NewYork-Presbyterian
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ADVANCES IN PULMONOLOGY

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SPECIAL EDITION

Innovative ECMO Program Offers Lifesaving Interventions For Respiratory Failure

Patients experiencing severe respiratory failure often have little recourse aside from invasive interventions that ultimately may worsen their condition. Extracorporeal membrane oxygenation (ECMO), first used in the 1970s for patients with respiratory failure, has generally received scarce consideration in the United States since that time. The Center for Acute Respiratory Failure at NewYork-Presbyterian/Columbia University Medical Center, however, has been at the forefront of a renewed appreciation of the clinical benefits of ECMO.

The Hospital's Medical ECMO Program treats patients with severe respiratory diseases, including those patients requiring a bridge to lung transplantation. It is the largest program offering ECMO for respiratory failure in the United States.

"Only in the last few years—really, since 2009—have people begun to recognize the greater potential for ECMO," said Daniel Brodie, MD, Co-director of the Center for Acute Respiratory Failure and Director of the Medical ECMO Program at NewYork-Presbyterian/Columbia.

According to Dr. Brodie, 2 events rekindled the medical community's interest in ECMO in 2009.

One was the CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) trial, which compared referral to a center that provides ECMO with standard ventilation in patients with severe acute respiratory distress syndrome (ARDS). The results showed that ECMO led to significant improvements in 6-month survival rates without disability compared with mechanical ventilation (63% vs 47%; P=0.03).[1] But the absence of a per-protocol control arm led to lingering skepticism among the medical community.

The second event was the 2009 influenza A (H1N1) pandemic, which led to cases of H1N1-associated ARDS. An observational multicenter study across Australia and New Zealand reported that the use of ECMO initially led to a 79% survival rate (54 of 68 patients) in patients with H1N1-associated severe ARDS.[2] A follow-up letter in March 2010 reported a 75% survival rate.

The Mobile ECMO Transport Team.

Over the past few decades, mortality rates from moderate ARDS have remained relatively steady at 20% to 40% with the use of low tidal volume mechanical ventilation, the standard of care for this condition. Mortality rates attributed to severe ARDS are even higher. However, adult patients with severe ARDS treated at the Medical ECMO Program have experienced significantly improved survival rates.

"A ventilator is a medieval instrument of torture for the lungs," said Dr. Brodie. "People think of ECMO in ARDS as a way to provide oxygen to severely hypoxemic patients, and it is. But what's often more important is that we're decreasing the amount of pressure and volume delivered to the lungs, so we're decreasing ventilator-associated lung injury."

Advancing ECMO

Dr. Brodie and Matthew Bacchetta, MD, Director of the Adult ECMO Program and Co-director of the Center for Acute Respiratory Failure at NewYork-Presbyterian/Columbia, have pioneered several new modalities for ECMO to alleviate the morbidity and immobilization caused by mechanical ventilation.

Dr. Bacchetta listed a few of these advancements, including a simplified ECMO circuit to reduce the risk for complications, as well as additional circuit and cannula configurations to treat patients with ARDS, refractory acute pulmonary embolism, and pulmonary hypertension.

See ECMO, page 3

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Genetics Research Across Medical Specialties Now Yielding Secrets and Improving the Practice of Medicine

The decoding of the human genome and subsequent concerted efforts by physician-scientists to decipher the relationships between specific genes and the diseases they influence have already yielded tremendous advancements in medicine. This work is fostering important strides in understanding and caring for people with diseases affecting all health systems, and much of the laboratory and translational studies, as well as clinical research, are being done at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital.

Research abounds in every field. The field of geriatrics, for instance, was intrigued by a study led by Columbia University researcher Lawrence S. Honig, MD, PhD, Professor of Clinical Neurology in the Taub Institute, an Alzheimer's disease research center funded by the National Institute on Aging.[1] Dr. Honig's research found that telomere length relates both to the likelihood of the patient developing dementia and his or her overall remaining life span. This research could lead to the use of telomere length as an accurate biomarker of aging in people, as well as an early warning sign for future dementia.

The researchers examined telomere lengths from DNA samples of white blood cells obtained from 1,983 individuals aged 66 to 101 years. These patients were followed for an average of 8 years. After adjusting for age and education, among other factors, researchers found that those individuals with shorter telomeres had higher rates of both dementia and mortality. The researchers must now examine whether shorter telomeres directly increase the risk for dementia and death, or if the telomeres are being influenced by some other factor that is both shortening telomere length while at the same time increasing dementia and mortality risk.

Within psychiatry, schizophrenia has long been known to be genetic in origin, but the networks of genes involved in this disability have not been well characterized. A recent paper published in *Nature Neuroscience* found a link between schizophrenia and autism.[2] Columbia researchers examined a collection of mutations associated with schizophrenia and found occult interrelations among genes that had previously been thought to be unrelated. The researchers found that most of the mutated schizophrenia genes were related to 2 main gene networks, which together affect key processes, including axon guidance, synapse function, neuron mobility, and chromosomal modification.

In research on the pathogenesis of cystic fibrosis, Dr. Stefan Worgall is investigating the interaction of alveolar macrophages with *P. aeruginosa.*

The research, which was led by Dennis Vitkup, PhD, Associate Professor in the Department of Biomedical Informatics at Columbia's Center for Computational Biology and Bioinformatics, also looked at genes mutated in patients with autism and found the similarities were surprisingly robust. Noting that the genetic networks for autism and schizophrenia are closely intertwined, the researchers postulated that many other psychiatric disorders also might share the same genetic networks and interrelated molecular processes.

Pulmonology has begun to explore the use of gene-based vaccines targeted against pulmonary infectious organisms. At Weill Cornell Medical College, a team led by Stefan Worgall, MD, PhD, Division Chief of the Pediatrics Pulmonology, Allergy and Immunology Division, has developed capsid-modified adenovirus vectors[3,4] to heighten immune responses from genetic vaccines against both *Pseudomonas aeruginosa* and respiratory syncytial virus. In research on the pathogenesis of cystic fibrosis, Dr. Worgall is investigating the interaction of alveolar macrophages with *P. aeruginosa.*

Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study in which Columbia University played an important role.[5] The study, led by Ali Gharavi, MD, Associate Director of the Division of Nephrology at NewYork-Presbyterian/Columbia, is the first to link congenital kidney disease, which together with urinary tract defects accounts for about one-fourth of all birth defects in the United States, with neurodevelopmental disorders. The study found that 10% of children born with kidney defects have genomic alterations that have been linked with neurodevelopmental delay and mental illness. The finding is important because it paves the way for identifying subgroups of patients with kidney defects whose treatment will be guided by specific genetic information. The finding also alerts physicians who care for children with congenital kidney disorders that there may be a genetic basis for a neurodevelopmental delay or a mental illness that will occur later in life.

Perhaps no area of medicine has been as affected by research into the genetic foundations of disease as much as oncology. Examples of genetic discoveries in oncology are plentiful. An important recent discovery is the revelation that certain cases of glioblastoma are caused by the fusion of 2 genes.[6] Researchers, led by Antonio Iavarone, MD, Professor of Pathology and Neurology at Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia, conducted genetic analyses of

patients with glioblastomas, searching for evidence of gene fusions. They found them, with the most common being fusions involving the fibroblast growth factor receptor (*FGFR1* or *FGFR3*) and transforming acidic coiled-coil (*TACC1* or *TACC3*) genes. The protein produced by the fusion of *FGFR-TACC* disrupts the mitotic spindle, causing aneuploidy, and from there tumorigenesis. The finding is important because it provides researchers with a protein target for pharmaceutical research for a cancer that is especially difficult to treat.

The field of clinical genetics is rapidly changing and improving the practice of medicine. As the field of genetics continues to grow so too the physician-scientists at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital will continue to be at the forefront of integrating genetics into all specialties.

References

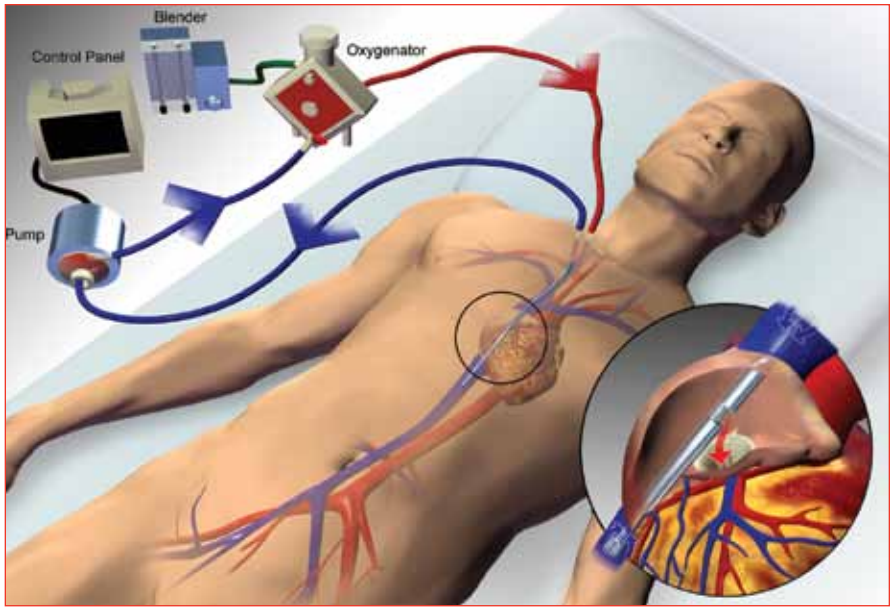
1. Honig LS, Kang MS, Schupf N, et al. Association of shorter leukocyte telomere repeat length with dementia and mortality. *Arch Neurol.* 2012;69(10):1332-1339.
2. Gilman SR, Chang J, Xu B, et al. Diverse types of genetic variation converge on functional gene networks involved in schizophrenia. *Nat Neurosci.* 2012;15(12):1723-1728.
3. Halbreiner M, Pagovich O, Finnin E, et al. Disrupted adenovirus-based vaccines against small addictive molecules circumvent anti-adenovirus immunity. *Human Gene Ther.* 2012 Nov 9. [Epub ahead of print]
4. Krause A, Worgall S. Delivery of antigens by viral vectors for vaccination. *Ther Deliv.* 2011;2(1):51-70.
5. Sanna-Cherchi S, Kiryluk K, Burgess KE, et al. Copy-number disorders are a common cause of congenital kidney malformations. *Am J Hum Genetics.* 2012;91(6): 987-997.
6. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science.* 2012;337(6099):1231-1235.

continued from **ECMO,** page 1

A team from the medical center, led by Drs. Bacchetta and Brodie recently showed that ECMO offers an effective bridge-to-lung transplant intervention for patients with end-stage lung disease who are on the lung transplant list and develop acute or chronic respiratory failure.[3] Eighteen such patients were placed on ECMO and 13 sufficiently recovered to allow extubation; 10 of these patients ultimately received lung transplants, and thus far all have survived.

Since that study, many other patients have been successfully bridged to lung transplant using this technique. Dr. Bacchetta now considers ECMO to be "part of the future of lung transplantation." Rather than ventilating patients and having them become too frail or deconditioned to ultimately be transplanted, patients who receive ECMO are frequently able to eat and take part in physical activities, including walking around the ICU.

Dr. Bacchetta also has introduced a form of venoarterial ECMO that accesses the subclavian artery.[4] This method offers benefits over traditional venoarterial ECMO, such as adequate oxygenation of the brain and heart while enabling patient ambulation, thus speeding up the recovery process.



Single-site approach to venovenous ECMO cannulation. This approach enables improved patient mobility and reduced recirculation, and avoids the femoral access site.

Image courtesy of www.coachsurgery.com.

"This technique lays the groundwork for a truly portable outpatient device that can be used as destination therapy for patients with chronic cardiopulmonary disease who may not be transplant candidates," said Dr. Bacchetta.

Dr. Bacchetta is also well versed in pulmonary thromboendarterectomy, a surgical technique that not many surgeons can perform, and the Center is one of the only places in the eastern United States that successfully performs it. But patients experiencing acute respiratory failure or in need of a rare procedure often are too sick to travel by conventional means.

To care for these debilitated patients, the Center for Acute Respiratory Failure created a Mobile ECMO Transport Team in 2008. The unit includes surgeons, perfusionists, and specially trained

See **ECMO,** page 4

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continued from ECMO, page 3

paramedics with the ability to care for patients with intra-aortic balloon pumps, transvenous pacemakers, and ECMO in the back of an ambulance.

"In other countries this is done, but very few places in the United States do this. The Mobile ECMO Team gives us the opportunity to safely transport the sickest patients to our Center when they need ECMO," said Dr. Brodie.

The Center's ability to bridge these areas of need and to overcome barriers to care offer hope for critically ill patients.

"Our greatest accomplishment at the Center has been to develop a truly fused medical/surgical program that eliminates traditional silos and allows for optimal management from a combined medical/surgical team with joint decision making," said Dr. Bacchetta.

Future Directions for ECMO

ECMO is currently offered at the Center for patients with severe hypoxemia from ARDS (ie, PaO_2 to FiO_2 <80 mm Hg), patients who cannot be ventilated, or those with high plateau airway pressures. Drs. Brodie and Bacchetta described these indications in their 2011 review article on the use of ECMO in ARDS.[5]

Mechanical ventilators often are used at low tidal volumes for patients with ARDS to avoid injury, but tidal volumes below the standard 4 to 6 mL/kg may not adequately remove CO_2 from the lungs, causing pH levels in the blood to fall.

"But if I have a device that can eliminate the CO_2 as it is produced by the body, then I don't have to eliminate it through the lungs and could use very low tidal volume ventilation. That concept is the key to why ECMO may be beneficial even in the setting of moderate ARDS," said Dr. Brodie.

This extracorporeal CO_2 removal also has potential benefits in the treatment of acute exacerbations of chronic obstructive pulmonary disease (an ongoing research focus at the Center) and asthma. ECMO can remove a great deal of CO_2 from a small amount of blood, which enables the use of smaller and, therefore, safer cannulas. This is essentially done all the time in ICUs when they perform continuous venovenous dialysis.

"That's actually where the future of a lot of this is going to be, dialysis for the lungs," added Dr. Brodie.

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-1363.
2. Davies A, Jones D, Bailey M, et al; ANZ ECMO Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA.* 2009;302(17):1888-1895.
3. Javidfar J, Brodie D, Iribarne A, et al. Extracorporeal membrane oxygenation as a bridge to lung transplantation and recovery. *J Thorac Cardiovasc Surg.* 2012;144(3):716-721.
4. Javidfar J, Brodie D, Costa J, et al. Subclavian artery cannulation for venoarterial extracorporeal membrane oxygenation. *ASAIO J.* 2012;58(5):494-498.
5. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med.* 2011;365(20):190-194.