderate to severe OSA (AHI > 15) had a similar number of CV risk factors as those with mild OSA ($P > .05$).

"A higher mSASI score, which represents worse disease, was associated with a higher Framingham risk score, which supported our hypothesis; however, the AHI was not found to be associated with an increased Framingham score," Dr. Huntley said.

These results suggest that the AHI, while a good metric, might not be the best tool for assessment of overall disease severity, given the complexity of OSA, the impact of the disease on patient quality of life, and the risk for downstream CV disease, Dr. Huntley said.

The findings were limited by the single center and retrospective design. Population-level data are needed to identify variables to create a future tool that provides the best picture of the individual patient's disease, he added. Prospective data are also needed to assess the impact of the scoring system on treatment outcomes.

"The current study is interesting as we are just beginning to understand the factors that predict cardiovascular risk for patients with OSA," said Megan Durr, MD, of the University of California, San Francisco.

"We primarily looked at the AHI and/or oxygen levels during sleep as risk factors, and we haven't looked as much at other factors," said Dr. Durr, who served as a session moderator.

The inclusion of patient anatomy and symptoms add to the knowledge of this topic, she added.

The study received no outside funding and researchers had no financial conflicts to disclose. Dr. Huntley disclosed receiving research support from Nyxoah and Inspire, and serving as a consultant for Nyxoah, Inspire, and Avivomed.

Dr. Durr had no financial conflicts to disclose.

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Exciting opportunities for tobacco treatment

Unpacking the CMS changes

BY MATTHEW BARS, MS, CTTS, CPAHA-TOBACCO TREATMENT, AND EVAN STEPP, MD, FCCP FOR THE CHEST TOBACCO/ VAPING WORK GROUP

Mr. Bars

Dr. Stepp

The recent changes enacted by the Centers for Medicare & Medicaid Services (CMS) are creating unprecedented opportunities for pulmonologists and medical centers to help treat people with tobacco use disorder. Specifically, these changes embed the integration of tobacco and nicotine addiction treatment more deeply into our nation's health care system. As we face a critical moment in the fight against tobacco-related morbidity and mortality, it is essential that we leverage these changes. In doing so, CHEST aims to serve as an active bridge, informing health care providers of this unique federal opportunity that benefits both patients and clinicians.

A quick primer on "incident to" services

These CMS changes create an important shift in how "incident to" services can be billed. These are any services that are incident to (occur because of) a provider evaluation. These previously required direct supervision of the provider (in the same building) to be billed at the provider rate. Now "general supervision" suffices, which means the physician can be available by phone/ video call. These services can then often be billed at a higher rate. In the case of treating dependence on tobacco products, any tobacco treatment specialist (TTS) employed by a practice who cares for the patient subsequent to the initial encounter can now be reimbursed in an increased manner. Better reimbursement for this vital service will ideally lead to better utilization of these resources and better public health.

The Medicare solution is here

With the CMS rule changes in 2023 and their reaffirmation in 2024, the structure has been put in place to allow physicians, medical centers, and TTSs to create contractual relationships that can significantly improve patient care. TTSs are health care professionals from a wide variety of disciplines who have received specialized training in tobacco and nicotine addiction and treatment strategies. By expanding billing and, thus, service opportunities, these CMS modifications empower health care providers to leverage the existing fee-for-service model, translating to better care and sustainable revenue streams.

Key changes in the CMS 2023 rule

One of the most notable changes involves the supervision requirements for auxiliary personnel, which now permit general supervision.

TOBACCO *continued on following page*

Top reads from the *CHEST* journal portfolio

Dive into the healthy adherer effect in OSA, ICU stays for asthma, and COPD exacerbations related to medication use frequency

Journal *CHEST*®

Association Between Healthy Behaviors and Health Care Resource Use With Subsequent Positive Airway Pressure Therapy Adherence in OSA

By Claire Launois, MD, PhD, and colleagues

It has long been a critique of studies that evaluate the impact of positive airway pressure (PAP) adherence on positive health outcomes that patients who are more adherent to PAP may also be more adherent to other health behaviors that contribute to those positive outcomes, such as incident cardiac events in patients with OSA. This study further contributes to that idea. This healthy adherer effect may lead to an overestimation of the treatment impact of PAP. An association was found between multiple proxies of the healthy adherer effect and later PAP adherence in patients with OSA, the highest being related to proxies of cardiovascular health. A preceding reduction in health care costs was also found in these patients. These findings may help contribute to interpretation and validation of new studies to help us better understand the impact of PAP treatment of OSA.

Dr. Naik

– Commentary by Sreelatha Naik, MD, FCCP, Member of the *CHEST Physician* Editorial Board

CHEST® Critical Care

Variation in Triage to Pediatric vs Adult ICUs Among Adolescents and Young Adults With Asthma Exacerbations

By Burton H. Shen, MD, and colleagues

Asthma is a common reason for hospital admission. Between 5% and 35% of patients who are admitted due to asthma are also admitted to the ICU during their hospital stay. For adolescents and young adults, there is variability in admission to the PICU vs adult ICU. This study specifically evaluated patients aged 12 to 26 years old and included hospitals with both a PICU and an adult ICU. The results show us that age, rather than specific clinical characteristics, is the strongest predictor for PICU admission. Patients aged 18 years and younger were more likely to be admitted to the PICU. This is an important consideration, as hospital bedspace is often more limited during viral season in pediatric hospitals and PICUs. This information is also important for outpatient asthma providers to consider as they counsel their patients and provide long-term management before and after these hospital stays.

Dr. Ulrich

– Commentary by Lisa Ulrich, MD, Member of the *CHEST Physician* Editorial Board

CHEST® Pulmonary

Short-Acting Beta-Agonists, Antibiotics, Oral Corticosteroids, and the Associated Burden of COPD

By Mohit Bhutani, MD, FCCP, and colleagues

Dr. Anjum

This study notably highlights the fact that high frequency use of short-acting beta-agonists, antibiotics, and oral corticosteroids may not directly raise the likelihood of an exacerbation but rather may be a sign of worsening disease or poorly managed COPD.

Future studies should investigate the factors that contribute to patients' frequent prescription use, such as understanding the underlying causes of their exacerbations and other pertinent factors. Additionally, details about patient adherence, a complete clinical history, and the treatment of any further chronic disorders are pivotal for a more complete picture. Enhanced methods for recognizing mild/moderate and severe exacerbations, including patient-reported outcomes, in order to have a better understanding of the influence on drug use and outcomes will be extremely helpful as well. To understand how medications impact results, further studies should look for causal links between medication use and exacerbations.

– Commentary by Humayun Anjum, MD, FCCP, Member of the *CHEST Physician* Editorial Board

TOBACCO *continued from previous page*

Specifically, physicians are not required to be physically present during clinical encounters but can supervise TTSs virtually through real-time audio/video technology. This is a vital shift that enhances flexibility in patient care and expands the capabilities of health care teams.

According to 42 CFR § 410.26, TTSs qualify as auxiliary health care providers, meaning that they can operate under the supervision of a physician or other designated providers. This revised framework gives practices maximum autonomy in their staffing models and enhances their ability to offer comprehensive care. For example, TTSs can function as patient navigators, ensuring patients using tobacco receive medically appropriate early lung cancer screening and other related medical services.

Expanding access to behavioral health services

The changes aim not only to increase the efficiency of health care delivery but also to reflect a commitment to expanding access to vital behavioral health services. Key takeaways from a summary of the CMS 2023 rule include:

- The goal of these changes is to enhance access to behavioral health services across the board.
- The change in supervision requirements applies to auxiliary personnel offering behavioral health services incident to a physician's services.
- Both patients and physicians will benefit from an expanded clinical team and improved reimbursement options for the services provided.

By leveraging these opportunities, physicians and their teams can collaborate with TTSs to make significant strides in helping patients address and overcome their dependence on tobacco and nicotine.

The outlook: CMS 2024 rule

The current outlook for 2024 and beyond promises even more opportunities as part of CMS' ongoing Behavioral Health Strategy. This includes enabling mental health counselors (MHCs) and marriage and family therapists (MFTs) to bill Medicare independently, initiating vital coverage for mental health services that align with tobacco cessation efforts.

Physicians and medical centers can contract with MFTs and MHCs who are TTSs to provide tobacco addiction services. TTSs will serve as essential partners in multidisciplinary care teams, enhancing the overall health care landscape while ensuring that patients receive comprehensive support tailored to their needs.

Telehealth policy changes: Making services accessible

The White House also recently reinforced the importance of telehealth services, providing further avenues for TTSs to reach patients effectively. With expanded geographic locations for service delivery, care can be provided from virtually anywhere, including when the patient is at home.

Key telehealth provisions include:

- Extended telehealth services through 2024
- Elimination of in-person requirements for mental health services
- Expanded eligibility for providers qualified to provide telehealth services

Practical implications for providers

These developments not only simplify the establishment of tobacco treatment programs but also create better avenues to develop partnerships between physicians, hospitals, medical centers, multidisciplinary practices, and TTSs. Importantly, these clinicians will be compensated directly for the tobacco treatment services they provide.

Conclusion

This is a pivotal moment for pulmonologists and TTSs to meaningfully claim their place within the health care space. As we strive to "make smoking history," we must act on these CMS opportunities. As providers, we must be proactive, collaborate across disciplines, and serve as advocates for our patients.

Together, we can turn the tide against tobacco use and improve health outcomes nationwide.

Call to action

CHEST encourages all health care professionals to engage with the available resources, collaborate with TTSs, and take appropriate advantage of these new policies for the benefit of our patients. Let's work together to ensure that we seize this moment and make a real difference in the lives of those affected by tobacco addiction. ■

Those interested in more information—or to access additional resources and assistance in locating TTSs—please contact Matthew Bars at matt@IntelliQuit.org or +1 (800) 45-SMOKE.

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NETWORKS

AI in pediatrics, aspiration vs chest tube, telehealth monitoring of exercise testing, and more

DIFFUSE LUNG DISEASE AND LUNG TRANSPLANT NETWORK

Pulmonary Physiology and Rehabilitation Section

Extending exercise testing using telehealth monitoring in patients with ILD

The COVID-19 pandemic revolutionized the use of monitoring equipment in general and oxygen saturation monitoring devices as pulse oximeters in specific. Home technology devices such as home spirometry, smart apps, and wearable sensors combined with patient-reported outcome measures are increasingly used to monitor disease progression and medication compliance in addition to routine physical activity.

The increasing adoption of activity trackers is geared toward promoting an active lifestyle through real-time feedback and continuous monitoring.

Patients with interstitial lung diseases (ILDs) suffer from different symptoms; one of the most disabling is dyspnea. Primarily associated with oxygen desaturation, it initiates a detrimental cycle of decreased physical activity, ultimately compromising the overall quality of life.

The use of activity trackers has shown to enhance exercise capacity among ILD and sarcoidosis patients. Implementing continuous monitor activity by activity trackers coupled with continuous oxygen saturation can provide a comprehensive tool to follow up with ILD patients efficiently and accurately based on established use of a six-minute walk test (6MWT) and desaturation screen.

Combined 6MWT and desaturation screens remain the principal predictors to assess the disease progression and treatment response in a variety of lung diseases, mainly pulmonary hypertension and ILD and serve as a prognostic indicator of those patients.

One of the test limitations is that the distance walked in six minutes reflects fluctuations in quality of life. Also, the test measures submaximal exercise performance rather than maximal exercise capacity.

Associations have been found in that the amplitude of oxygen desaturation at the end of exercise was poorly reproducible in 6MWT in idiopathic Interstitial pneumonia.

Considering the mentioned limitations of the classic 6MWT, an alternative approach involves extended desaturation screen using telehealth and involving different activity levels. However, further validation across a diverse spectrum of ILDs remains essential.

All references are available online at chestphysician.org.

– Rania Abdallah, MD, MSc, FCCP, Member-at-Large
– Rana Hejal, MD, FCCP

PULMONARY VASCULAR AND CARDIOVASCULAR NETWORK

Pulmonary Vascular Disease Section

Major takeaways from the seventh world symposium on PH

The core definition of pulmonary hypertension (PH) remains a mean pulmonary arterial pressure (mPAP) > 20 mm Hg, with precapillary PH defined by a pulmonary arterial wedge pressure (PCWP) ≤ 15 mm Hg and pulmonary vascular resistance (PVR) > 2 Wood units (WU), similar to the 2022 European guidelines. There was recognition of uncertainty in patients with borderline PAWP (12-18 mm Hg) for postcapillary PH.

Dr. Ejikeme

Dr. Bernardo

Dr. Estrada

A new staging model for group 2 PH was proposed to refine treatment strategies based on disease progression. It's crucial to phenotype patients, especially those with valvular heart disease, hypertrophic cardiomyopathy, or amyloid cardiomyopathy, and to be cautious when using PAH medications for this PH group.

Group 3 PH is often underrecognized and associated with poor outcomes, so screening in clinically stable patients is recommended using a multimodal assessment before hemodynamic evaluation. Inhaled treprostinil is recommended for PH associated with interstitial lung disease (ILD). However, the PERFECT trial on PH therapy in COPD was stopped due to safety concerns, highlighting the need for careful evaluation in chronic lung disease (CLD) patients. For risk stratification, further emphasis was made on cardiac imaging and hemodynamic data.

Significant progress was made in understanding four key pathways, including bone morphogenetic protein (BMP)/activin signaling. A treatment algorithm based on risk stratification was reinforced, recommending initial triple therapy with parenteral prostacyclin analogs for high-risk patients. Follow-up reassessment may include adding an activin-signaling inhibitor for all risk groups except low risk, as well as oral or inhaled prostacyclin for intermediate-low risk groups.

All references are available online at chestphysician.org.

– Chidinma Ejikeme, MD, Fellow-in-Training
– Roberto J. Bernardo MD, MS, Member-at-Large
– Rodolfo A. Estrada, MD, FCCP, Member-at-Large

CRITICAL CARE NETWORK

Mechanical Ventilation and Airways Management Section

Mechanical power: A missing piece in lung-protective ventilation?

The ARDSNet trial demonstrated the importance of low tidal volume ventilation in patients with ARDS, and we have learned to monitor parameters such as plateau pressure and driving pressure (DP) to ensure lung-protective ventilation. However, severe hypercapnia can occur with low tidal volume ventilation and respiratory rate would often need to be increased. What role does the higher respiratory rate play? There is growing evidence that respiratory rate may play an important part in the pathogenesis of ventilator-induced lung injury (VILI) and the dynamic effect of both rate and static pressures needs to be evaluated.

Dr. Zhang

The concept of mechanical power (MP) was formalized in 2016 by Gattinoni, et al and defined as the product of respiratory rate and total inflation energy gained per breath.[1] Calculations have been developed for both volume-controlled and pressure-controlled ventilation, including elements such as respiratory rate and PEEP. Studies have shown that increased MP is associated with ICU and hospital mortality, even at low tidal volumes.[2] The use of MP remains limited in clinical practice due to its dynamic nature and difficulty of calculating in routine clinical practice but may be a feasible addition to the continuous monitoring outputs on a ventilator. Additional prospective studies are also needed to define the optimal threshold of MP and to compare monitoring strategies using MP vs DP.

All references are available online at chestphysician.org.

– Zhenmei Zhang, MD, Member-at-Large

AIRWAYS DISORDERS NETWORK

Pediatric Chest Medicine Section

AI applications in pediatric pulmonary, sleep, and critical care medicine

Artificial intelligence (AI) refers to the science and engineering of making intelligent machines that mimic human cognitive functions, such as learning and problem solving. AI tools are being increasingly utilized in pediatric pulmonary disease management to analyze the tremendous amount of patient data on environmental and physiological variables and compliance with therapy. Asthma exacerbations in young children were detected reliably by AI-aided stethoscope alone. Inhaler use has been successfully tracked using active

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and passive patient input to cloud-based dashboards. Asthma specialists can potentially use this knowledge to intervene in real time or more frequent intervals than the current episodic care.

Dr. Kalra

Sleep trackers using commercial-grade sensors can provide useful information about sleep hygiene, sleep duration, and nocturnal awakenings. An increasing number of "wearables" and "nearables" that utilize AI algorithms to evaluate sleep duration and quality are FDA approved. AI-based scoring of polysomnography data can improve the efficiency of a sleep laboratory. Big data analysis of CPAP compliance in children led to identification of actionable items that can be targeted to improve patient outcomes.

The use of AI models in clinical decision support can result in fewer false alerts and missed patients due to increased model accuracy. Additionally, large language model tools can automatically generate comprehensive progress notes incorporating relevant electronic medical records data, thereby reducing physician charting time.

These case uses highlight the potential to improve workflow efficiency and clinical outcomes in pediatric pulmonary and critical care by incorporating AI tools in medical decision-making and management.

All references are available online at chestphysician.org.

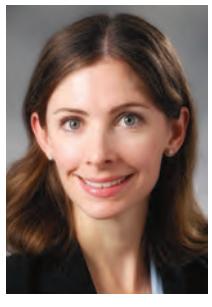
– Maninder Kalra, MD, PhD, Member-at-Large

THORACIC ONCOLOGY AND CHEST PROCEDURES NETWORK

Pleural Disease Section

Revival of the aspiration vs chest tube debate for PSP

Considerable heterogeneity exists in the management of primary spontaneous primary spontaneous pneumothorax (PSP). American and European guidelines have been grappling with this question for decades: What is the best way to manage PSP? A 2023 randomized, controlled trial (Marx et al. AJRCCM) sought to answer this.



Dr. Scott

The study recruited 379 adults aged 18 to 55 years between 2009 and 2015, with complete and first PSP in 31 French hospitals. One hundred eighty-nine patients initially received simple aspiration and 190 received chest tube drainage.

The aspiration device was removed if a chest radiograph (CXR) following 30 minutes of aspiration showed lung apposition, with suction repeated up to one time with incomplete re-expansion. The chest tubes were large-bore (16-F or 20-F) and removed 72 hours postprocedure if the CXR showed complete lung re-expansion.

Pulmonary re-expansion at 24 hours was the primary outcome of interest, analyzed for noninferiority. Simple aspiration was statistically inferior to chest tube drainage (29% vs 18%). However, first-line simple aspiration resulted in shorter length of stay, less subcutaneous emphysema, site infection, pain, and one-year recurrence.

Dr. Nadig

Dr. Debiane

Since most first-time PSP occurs in younger, healthier adults, simple aspiration could still be considered as it is better tolerated than large-bore chest tubes. However, with more frequent use of small-bore (≤14-F) catheters, ambulatory drainage could also be a suitable option in carefully selected patients. Additionally, inpatient chest tubes do not need to remain in place for 72 hours, as was this study's protocol. Society guidelines will need to weigh in on the latest high-quality evidence available for final recommendations.

– Ashley M. Scott, MD, Fellow-in-Training
– Tejaswi R. Nadig, MBBS, Member-at-Large
– Labib G. Debiane, MD, MS, FCCP, Member-at-Large

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Improved *CHEST Physician*® coming in 2025

Some exciting changes are underway for the *CHEST Physician* publication in 2025. Building on nearly three decades as a leading source for news and clinical commentary in pulmonary and critical care medicine, *CHEST Physician* will roll out several notable improvements, including a digital-forward release of content for increased access and timeliness.

First, the *CHEST Physician* website, chestphysician.org, will undergo a complete transformation. With an improved user experience, you'll be able to find content relevant to your interests and specialties more easily. In addition, *CHEST Daily News*, which features the best of the annual meeting, will be delivered alongside expanded *CHEST Physician* content.

Second, a brand-new email newsletter will hit your inbox twice a month starting in January 2025. The email will feature a quick look into a cross-section of content covering research and clinical practice. This digital-first approach will also get you the news and research you rely on sooner.

Lastly, the redesigned *CHEST Physician* print issue will be produced and delivered quarterly. The first issue will arrive in March 2025. These special issues will feature print-exclusive content and infographics, as well as offer a deeper dive into the most relevant news stories from recent months.

Notably, the editorial team will tailor content to the interests of our readership and will address the issues and topics most relevant to pulmonary and critical care clinicians.

We want to hear from you as the *CHEST Physician* publication undergoes this transformation. What topics do you want more of? How can CHEST continue to serve the chest medicine community best? Email chestphysiciannews@chestnet.org to share your ideas.

Thank you for being a loyal *CHEST Physician* reader. We look forward to bringing you elevated content and an enhanced reader experience in the new year. ■

CRITICAL CARE COMMENTARY

Biomarker use in ARDS resulting from COVID-19 infection

BY GEORGE A. ALBA, MD, AND JEHAN W. ALLADINA, MD

Dr. Alba

Dr. Alladina

There is renewed interest in the use of immunomodulator therapies in patients with acute hypoxemic respiratory failure.

Multiple investigations during the course of the COVID-19 pandemic, including the large RECOVERY and CoDEX trials, demonstrated that dexamethasone administration improved mortality in patients with severe COVID-19. Beyond COVID-19, studies have also shown corticosteroid therapy improves clinical outcomes in patients with severe community-acquired pneumonia. However, the overwhelming majority of studies identifying plasma biomarkers that are associated with clinical outcomes in severe lung injury predate the routine use of corticosteroids. Two investigators at Massachusetts General Hospital, Jehan W. Alladina, MD, and George A. Alba, MD, performed a study to assess whether plasma biomarkers previously associated with clinical outcomes in ARDS maintained their predictive value in the setting of widespread immunomodulator therapy in the ICU. Drs. Alladina and Alba are physician-scientists and codirectors of the Program for Advancing Critical Care Translational Science at Massachusetts General Hospital in Boston.

In a study published in *CHEST*® *Critical Care* earlier this year, they prospectively enrolled patients with ARDS due to confirmed SARS-CoV-2 infection during the second wave of the COVID-19 pandemic from December 31, 2020, to March 31, 2021, at Massachusetts General Hospital. Plasma samples were collected within 24 hours of intubation for mechanical ventilation for protein analysis in 69 patients. Baseline demographics included a mean age of 62 plus or minus 15 years and a BMI of 31 plus or minus 8, and 45% were female. The median PaO_2 to FiO_2 ratio was 174 mm Hg, consistent with moderate ARDS, and the median duration of ventilation was 17 days. The patients had a median modified sequential organ failure assessment score of 8.5, and in-hospital mortality was 44% by 60 days. Notably, all patients in this cohort received steroids during their ICU stay.

Interestingly, the study investigators found no association between clinical outcomes and circulating proteins implicated in inflammation (eg, interleukin [IL]-6, IL-8), epithelial injury (eg, soluble receptor for advanced glycation end products, surfactant protein D), or coagulation (eg, D-dimer, tissue factor). However, four endothelial biomarkers—von Willebrand factor A2 domain; angiopoietin-2; syndecan-1; and neural precursor cell expressed, developmentally downregulated 9 (NEDD9)—were associated with 60-day mortality after adjusting for age, sex, and severity of illness. A sensitivity analysis, in which patients treated with the IL-6 inhibitor tocilizumab (n=4) were excluded, showed similar results.

Of the endothelial proteins, NEDD9 demonstrated the greatest effect size in its association with mortality in patients with ARDS due to COVID-19 who were treated with immunomodulators. NEDD9 is a scaffolding protein highly expressed in the pulmonary vascular endothelium, but its role in ARDS is not well known. In pulmonary vascular disease, plasma levels are associated with adverse pulmonary hemodynamics and clinical outcomes. Pulmonary artery endothelial NEDD9 is upregulated by cellular hypoxia and can mediate platelet-endothelial adhesion by interacting with P-selectin on the surface of activated platelets. Additionally, there is evidence of increased pulmonary endothelial NEDD9 expression and colocalization with fibrin within pulmonary arteries in lung tissue of patients who died from ARDS due to COVID-19. Thus, NEDD9 may be an important mediator of pulmonary vascular dysfunction observed in ARDS and could be a novel biomarker for patient subphenotyping and prognostication of clinical outcomes.

In summary, in a cohort of patients with COVID-19 ARDS uniformly treated with corticosteroids, plasma biomarkers of inflammation, coagulation, and epithelial injury were not associated with clinical outcomes, but endothelial biomarkers remained prognostic. It is biologically plausible that immunomodulators could attenuate the association between inflammatory biomarkers and patient outcomes. The findings of this study highlight the association of endothelial biomarkers with clinical outcomes in patients with COVID-19 ARDS treated with immunomodulators and warrant prospective validation, especially with the increasing evidence-based use of antiinflammatory therapy in acute lung injury.

However, there are several important limitations to consider, including a small sample size from a single institution, the single time point studied (the day of initiation of mechanical ventilation), and absence of a comparator group. Whether the findings are generalizable to all patients with ARDS treated with immunomodulators also remains unknown. Overall, these data suggest that circulating signatures previously associated with ARDS, particularly those related to systemic inflammation, may have limited prognostic utility in the era of increasing immunomodulator use in critical illness. A deeper understanding of the pathobiology of ARDS is needed to identify prognostic biomarkers and targeted therapies that improve patient outcomes. ■

All references are available online at chestphysician.org.

Drs. Alba and Alladina are in the Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School.

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SLEEP STRATEGIES

Should napping be a recommended health behavior?

BY SARA C. MEDNICK, PHD


Dr. Mednick

I was invited to a cardiology conference to talk about sleep, specifically the benefits of napping for health and cognition. After the talk, along with the usual questions related to my research, the cardiac surgeons in the room shifted the conversation to better resemble a group therapy session, sharing their harrowing personal tales of coping with sleep loss on the job. The most dramatic story involved a resident in a military hospital who, unable to avoid the effects of her mounting sleep loss, did a face plant into the open chest of the patient on the surgery table.

Sleep is inexorable.

Yet humans generally do not get sufficient sleep, and a growing body of research indicates that this deficit is taking a toll on day-to-day functioning, as well as long-term health outcomes. Epidemiology studies have associated insufficient sleep with increased disease risk, including cardiovascular and metabolic disease, diabetes, cancer, Alzheimer's disease and related dementias, as well as early mortality. Laboratory studies that experimentally restrict sleep show deficits across many cognitive domains, including executive functions, long-term memory, as well as emotional processing and regulation. Insufficient sleep in adolescents can longitudinally predict depression, thought problems, and lower crystallized intelligence, as well as structural brain properties. In older adults, it can predict the onset of chronic disease, including Alzheimer's disease. Repeated nights of insufficient sleep (eg, three to four nights of four to six hours of sleep) have been shown to dysregulate hormone release, elevate body temperature and heart rate, stimulate appetite, and create an imbalance between the two branches of the autonomic nervous system by prolonging sympathetic activity and reducing parasympathetic restorative activity.

Given this ever-increasing list of ill effects of poor sleep, the quest for an effective, inexpensive, and manageable intervention for sleep loss often leads to the question: What about naps? A nap is typically defined as a period of sleep between five minutes to three hours, although naps can occur at any hour, they are usually daytime sleep behaviors. Between 40% and 60% of adults nap regularly, at least once a week, and, excluding novelty nap boutiques, they are free of charge and require little management or oversight. Yet, for all their apparent positive aspects, the jury is still out on whether naps should be recommended as a sleep loss countermeasure due to the lack of agreement across studies as to their effects on health.

Naps are studied in primarily two scientific contexts: laboratory experimental studies and epidemiological studies. Laboratory experimental studies measure the effect of short bouts of sleep as a fatigue countermeasure or cognitive enhancer under total sleep deprivation, sleep restriction (four to six hours of nighttime sleep), or well-rested conditions. These experiments are usually conducted in small (20 to 30 participants) convenience samples of young adults without medical and mental health problems. Performance on computer-based cognitive tasks is tested before and after naps of varying durations. By varying nap durations, researchers can test the impact of specific sleep stages on performance improvement. For example, in well-rested, intermediate chronotype individuals, a 30-minute nap between 13:00 and 15:00 will contain mostly stage 2 sleep, whereas a nap of up to 60 minutes will include slow wave sleep, and a 90-minute nap will end on a bout of rapid eye movement sleep. Studies that vary nap duration and therefore sleep quality have demonstrated an important principle of sleep's effect on the brain and cognitive processing, namely that each sleep stage uniquely

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contributes to different aspects of cognitive and emotional processing. And that when naps are inserted into a person's day, even in well-rested conditions, they tend to perform better after the nap than if they had stayed awake. Napping leads to greater vigilance, attention, memory, motor performance, and creativity, among others, compared with equivalent wake periods. Compared with the common fatigue countermeasure—caffeine—naps enhance explicit memory performance to a greater extent.

In the second context, epidemiological studies examining the impact of napping on health outcomes are typically conducted in older, less healthy, less active populations who tend to have poorer eating habits, multiple comorbidities, psychological problems, and a wide range of socioeconomic status. The strength of this approach is the sample size, which allows for correlations between factors on a large scale while providing enough data to hopefully control for possible confounds (eg, demographics, SES, exercise and eating habits, comorbidities). However, as the data were usually collected by a different group with different goals than the current epidemiologist exploring the data, there can be a disconnect between the current study goals and the variables that were initially collected by the original research team. As such, the current researcher is left with a patchwork of dissimilar variables that they must find a way to organize to answer the current question.

When applied to the question of health effects of napping, epidemiology researchers typically divide the population into two groups, either based on a yes or no response to a napping question, or a frequency score where those who indicate napping more than one, two, or three times a week are distinguished as nappers compared to non-nappers who don't meet these criteria. As the field lacks standard definitions for categorizing nap behavior, it is left to the discretion of the researcher to make these decisions. Furthermore, there is usually little other information collected about napping habits that could be used to better characterize napping behavior, such as lifetime nap habits, intentional vs accidental napping, and specific motivations for napping. These secondary factors have been shown to significantly moderate the effects of napping in experimental studies.

Considering the challenges, it is not surprising that there is wide disagreement across studies as to the health effects of napping. On the negative side, some studies have demonstrated that napping leads to increased risk of cardiovascular disease, dementia, and mortality. On the positive side, large cohort studies that control for some of these limitations report that habitual napping can predict better health outcomes, including lower mortality risk, reduced cardiovascular disease, and increased brain volume. Furthermore, age complicates matters as recent studies in older adults report that more frequent napping may be associated with reduced propensity for sleep during morning hours, and late afternoon naps were associated with earlier melatonin onset and increased evening activity, suggesting greater circadian misalignment in nappers and strategic use of napping as an evening fatigue countermeasure. More frequent napping in older adults was also correlated with lower cognitive performance in one of three cognitive domains. These results implicate more frequent and later-in-the-day napping habits in older adults may indicate altered circadian rhythms and reduced early morning sleep, with a potential functional impact on memory function. However, the same cautionary note applies to these studies, as few nap characteristics were reported that would help interpret the study outcomes and guide recommendations.

Thus, the important and timely question of whether napping should be recommended does not, as of yet, have an answer. For clinicians weighing the multidimensional factors associated with napping in efforts to give a considered response to their patients, I can offer a set of questions that may help with tailoring responses to each individual. A lifetime history of napping can be an indicator of a health-promoting behavior, whereas a relatively recent desire to nap may reflect an underlying comorbidity that increases fatigue, sleepiness, and unintentional daytime sleep. Motivation for napping can also be revealing, as the desire to nap may be masking symptoms of depression and anxiety.[11] Nighttime sleep disturbance may promote napping or, in some cases, arise from too much napping and should always be considered as a primary health measurement. In conclusion, it's important to recognize the significance of addressing nighttime sleep disturbance and the potential impact of napping on overall health. For many, napping can be an essential and potent habit that can be encouraged throughout the lifespan for its salutary influences. ■

All references are available online at chestphysician.org.

PULMONARY EMBOLISM

ILD linked to poorer outcomes in PE

BY JIM KLING

FROM CHEST 2024 ▪ BOSTON — Patients with pulmonary embolism (PE) who also present with interstitial lung disease (ILD) have worse outcomes with respect to in-hospital mortality, length of hospital stay, hospital cost, and all-cause readmission, according to results from a retrospective analysis.

"There's a lot of evidence now that demonstrates that ILD, in general, leads to worse mortality, morbidity in hospital complications, and overall [outcomes]. It's not hard to extrapolate this to PE outcomes, too. Unfortunately, there's not a whole lot of evidence out there to really demonstrate it," said Leah Yuan, MD, during a presentation at the CHEST Annual Meeting.

The question is complicated by the nebulous nature of ILD, which includes a diverse set of diseases, etiologies, and levels of inflammation and fibrosis. It has been employed in the Pulmonary Embolism Severity Index but counts for only 10 points out of 210. "If you look at ILD and PE outcomes, there's nothing really out there [in the literature]," Dr. Yuan said. She is a resident physician at Cook County Health and Hospitals System in Illinois.

The study suggested that ILD should have greater weight in risk stratification of patients with PE, she said. "We looked at all-cause readmissions and we looked at in-hospital mortality, [both] of which are significant for increased odds ratio. One thing that I'm very curious to see is whether there is increased PE readmissions [associated with ILD], which is something that we couldn't find to be significant in our study," Dr. Yuan said.

The researchers used data from hospitalizations for PE drawn from the Nationwide Readmissions Database in 2019, using International Classification of Diseases, Tenth Revision, codes to identify admissions. Among a total of 105,133 patients admitted for PE, 158 patients also had ILD. The mean age was 63.6 years for those without ILD (SD, 0.1) and 66.5 years for those with ILD (SD, 1.3). Admission with ILD was associated with all-cause readmission (odds ratio [OR], 4.12; $P < .01$), in-hospital mortality (OR, 2.17; $P = .01$), a longer length of stay (+2.07 days; $P < .01$), and higher hospitalization charges (+$22,627; $P < .01$).

In the Q&A after the presentation, Parth Rali, MD, professor of thoracic medicine and surgery at Temple University, Philadelphia, suggested phenotyping patients to better understand the location of the PE in relation to the ILD. "It may not fall into your classic PE classification. It may just depend on where the clot is in relationship to the ILD. I think that's where the field is going to evolve," he later said. "What is interesting is that patients with ILD have a lot of fibrotic disease, and they do not need to have a large clot burden to make them sick," Dr. Rali said.

He advised physicians to pay close attention to the location of PEs in relation to fibrotic tissue in patients with ILD. A PE in healthy lung tissue could have an outsized effect on hemodynamics, whereas a PE in fibrotic tissue may be clinically insignificant and not require treatment.

Drs. Yuan and Rali disclosed no relevant financial relationships. ■

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