Two decades of ongoing progress in lung protective strategies in mechanical ventilation
The Hospital das Clínicas in Sao Paulo, Brazil is a university teaching hospital as well as one of the largest hospitals in South America, serving a population of around 3.5 million inhabitants. The institution has a medical staff of over 600 physicians, and provides comprehensive intensive care facilities for adult, pediatric and transplant patients.

The institution is also well-known for its research, and Dr Marcelo BP Amato of Clínicas has maintained a high global profile in intensive care for over two decades, combining research and bedside practice in his ongoing search for defining and refining lung protective strategies and tools. Critical Care News interviewed Dr Amato to obtain his reflections of the research milestones of the past that led to his study in NEJM 1998, the recent advances in clinical trials and his views on future opportunities in lung protection, as well as his current experience and opinions of the H1N1 virus.

Two decades of ongoing progress in lung protective strategies in mechanical ventilation

Dr Marcelo BP Amato is an internationally known intensive care profile for his many years of research regarding lung protective strategies.
Your dedication to clinical work and research within the areas of mechanical ventilation and pulmonary monitoring has become world famous. What has been your personal driving force for this total commitment?

I think it is the quest for the truth, and the work with post-graduate students, which has been very rewarding. I like this environment where we are trying to really understand what is going on. Let me give an example. I still take care of patients, and you are always learning from them; but once you finish your case, you always have a question in mind “was it enough?” “Could I have done something else or something more?” By doing research, we can address this uncomfortable feeling. It is a natural process: the attempt to solve such questions that come to your mind at the bedside. I am very lucky that the structure here at Clinicas hospital has allowed me to go in that direction. I have seen many researchers around the world, even in well developed countries, and I know it is very unusual that someone can be so focused in research. For instance, nowadays physicians usually have a heavy clinical load, but I can spend 70-80% of my time with research, which is great. This whole environment of research, and being among the post-graduate students, is what I really enjoy, much more than the atmosphere of congresses.

Your unit in Hospital das Clinicas in Sao Paolo has always had an extremely high rate of severely sick patients already upon admission compared to other ICU’s around the world. In several published studies you have reported improvements in outcome and mortality for these patients. As a comparison, how would you estimate the overall numbers for outcome and mortality have changed if you look at all admitted ICU patients for the last 20 years?

Absolutely, just for comparison even today the average percent of patients under mechanical ventilation is 35% in any ICU in general - if you take an average ICU around the world, 35% of patients that day are going to be undergoing mechanical ventilation. In our hospital, this average is close to 50%, which is significantly higher. We have more patients with severe disease and on mechanical ventilation, and among these patients in mechanical ventilation, the average mortality is around 40% and here at our hospital it is close to 50%. Obviously, we all have to improve our care, and this hospital is very heterogeneous, so it means that some units have a better outcome than others.

We don’t have reliable numbers from the past in terms of outcome in absolute terms, but only from the past 2-3 years. But it is absolutely obvious that in the past, a patient with ARDS had a very bad prognosis, but nowadays we see many patients surviving in many units of this hospital and this is related to lung protective strategies.

In your endless endeavor to improve how to apply true protective mechanical ventilation in the ICU you have explored various methods how to accomplish this. What was the starting point for your research concerning lung recruitment procedures?

The starting point was when I was a resident (1987-88), it was very common to see these patients under mechanical ventilation with the ventilator circuits full of blood, and we had to frequently disconnect the patients, remove the blood, and then re-connect. Usually, when this happened, we could anticipate a 100% mortality. My colleagues Dr Carmen Valente and Dr Carlos Carvalho and I realized at that time that depending on what we were doing with mechanical ventilation, the bleeding could be stopped. The first thing we realized was that increasing PEEP was good, and decreasing tidal volume was good. But how did we have this intuition? I think it was related to the fact that we started to read experimental studies on ventilator induced lung injury at that time, for instance the famous Webb and Tierney study in rabbits (1974) was regaining some attention through the works of Dreyfuss (1985) and Kolobow (1987). I was not familiar with Professor Lachmann at that point, I got into contact with him 2 or 3 years after we started our protocol of increased PEEP and decreased tidal volume in these patients. Thus, it was a very nice coincidence that two people in different parts of the world came to the same concept. This was about in 1989-1990. Professor Lachmann came to Brazil in 1992, and it was a good convergence.

This is how it all started: because of
Leptospirosis. Let me tell you something interesting, think about this: imagine that you are taking care of a patient, and that you are changing ventilator parameters, trying to apply a protective lung strategy. The first thing that you see is a drop in oxygenation, provided that you don’t use PEEP. I mean, provided that you just decrease the tidal volume. Imagine this drop in oxygenation and the subsequent increase in carbon dioxide: how could you (or any physician) do this for the first time, at the bedside? It seemed impossible, non-intuitive and causing an immediately bad result. The only reason we could withstand such “apparently” bad effects of hypercapnia was because we could see the immediate stopping of bleeding in patients with Leptospirosis. We could see a positive result in terms of the bleeding process. Then we wanted to check the same procedure in ARDS patients, to see if it provided the same beneficial effect. That is how we started, and that is how we expanded the treatment strategy from patients with Leptospirosis to patients with ARDS. We decided to use the same protective strategies: high PEEP and decreased tidal volumes, which finally became the NEJM study. It is interesting to note that when Prof. Lachmann came to visit us, in 1992, he told us that our permissive hypercapnia strategy was a mistake. He was in agreement with the recruitment strategy, but not with high CO2 levels, which he believed to be bad.

Your landmark study “Effect of a protective ventilation strategy on mortality in acute respiratory distress syndrome” was published in the New England Journal in 1998 and investigated a combination of concepts at that time: reducing tidal volumes and plateau pressure, allowing CO2 to rise preventing overdistention and higher levels of PEEP based on the lower inflection point of the PV curve. This led to a host of other studies, including the ARDSNet trial. Which lung protective ventilation studies published in recent years do you find to be of special interest, and why?

I think that in terms of big changes in our perceptions, I would list experimental studies. I consider that the recent PEEP studies - LOVS, ALVEOLI and Express, the three studies testing high PEEP strategies - form together an important theoretical and critical mass of background data, according to which we can now say that using high PEEP is safe, and eventually can decrease the length of stay in the ICU. I consider these three studies to be very good, as they are now telling us that even if you apply a very rough or simple, non-elaborated strategy of PEEP, you can still have some positive results, like decreasing progressive respiratory failure and length of stay. But obviously, I still believe we can do much more by applying physiology at the bedside. In this regard, these studies are important, but they are not capable of answering the main questions – we still need more studies.

I still believe that the most important studies are the physiological ones, for example the study from Fernando Suarez Sipmann showing us that we can use compliance to titrate PEEP, or the theoretical study of Keith Hickling, when he showed in a mathematical model that we can use compliance to titrate PEEP and also some other experimental studies about ventilator induced lung injury. In humans, we have 2 recent clinical but physiological studies, from Terragni and Grasso, showing that the titration of PEEP based on PEEP/FiO2 tables is evidently suboptimal. However, according to my personal perception, they do not point to an appropriate alternative to that. I also like very much one study from Matthay et al where he shows that decreasing tidal volume further from 6 to 3 ml/kg can cause a further attenuation in the VILI process.

To summarize, in my opinion the most important studies in recent years are the combined multicenter PEEP studies and some of these experimental studies quoted above, which means that we know a little bit more about where we are in terms of lung protective strategies. However, I hope that, in the next few years, we will have even nicer studies about PEEP.

What about the ARDSNet trial?

The first ARDSNet study focusing on low tidal volumes was a very interesting and important study – in fact a relief for us after two years alone, being the only group showing significant effects of protective strategies - but this study only focused on one aspect of our concept of lung protective strategy. The second study from the ARDSNet group, the ALVEOLI study, used a kind of “recruitment” that was a simplified maneuver, with results that were theoretically suboptimal. It is very hard to do recruitment at the bedside. This is why a good PEEP approach at bedside requires better monitoring tools. When I first visited Professor Lachmann in his lab at Rotterdam in 1997, I was convinced, before going there, that we could use lung mechanics to determine the optimal PEEP. But after my visit in Rotterdam, it was obvious to me that we needed better monitoring tools. He had an online blood gas monitoring system, and there, for the first time, I saw electrical impedance tomography, EIT – a very rough prototype that did not work online, and which had terrible images. But offline, the results were amazing: we saw detailed information about regional mechanics which was a revelation to me. I came back to Brazil and I felt I had to construct an EIT device. I was 100% sure that, even having nice tools - like we have today to measure online compliance- we still needed more. It became also obvious that we needed to use the concept of compliance on the descending curve, but regionally, not globally.

Lung recruitment procedures have today been acknowledged by many physicians around the globe to be helpful in preventing injurious pulmonary stress by keeping the lungs open at lowest possible pressures. However, there are still quite a few “disbelievers” and “uninformed clinicians” that need to be recruited to fully extend the clinical use of lung recruitment procedures. In your mind, what have been the most difficult hurdles in establishing lung recruitment as a general practice in the ICU?

We have to create tools to provide a better feedback to physicians. A better monitoring of the physiological effects of recruiting maneuvers. That
must be our target. It is our mission in terms of software for the ventilators, interfaces, and also for the combination of compliance and EIT monitoring.

You realized early in your lung recruitment research that there is a need for an extended real-time pulmonary monitoring at the bedside to be able to see the changing dynamic process that takes place during a lung recruitment procedure. When and why did you start investigating the possibility to use EIT for this purpose?

I realized at my visit in Rotterdam that, during recruitment, you have a complex lung system with many different parts, each one behaving differently. When you analyze conventional mechanics, you have a single output, which is trying to measure and represent this complexity. It is a kind of impossible mission: for this complexity to be described by one single parameter. I had this very strong feeling in Rotterdam that we needed something to track regional changes.

I think the best alternative we have at bedside - at the current time - is to use compliance on the descending curve. But this is still not fully optimal, it is a global parameter with all intrinsic limitations – and we always have room for improvement and development.

Your EIT project has now had several units internationally distributed for research and clinical use. Can you say something about the initial experience from this so far, and share your thoughts on future clinical applications?

I think I have received two important feedbacks from the field – the first has been very positive: whenever someone gets used to perform PEEP titration with EIT, the results are remarkable and looks like we are on the right track. On the other hand, I have received some feedback that we have to improve the EIT interface and the clinical significance of the information that goes with EIT, since it is not easy to interpret the images, at the current stage of the technology. That is the challenge for us: to provide an easier and more user-friendly version.

In general, the feedback has been very good and I can anticipate that we have a big challenge in front of us, which is to transform this technology into a user-friendly technology: a long pathway.

Your contribution to the development of the Open Lung Tool has been extremely valuable. Did it meet your expectations of clinical usefulness? Is there additional functionality you would like to see in this tool in future?

Certainly, in the same way as we have a compliance tool, we need a better recruitment tool. I think we should create a much better tool to use at the bedside. An example: I do recruitment every day, I go to many patients around the world and I always see the same difficulty, which is to perform many operations at the same time during the maneuver. Also, you have to track and check at the same time if nothing is going wrong with hemodynamics, air-leaks or plateau pressures. You have to be sure that the ventilator does not go to backup modes, which is very dangerous: if the backup ventilation is activated during the recruitment phase, you have a high back up tidal volume on top of a high PEEP!

We have to create better recruitment tools where one could program some parameters and operations and then you press GO: and then you just focus on monitoring complications, like bad hemodynamics, excessive pressures, and so on, enabling you to see the whole behavior of the system. We need this type of facility in the ventilator, which we do not yet have at the present time. By making a more user-friendly recruitment maneuver...
process, you would give to the physician more opportunity to just focus on the patient, on the side-effects and also in the physiological benefits during the process. With some smart calculations, you could give information if you were successful or not with your recruitment maneuver – some feedback during your recruitment process and just afterwards.

Automated servo control systems have been implemented in ventilators for decades now. Closed or semi closed loop system for user pre-set ventilator management has also been implemented for dedicated limited functionality in modern ventilators. With currently available technology do you think it would be clinically useful and safe to further develop this type of automated ventilator management in the near future?

I think that this is an extremely slow process. When you think about the old times, when I started to study mechanical ventilation, I was pretty much involved in the process of transitioning from volume-controlled ventilation to pressure-controlled ventilation. This was the precise reason why we created dual modes, called VAPS at that time – volume assured pressure support- or PRVC – pressure regulated volume control – both to be used as a bridge between volume-controlled and pressure-controlled. As soon as we started to work with the bridge, we could see that it was no longer necessary, and I gradually stopped my research in this field. I could envisage that we could jump directly to pressure-support, without fear. Think about the different perspective today: if you take an average patient from any ICU around the world, approximately half of them are under pressure support ventilation. We learned that giving some freedom is not bad.

Now we have a new challenge, which is jumping from Pressure Support to NAVA or PAV, another big transitional step. If you think about NAVA or PAV, they are both a kind of closed loop method, to a certain extent, since they are using as inputs some direct information from the patient. They are not completely controlled by physicians. There are some clinical studies on NAVA and PAV which have shown that we can give this next degree of freedom to patients without too many problems. It is very preliminary, but we are learning that giving a little more freedom can be good, under special circumstances. We are starting to do some research on that here, and in particular, for me, I am interested in a very simple question: if you give a lot of freedom to the patient, will the patient use it in a good way? For example, if you have a patient with acute lung injury, if you give him too much freedom, will he promote too high levels of tidal volume or driving pressures to be applied on himself? We don’t know yet. We are starting some research in this area, and it is a very interesting topic for me. I believe that, under certain conditions, the patient will not choose the right tidal volume. There are some preliminary studies on NAVA that show that the patients do choose a proper physiological level of tidal volume for themselves, but I am a bit skeptical about this point yet. We have to look at different patients and disease categories to check the consistency of such behavior.

In summary, closed-loop is something that has to evolve. Today we are starting to use some neurological input as in NAVA, or some mechanical inputs as in PAV, to feed the closed-loop system. It is likely that EIT will also be used in the future as an input to closed-loop ventilation. Like in a plane, the more inputs you have, the better your controlling system is, and the safer your system is. If you rely on only one parameter, and there is a problem with the reliability of that parameter, the whole system is at risk. I think we need a multiplicity of inputs in future for a reliable closed loop system.

The leap from volume to pressure in past decades was very radical at that time, and I think we are facing the same challenge today, going from pressure to NAVA or PAV. When we jumped from Volume Control to Pressure Support – suddenly the patient could control the flow, which he could not do before. Now, from Pressure Support to NAVA or PAV, suddenly the patient can control pressure coming from the ventilator – it is a big step.

Maybe too big. We do not know yet.

The decades of research you have conducted within lung protective strategies and lung mechanics includes a focus on physiology as well. What general opinions would you like to share in regard to your clinical experience of Neurally Adjusted Ventilatory Assist (NAVA) at the present time?

Besides investigating how much freedom we can give to the patient in acute lung injury, there is another question that I am interested in, related to the fact that some experimental studies have shown that monotonous ventilation can cause problems, and that some variability in tidal volumes or pressures are good for the patient’s system, since they work like a recruitment maneuver. There are some good studies about noise ventilation that I like very much. It seems that noise ventilation is even better than intermittent sighs, for some reason that we don’t understand very well. But maybe if we find a very good pace or repetition, or size for the sighs, it could be as good as noise ventilation. But the fact is that noise ventilation, with a random variation of tidal volumes, seems to be a good recruiting maneuver. I have seen patients that we have recruited, in which we found the optimum PEEP, but in which you could clearly see some slow derecruitment over time. I feel that if we keep such patients in a mode in which we have a little more variability, like NAVA or PAV, maybe we could maintain the recruitment in a more efficient way. This is a hypothesis, but I would like to investigate this and I have seen some cases that have called my attention into this direction. There is a theoretical trade off though: more variability also means a looser control over the VILI process. There are plenty of evidences showing that spontaneous ventilation can be as deleterious, or even more deleterious than controlled ventilation in terms of VILI production. Everything depends on the driving pressure applied on the respiratory system. It does not matter if it comes from the diaphragm or from the ventilator.
As a summary of our discussion, can you point out some historically important landmarks and milestones which in your mind constitute the basis for the development of protective mechanical ventilation and lung recruitment strategies that are in clinical use today?

As I mentioned in some aspects earlier, I think in addition to our early research and experimental studies on VILI, we must start with Professor Lachmann and his open lung concept; the initial accumulated experience ofGattinoni, when he was promoting the venous-venous CO₂ removal and giving the lungs some rest; the concept of permissive hypercapnia promoted by Hickling for the first time in ARDS patients; Professor Hedenstierna and his concepts of atelectasis - early during general anesthesia and during high FIO₂ use (he was calling attention to the fact that atelectasis was much more prevalent than we initially thought, even in patients with normal lungs). I would like also to quote the recent studies from Kavanagh in Canada showing that hypercapnia can be protective in terms of lung injury - I think this is a very important development in recent years. And obviously, the three clinical studies that showed that protective ventilation improves survival: the low tidal-volume ARDSNet study, our study at the NEJM and the recent Jesus Villar paper. These are particularly important ones, as they create a bulk of evidence that we should really pay attention to protective strategies. I would like also to not forget the tremendous evidence created by experimental studies, like Dreyfuss, Marini, Slutsky, Taskar, Tsuno, Kolobow and others. I would conclude with the PEEP studies I mentioned earlier, as we can now say that high PEEP is not damaging, which is a very important result.

Your expertise and know-how of the frontier within the area of advanced mechanical ventilation and pulmonary monitoring is well known on a worldwide basis. What quantum leap in technology would be required in order to significantly improve efficacy and safety in ventilator management for the future compared to what is available today?

I strongly believe in EIT, I strongly believe in multiple inputs to improve safety, because then you can have closed loop systems. Without multiple inputs, it is hard to have closed loops, because you cannot rely on one single parameter; if it fails you are in big trouble. I think there is lots of work to do with the interfaces of ventilators. I have participated in the development of interfaces of some ventilator products and I have seen the challenges the manufacturers have with some regulatory agencies. They are always a conservative force in this process, as the regulatory authorities try to keep the interface at the very simple level, but we have to push hard in the opposite direction. It is like the invention of the joystick in planes – we all know that this is a remarkable invention, especially for complex missions and difficult targets for the pilots. I think we have to create something similar for the ventilator – a tool that makes the whole mission much more simplified and intuitive. This is a challenge, but I strongly believe in that.

In terms of specific tools that can be improved, one is EIT, that should be linked to the ventilator – this has been my dream for many years. I would like to integrate it into a ventilator. I think we should improve the use of capnography – it is still very complex. The technology per se is simple but the way you give information to the physician is still very complex – we should have a concept that would make the physician more comfortable with the results. For example, we should use capnography during PEEP titration and in a smarter way to make it easier for the physician to understand what is going on. I believe that EIT will be used one day to analyze the perfusion of the lung, and this is something I think will add information at bedside, in terms of hemodynamics and lung perfusion necessary to optimize V/Q match at the bedside.

I think some technologies to have online blood gas analysis are needed urgently. The old Paratrend project was very valuable and I learned so much from that. Obviously, we are evolving to non-invasive technologies to do measurements of blood gases in real time. I have also some insights that we need better substances to infuse into the lung that are better than surfactant.
Surfactants theoretically should work, and the neonatologists love it. But for adult patients we need something better. I am starting to understand about what is problematic about the surfactant trials we have seen, a hypothesis about what has gone wrong, and I see the need for a new substance to fill into the lung, promoting better air ventilation. Lots of work to do, and we need all of these monitoring tools to get more data.

Lastly, the subject in everyone’s mind in intensive care: the H1N1 virus – what was your experience during the past year, and what are your concerns and preparations for the coming new flu season in Brazil?

I faced the worst cases of acute respiratory failure that I have ever seen in my life with the H1N1 virus in the past year. During the peak of the flu season, I received 5-10 calls a week from all over South America, asking me to recommend what to do or what not to do. ICU physicians became lost in treating these patients, since the reaction of the blood gas to the pressures applied with the ventilator, were completely disassociated in these patients. For example, if you do a recruitment maneuver, you usually don’t expect too much improvement in oxygenation during the maneuver, but you can expect some improvement afterwards. However, with these viral patients – there was no response like this in most patients. If you increase PEEP in these patients, oxygenation frequently drops. Sometimes if you decrease PEEP, oxygenation improves. So weird things are happening frequently in the H1N1 patients. I realized that this behavior is caused by the fact that this H1N1 disease is very heterogeneous, associated to some poor hypoxic pulmonary vasoconstriction. You may have areas of the lungs of these patients that are completely preserved, and areas that are totally damaged. This is not common in ARDS, where you have a more diffuse disease. When you have a more impaired hypoxic vasoconstriction in this disease, any degree of pressure you put within the normal areas is going to divert blood flow to the bad areas: if you increase pressures, you will have more shunt. Then the physicians get lost in the vicious cycle. I monitored some of the patients with EIT and CT, and I realized that in some respects these patients are like any other patients – they recruit, and if you decrease PEEP they collapse. But the output in terms of blood gas is a disaster, and this is what is causing confusion to the physicians. When you get lost with PEEP tidal volumes and CO2, it is hard to manipulate these patients at the bedside. We spoke about the topic of improved monitoring tools. Here at Hospital das Clinicas we are advising the clinicians to only focus on lung mechanics for these patients, and to forget blood gases in treating these patients.

As an interesting episode, I was called in to give advice for a patient and the patient had been ventilated with a PEEP of 24 cm H2O. It was the first time in my life that I came to the conclusion that I had to reduce dramatically the PEEP based on his mechanics and EIT data – this patient only needed 16 cm H2O. It was an interesting experience for me.

I am starting an experimental study with the support of Maquet to study ECMO with the Cardiohelp device. I believe that, in the case of future H1N1 patients, we will need to keep these patients alive for one month, to allow them to recover from their tissue injury. If you look at the lung tissue of these patients, it is completely infested by the virus. It takes a long time to recover, the vessels are destroyed, the bronchi are destroyed, and it is a big mess. In the most severe cases, you have to keep the patient alive, not causing more harm with the ventilator. And in these specific cases, ECMO is needed. This is how we are preparing ourselves for the next flu season with this device.

I had experience with ECMO during the 90s and I surrendered, due to the bleeding the technology caused in unstable patients. For me, it is clear that the least invasive and the lower the flow rate (blood flow entering the external oxygenator), the better for the patient. This is why I am doing some research to establish the lowest level of blood flow that I can induce with this device to have a reasonable result. I am also interested in using this Cardiohelp device together with some ultra-filtration in series, which could eventually enhance CO2 removal: with less blood flow you could further improve CO2 removal. I am interested in looking at these matters in preparation for the next H1N1 flu season, which I am very concerned about. If it is the same or even less than last year, we can perhaps save many more patients with this system. We lost many of these patients due to progressive respiratory failure in this last year. The Cardiohelp device may give us time to keep the patient alive to resolve these problems.

In summary regarding the H1N1 virus, my advice is that if the H1N1 patients are on a ventilator; focus on lung mechanics and not on blood gases. In the most severe cases, consider ECMO as a way to gain time and keep the patients alive to recover from respiratory failure.

Biography

Dr Marcelo BP Amato received his initial medical degree in 1985 from Faculdade de Medicina da Universidade de Sao Paulo. After his residency in internal medicine and intensive care, Dr Amato specialized for two years in Pneumology and Intensive Care Medicine at the Pulmonary Division of Hospital das Clinicas in Sao Paulo. He obtained his doctoral post-graduation in 1996. Dr Amato presented his thesis and attained the level of Professorship at the University of Sao Paulo, Pulmonary Department in 2008.

Dr Amato has conducted extensive research over the past two decades, resulting in publication of over 53 original articles in international peer-reviewed journals, and has also obtained several scientific awards. Dr Marcelo Amato is a globally known profile as lecturer in international intensive care meetings.
References


