

Midwest Surgical Association: Presidential Address

# The diaphragm: how it affected my career and my life. The search for stability when the problem is instability



Raymond P. Onders, M.D.\*

*Department of Surgery, University Hospitals Case Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106-5047, USA*

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The story of the diaphragm begins over 300 million years ago when primitive vertebrates evolved to have a membrane separating the upper digestive system from the lower. Only with the evolution of warm blooded animals did the diaphragm begin to function for respiration as the lungs herniated into the chest. Some of you in the audience may be starting to look at your watch and wondering how long will this presidential speech last since we still have 100 million years to go? This presidential address will be unlike my usual scientific presentations about diaphragm pacing in which I typically present another analysis from one of my multiple Institutional Review Board protocols of the laparoscopic placement of electrodes into the diaphragm to help with



Raymond P. Onders, M.D.

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Dr Raymond Onders, University Hospitals of Cleveland and Case Western Reserve University School of Medicine, has intellectual property rights involved with the diaphragm pacing system and equity in Synapse Biomedical who manufactures the device.

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\* Corresponding author. Tel.: +1-216-844-5797; fax: +1-216-983-3069.

E-mail address: [Raymond.onders@uhhospitals.org](mailto:Raymond.onders@uhhospitals.org)

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respiration. Instead, I will present my thoughts about the great muscle of respiration, the diaphragm, and how it has affected my life with consideration to “stability and instability.” So I am going to fast forward a little bit to 1987 when James Taylor was in concert at the old Public Hall in Cleveland. How is that related to this diaphragm talk?—for several reasons: (1) I have always believed that one has to end their lecture early so I cannot review every esoteric but important fact about the diaphragm—that could be in a full-length book—which would never be made into a movie. Only a few diaphragm stories will be told today. And (2) it was at this concert where I met my wife Traci, who is here today. So I would like to start this presidential address by thanking my wonderful wife who has put up with this journey of my life with the diaphragm. She has been the stability that helped in raising our 2 wonderful children—Rachel and Ryan—who are also here today. So I thank them for always being there for me. I also want to apologize to them for missing so much time with this diaphragm odyssey of mine. I have caused instability by traveling over 1 million miles in the last decade and being away from home for 758 days in the last decade. Traci, I apologize for all this has caused and neither one of us would have imagined at a James Taylor concert in 1987 how our lives would have been shaped by the diaphragm.

I wish my extended family could have been here with me today, but we celebrated my father’s 80th birthday several weeks ago at Kelley’s Island on Lake Erie where my grandparents are buried. If you could see a picture of the Onders’ clan you would appreciate that we would have struggled with the dress code of the Grand Hotel here on Mackinaw Island. I am the 5th of 10 children with 27 nieces and nephews. Just trying to get all of us together leads to instability. Some aspects of life are “stable.” Traci and I went to another James Taylor concert last week at Blossom Music Center, which has been a stable concert location for decades. He sings the same and has stability in his music. He also looks the same—I, on the other hand, have aged significantly since 1987—again thank you Traci for hanging with me.

The Midwestern Surgical Association (MSA) has also been a stability in my life and in analyzing this now has had a role in understanding the diaphragm and helping patients breathe. The MSA also entered my life in 1987 when Don Mortimer, one of the past presidents of MSA, convinced me to enter surgery instead of family practice. Thank you Don. Subsequently in 1996, I presented at the MSA one of my early academic papers here at the Grand Hotel.<sup>1</sup> Rachel was just a child and Ryan was a glimmer. Tom Stellato (another past president of Midwest Surgical) was at that meeting. He either liked my talk or perhaps he just felt sorry for Traci because I had dragged her to North Dakota for 3 years with me when I was in the US Air Force and he offered me a job back in Cleveland. Tom subsequently introduced me to Tom Mortimer who became my early research mentor in trying to understand the diaphragm. Tom Mortimer saw that there had to be a simple way to help patients breath and instilled in me the passion to continue this project even though he retired shortly after infecting me with his passion. Over the years, you all

have listened to me present this research at this wonderful forum multiple times—probably more than you have ever wanted.<sup>2–4</sup> I thank you for that and for allowing me to be your president this year. This MSA is also one of the only forums where families are welcomed. Only at this meeting can you learn, add to your CV, and obtain a family photo.

I have used the word stable several times already. The stable steady force of my wife, the constant stability of the Midwestern Surgical and yet what I thought was a simple stable research project of helping the diaphragm contract 17 years ago has shown me some major instabilities. Just a few of the instabilities of my diaphragm journey include the following: the instability of trying to get a device regulatory approval, the instability of the financial markets affecting business, and what may become the unifying aspect of my research of the diaphragm—the instability of respiratory control of ventilation. So, I will try to share with my fellow members of Midwest Surgical in the next 15 minutes how the diaphragm has affected my academic career, my business career, my research, and how the underlying stability of our surgical ideal of putting the needs of the patient first has permeated everything I have tried to do. As surgeons we must always look out for the patients and this has to always be the stability of what we do. I will comment on how stability and instability affect my academic activities, business activities, and most importantly patient care. This was all occurring simultaneously in my life, but for simplicity, I separated them.

## Academic Career

The diaphragm pacing project became the primary focus of my academic career fairly early. Using myself as an example when I mentor young surgeons, I tell them just find some esoteric muscle or condition and learn everything you can about that entity. Become the expert. I have published over 30 articles in peer-reviewed journals involving the diaphragm, 7 book chapters, and given over 300 invited lectures around the world. I have been involved in over a dozen patents or pending patents. I developed an academic career based on one muscle. One of the early believers in this technology to help patients subsequently endowed the chair that I now hold: The Margaret and Walter Remen Chair of Surgical Innovation. Thank you Walter and Margaret. Your endowment has allowed me some stability to spend time needed in this research endeavor.

Academically, when doing research you need a stable leader or chairman to protect you. Fortunately, for the last 9 years I have had a stable chairman in Jeff Ponsky who gave a wonderful William H. Harridge Memorial lecture yesterday. He helped protect this diaphragm research and allowed the travel that was needed. Unfortunately, as we search for a new chairman at my institution, instability has entered this environment. There are no relative value units with research. There are no extra relative value units working on orphan diseases. As the interim Division Chief for our interim Chairman, Conor Delaney (president elect of MSA), I receive a biweekly report of our charges detailing how close or distant

we are from our budget. Nowhere on these reports is there listed what research is being done to develop new technology for patients. The pressure to produce financially is definitely different than when I started the diaphragm pacing project 17 years ago. If this daily financial pressure existed 17 years ago, I am unsure if the development of diaphragm pacing and all of its applications would even have been possible. I am not being facetious in saying that with this financial pressure to produce, would we have ever been able to free a child from a tracheostomy mechanical ventilator with diaphragm pacing?<sup>5</sup> This is the pressure I am sure all chairpersons are facing. For surgical innovation to occur, we need to practice in an environment where financials are analyzed but innovative patient care has to be respected. Fortunately, I have had stable leadership for many years in my department, my hospital, and my ever expanding hospital system with Jeff Ponsky, Fred Rothstein, and Tom Zenty, respectively. Their stable leadership has allowed me freedom in the diaphragm pacing project that has led to this technology and helping patients throughout the world. The other stabilities of this project have been part of the team that includes my secretary Jenny Pelcic (17 years), MaryJo Elmo ACNP (12 years), and Cindy Kaplan RN (5 years). They have more knowledge of how patients present with diaphragm abnormalities than all of you in the audience combined! Their compassion for patients who have difficulty breathing is amazing.

## The Business

Early on in diaphragm pacing, I realized that this was more than a simple research project. Tom Conlan was a ventilator-dependent quadriplegic spinal cord injured patient as a result of diving into a pool and the first patient I implanted in 2000. He required a second operation after we realized that not all of our animal data translated exactly into humans. We then had complete success. He was freed from the ventilator. It completely changed his life. This works!! It is great!! Let's order one hundred more!! Let's do this everyday! But there was a problem. There was no one to order this from. Everything for this first case was built in our research laboratory and to actually offer this to more patients required some input from this previously foreign entity to me called the "Food and Drug Administration—the FDA." I never had any training about the FDA in medical school or surgical residency. So we thought since this works some other big company will make it—a Medtronic, for example. This is when I started to learn about the economics of medical devices. Fortunately, there are only 300 to 500 new ventilator-dependent spinal cord injured patients a year in the United States. Unfortunately, this is not an economic model that any company wants to enter into. So to provide this for patients we had to found our own company—Synapse Biomedical.

Because I am one of a small group of surgeons who has founded a successful medical device company, I am asked how did I do this? The answer is to find someone smarter than you to partner with. I was fortunate to find someone to partner with,

but in reality he found me. Tony Ignagni and I partnered on this project in 2001. He had left another company and was looking for the next project. I recommend to any of you who have an idea for a device to partner with someone who has your same moral and ethical obligations to patients. Your partner should not just be trying to make financial decisions to improve shareholder prices, but should always consider if a financial decision is in the best interest of the patient? As a board member of Synapse Biomedical, I take to heart the fiduciary responsibility not only to shareholders but to the patients who use this technology. As we know with device recalls, this moral responsibility may not be the same with all companies.

I also did not realize when we took on the founding of this company what the financial implications were. I had no idea how much money is required to get a device to market. To date, I have been involved in spending over 25 million dollars to obtain FDA approval to allow patients access to the diaphragm pacing technology. I have learned how to raise money from venture capitalists and I unfortunately learned how to weather the instability of the marketplace. In 2008, we received FDA approval for diaphragm pacing for spinal cord injured patients, were nearing the end of our trial in amyotrophic lateral sclerosis (ALS), and our future looked bright. We were about to successfully raise additional funds to fast track this technology and then the markets collapsed. Synapse Biomedical was running out of money and there was no available capital. This was the dark days of diaphragm pacing. This is where it was critical to have the business partner of Tony Ignagni, who held the same moral obligations to patients that I had. Diaphragm pacing is life changing for spinal cord injured patients and it can change the survival in patients with ALS. Two orphan diseases with really no other therapeutic options. We also at this time had begun researching our next application of our technology—temporary use of diaphragm pacing to help patients in the intensive care unit (ICU) by decreasing their time on ventilators. This was what is considered a large market opportunity—over 100,000 tracheostomies are performed a year in the United States for failure to wean from the ventilator. In December 2008, Tony and I were faced with a decision: shut down the spinal cord injury (SCI) and ALS projects and focus only on this large market opportunity or try to do it all. I felt it was morally wrong to not continue in ALS and SCI and Tony completely agreed. This may not have been the best personal financial decision I have ever made. We unfortunately had to lay off half the company. I also learned what having a Conformance Europe (CE) mark meant. This meant that we could sell the device in Europe while we await FDA approval for ALS. This allowed continued income for the company to keep it alive but it significantly slowed down our work in obtaining approval for ALS patients. The company did not have enough bandwidth to do multiple projects at once.

The eventual book about diaphragm pacing may give the full story of how we kept the company alive but for the brevity of this report I will discuss some key aspects. One person who became an integral part of our survival was Moustapha Diop. Moustapha had been a friend, worked with Tony in the past, and

became one of the earliest employees of Synapse Biomedical. He had the same moral fiber of Tony and I and is considered, like Tony and I, part of the “soul” of the company. Because of his dual citizenship in France, he was ideal for the rest of the world sales. This became critical when the economy crashed in 2008 and we needed sales to keep the company alive. So Moustapha and I traveled more than I ever thought possible. He held the same ideals as Tony and I held. If a patient in the world needed help breathing and we thought diaphragm pacing could help, was there a financial way to make it happen while helping to keep the company alive? These were the dark days with increased stress, time away traveling, and mentally away while still at home. This instability was at times unfathomable. But fortunately the stability of my wife Traci was always there, although I know I can never replace that time and relive events with her and my family. I again apologize.

To this day, we continue with this same ideal and continue to expand to countries that need this technology. I have trained surgeons in over 25 countries spanning the globe from Iceland to Australia and multiple states in the United States. In training and collaborating, I have been fortunate to meet surgeons and researchers who also share this passion for helping patients and I have learned from everyone and every place I traveled. I spent hours and hours discussing respiratory physiology. This diaphragm odyssey has also given me other life lessons and here are a few of them: whale is delicious in Iceland; quick dry undergarments are a must for washing in your hotel sink; never check your luggage; you can safely carpool with Syrians from Bahrain to Riyadh, Saudi Arabia, when you miss a flight; foldable running shoes in your luggage will at least allow you to consider working out; and so on.

As a company we still try to meet any patients' needs. Earlier this year, an 18-month old spinal cord injured child in Spain who was hurt on Christmas Eve needed our device. We figured out a way to meet that need and 2 hours after the surgery in Barcelona, I watched the youngest child ever implanted breathe off the ventilator. The mother cried, I shed a tear, and the employees of the company that Tony and I founded knew that what they did directly affects patients. Our company, now with over 35 employees, realizes every day that they have an important role in helping patients.

We did receive FDA approval for ALS patients after long regulatory discussions in 2010. As you will hear shortly that this was also a very difficult personal time for me, but our company goal of always doing what was best for patients has been our underlying concern. So now 6 years after we almost shut down our orphan disease applications to focus on the large market opportunity of ICU, Synapse Biomedical is starting this project. Yes there was a delay, but the diaphragm pacing project survived and we were able to help patients with these orphan diseases around the world.

## The Patients

As surgeons we all like certain surgical procedures more than others. For me a very nice operation is a laparoscopic cholecystectomy for biliary dyskinesia in a patient with a

BMI of 15. But a great operation is helping someone to breathe again when nobody thought it was possible. I have met some patients with disabilities that I could never imagine living with, but their joy in living their life to the fullest is amazing. After we were successful in our first SCI patient, we were contacted by Christopher Reeve (Superman). All I could think about was if I hurt superman my career would be like kryptonite. Did he realize that our first patient required 2 operations?<sup>6</sup> But he told me, “What do I have to lose with a laparoscopic operation? I am a quadriplegic on a ventilator?” Not exactly a huge vote of confidence in me! Ironically, there is the connection between the MSA and its' meeting place at The Grand Hotel, which is same location of one of Christopher Reeve's best movies, “Somewhere in Time.” Christopher Reeve was one of the best patients anybody could ever want, although he died much too young. His operation indirectly lead to my second research project. When I was being interviewed by Katie Curic on a national morning news program, she asked me if diaphragm pacing could help patients with ALS. This stimulated us to consider whether our diaphragm pacer could be used to overcome the loss of upper motor neuron control of the diaphragm in ALS. We began this ALS research after only implanting 2 SCI patients. We utilized what was considered a standard research protocol in 2003 of following patients before and after our therapy of diaphragm pacing. Briefly, we wanted to decrease their decline in pulmonary function. We statistically designed the trial for a set number of patients who were not using noninvasive ventilation (NIV), since NIV use could make the diaphragm weaker. In 2003, only about 30% of ALS patient were using NIV but by the time we finished the trial almost 70% of our subjects were using NIV. This instability or change of clinical practice affected our research plan. Our secondary endpoint was survival and in analyzing our results we had a significant improvement in survival, but in an FDA IDE trial you cannot elevate your secondary endpoint to receive FDA approval. This data analysis was identified in 2008, in the midst of the “unstable” market, where financially we could not increase the number of patients in the trial or change the trial. Instead, we were able to use the secondary endpoint under the FDA orphan device program with a humanitarian device exemption. This became a very tedious and prolonged process. Our lack of manpower and finances delayed the eventual approval.

Throughout this time of doing research on ALS, I realized what a devastating disease it is. ALS affects people in the prime of their life. The disease shows the instability of life. Little did I realize after working on this for years that it would affect my family. My sister was diagnosed with ALS and subsequently died in less than a year. She died in less time than the review process took with the FDA for diaphragm pacing. This was again a very unstable time of my life and in my research. We were in conversation with the FDA, had very little money, and knew that the device worked very well in the right patient. Our pilot patients were doing well. Last year at our meeting, I presented the final report because the last study patient expired when he turned off the diaphragm pacing

system after 6 years—well beyond his expected life expectancy.<sup>4</sup> After treating and becoming friends with ALS patients for years, I am also dealing with my sister's rapid decline. During meetings with the FDA, my partner Tony and our lawyer consultants would mute me on the phone as my frustrations grew with minor revisions that would be required on our labeling and would delay access of diaphragm pacing for patients for months. Because diaphragm pacing was not FDA approved yet, my sister would not have been able to be implanted even if she was a candidate. Finally, we received FDA approval for diaphragm pacing in ALS in 2011—7 months after my sister died.

During this time and after her death, I began evaluating all our diaphragm pacing data from all our trials. We were gaining an increased understanding of what role diaphragm pacing actually had in these patients. The concept that we saw was that diaphragm pacing overcomes the instability of respiration that is affecting ALS patients. As we gained this knowledge, we could see that the design of our initial trial did not have a means of testing how we were able to improve survival. This was the basis of my presentation at this meeting on Monday and the article that will be in our fine journal when you read this presidential address.<sup>7</sup> ALS patients develop an instability of respiration that is based in our brainstem's "breathing center," which involves the lateral medulla and the pre-Botzinger complex. This area of control was not completely described until the 1990s.

Because of simultaneous experience in our spinal cord injured patients receiving diaphragm pacing, we identified a group of patients who were implanted with diaphragm pacing (DP) and who recovered their ability to breath. We showed that these patient also developed an instability of respiration and control of breathing that required tracheostomy mechanical ventilation. After we implanted DP and freed them from the ventilator, they recovered their own control of ventilation and the DP wires were easily pulled out percutaneously.<sup>8</sup> The functional electrical stimulation of DP helped in the neuroplasticity and recovery of respiratory pathways. DP can induce changes in our brainstem and our automatic control of breathing.

My initial research goals of a simple stable bypass of control of diaphragm function with electrodes is actually having much greater effects on the instability of respiratory control. This instability of respiratory control in ALS patients is what we are treating. This has also become the central piece of our present temporary use of DP in the ICU to help decrease the amount of time patients are on ventilators and hopefully decrease the greater than 100,000 tracheostomies done in the United States for failure to wean from ventilators.<sup>9</sup> A pneumonia can affect

the brainstem's control of respiration leading to an acquired central sleep apnea that leads to diaphragm atrophy and conversion to Type IIb muscle fibers of the diaphragm. Could DP treat this by always allowing use of the diaphragm and maintain muscle strength and the good slow twitch Type I muscle fibers? This is one of the goals of all our research now.

So after 17 years on this diaphragm pacing project, I realize there is no such thing as complete stability. There are instabilities in our life, in our academic career, and in our research. But there are also stabilities that we need to depend on. The stability of my wonderful wife Traci who has been with me throughout. The stability of our surgical ethics—always do what is right for the patients. Finally, the stability of this fine organization of the Midwest Surgical Association. We will always present clinically relevant great research with the ability to have our families join us for the meetings.

Thank you for allowing me to be your President.

## References

1. Onders RP. Detection methods of *Helicobacter pylori*: accuracy and costs. *Am Surg* 1997;63:665–8.
2. Onders RP, Aiyar H, Mortimer JT. Characterization of the human diaphragm muscle with respect to the phrenic nerve motor points for diaphragmatic pacing. *Am Surg* 2004;70:241–7.
3. Onders RP, Calin AM, Elmo MJ, et al. Amyotrophic lateral sclerosis: the midwestern surgical experience with diaphragm pacing stimulation system shows that general anesthesia can be safely performed. *Am J Surg* 2009;197:386–90.
4. Onders R, Elmo M, Kaplan C, et al. Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long term follow-up: diaphragm pacing positively affects diaphragm respiration. *Am J Surg* 2014;207:393–7.
5. Onders RP, Ponsky TA, Elmo MJ, et al. First reported experience with intramuscular diaphragm pacing in replacing positive pressure mechanical ventilators in children. *J Pediatr Surg* 2011;46:72–6.
6. Onders RP, Ignagni AI, DeMarco AF, et al. The learning curve of investigational surgery: lessons learned from the first series of laparoscopic diaphragm pacing for chronic ventilator dependence. *Surg Endosc* 2005;19:633–7.
7. Onders R, Elmo MJ, Kaplan C, et al. Identification of unexpected respiratory abnormalities in patients with amyotrophic lateral sclerosis through electromyographic analysis using intramuscular electrodes implanted for therapeutic diaphragmatic pacing. Accepted for *Am J Surgery*. 2014.
8. Posluszny JA, Onders R, Kerwin AJ, et al. Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. *J Trauma Acute Care Surg* 2014;76:303–10.
9. Onders R, Elmo MJ, Kaplan C, et al. Extended use of diaphragm pacing in patients with unilateral or bilateral diaphragm dysfunction: a new therapeutic option. *Surgery* 2014;156:776–84.