First Regional Workshop „CCSVI and Multiple Sclerosis“ – April 24, 2010

Sassari, Sardinia c/o Hotel „Il Vialetto“ - Room „Piazza d’Italia“

Youtube in 14 parts (engl subs): http://www.youtube.com/watch?v=y9fn3tbDj1s

Translation source:
http://www.facebook.com/note.php?note_id=388987558015
http://www.facebook.com/note.php?note_id=391031593015

Speakers:

Prof. Paolo Zamboni (University of Ferrara)
CCSVI in Multiple Sclerosis

Roberto Galeotti (University of Ferrara)
Liberation Treatment

Fabrizio Salvi (Bellaria Hospital, Bologna)
Neurological aspects after the Liberation treatment

Moderator:

Gian Tomaso Marchio (President of the non profit Sa.S.M.)

PART ONE

Welcome and presentation by President Sa.SM GianTomaso Marchio.

President:

I am the President of the SASM, Sardinian Multiple Sclerosis non profit association. I would like to thank the Movement CCSVI Sardinia, SASM, the Internet Movement and Facebook. We decided to present this meeting worldwide using the Internet, from this moment forward. First of all, I would like to thank all of you and I thank the MS patients that are present.

I ask you not to give up, to remain united and to be as strong as we are at this moment. We have already demonstrated our strength.

I want to thank Professor and Dr. Flumene and her husband Professor Trignano for allowing me to contact Paolo Zamboni and bring him here, I want to thank Stefania Calledda and Matteo Pisanu that, with their movement, have raised awareness and got people involved not only in the region of Sardinia, I want to thank the Board of SaSM, all volunteers that have been working tirelessly for months with courage and without asking anything to others.

I left Prof. Zamboni, Dr. Salvi and Dr. Galeotti for the end part of my message, so I can leave plenty of room for all of your questions and I would like to thank him with your warm applause because he came here to Sardinia for all of us.

I think that the person you have interest in is here on my right.

Please, professor.

Dr. Zamboni:

While we are fixing the computer I would like to say two things to you all.

First of all, I would like to say that a group is present here today, a multidisciplinary team, and this is the first part of my message. This is a new way of tackling the disease, to explore new possibilities, which we

will discuss today, it's about opening new frontiers, and doing it while we are being able to be at the service of people coming out of the ranks of the individual disciplines. We are in place to create team work, so we can say that the central figure is the neurologist because multiple sclerosis is a complex neurological disease, it's a lifelong disease and therefore we must always have a main, central doctor just like we need a conductor in an orchestra. There are also the vascular and radiological aspects that are at part of the program. If you are saying, "I will go down, I'll go up, I'll let others do, I will do"…well, this will fail!

This is not a good attitude. A good attitude is to encourage people to talk and cooperate together, this is the first thing because otherwise the patient remains without a reference, so the solution is to communicate, to work together and it's not good to take different roads. It's like saying that I read about CCSVI and now I take this information and go to India or to Japan, but no! You don't have to go anywhere, because here in Sardinia, for example, I worked in an angiogram room and I can say that in Sassari, that I know of (and I think there is another one just as good in the city of Cagliari) there are all the equipment and all the skills that are required to do a good job, no need to go anywhere else.

What you have to understand is that it takes time for people to speak to each other, to take a model of what we created. We are working with Roberto Galeotti and Doctor Salvi, Salvi is the person that follows our patients because he is the director of a Multiple Sclerosis Center and he has been following MS patients for the past twenty-five years and therefore he has specific experience in this field and he is following them the best way while we add our expertise in diagnostic, in the vascular field, in research because we must go forward there too. But this is just the first step, we must urge everyone so then people can talk to each other.

Dr. Galeotti is an interventional radiologist and he is a part of the group that we created, a group that has our ideas and our hopes and the message that I would like to give you here is that this team must be formed in the right territory, the right area. For example, I think that two areas in Sardinia will be good, one in the north and one in the south, areas in which there will be a willingness to understand and to study. This will allow patients to have a well-organized and integrated path where professionals will be willing to work together with you. This is the message I give you at this moment and I want you to stay together, not to create divisions, but to create synergies because the synergies are those that will allow us to move forward.

So now I'll tell you where we are, what Cerebrospinal Venous Insufficiency is, how we can see it and what we can do about it and, I underline this, I am interested in this for the pure love of science and truth, and I have no conflict of interest or want to have any of them, and there are a very few people that can say this.

The first message that I would like to say to you is that the blood must leave the brain and the human body is perfectly built to facilitate this exit, because we don't spend most of the time lying in bed (and only a few lucky people get to spend eight hours in bed) we spend about two thirds of our lives standing. So it's like liquid that must come out from a higher area and that must be sent down to a lower area.

The highest area is the brain, where the arteries carry oxygen to through the heart. Once the oxygen was given to the brain, the exit with all catabolites must go back to the starting point, which is the heart. Naturally, through the veins, this is very easy because, as a gravitational phenomenon, the head is higher than the heart, as if you were on the windowsill and you through some water down, the water would go on the pavement of the road.

There is a device that is made to returning the blood back and is very easy to make it go back because there is a physical reason for this. There is the force of gravity that allows this to happen and it so obvious that probably no one in the field of medicine thought that this device could have a problem. It is something guaranteed by the force of gravity and no one thought that it might have problems.

Now you can all see this on the screen: the blue thing that you see is the carotid artery that is pulsing (this is the vessel that carries oxygen from the heart) the other side you see the red veins that discharge (which is the jugular vein in the neck) the blood into the heart. At one point we began to see that people had the same color in both the carotid artery and the jugular for a long time…although we were throwing the water out of the window sill, it was returning into the house back to us.

This is a physical phenomenon that is so easily demonstrated and that didn't have an explanation so we decided to give it one because it's not normal that you look out the window one morning and throw the water outside the window sill and the water returns into your house! The water should fall to the ground! This is

something undeniable, undeniable to everyone. A doctor that is presented with such a phenomenon must be motivated to understand the reason why this happens, he can't pretend not to see, he should give an explanation, because this is not normal.

These aspects are very simple, they are morphological and reproducible. Before I came here for you, and before writing articles in neurology magazines, in vascular medicine and surgery, I traveled and I saw these things in the United States, in central Europe, I taught people that live in the Middle East and in other countries. They sent me their films, and many sent me things that are associated with multiple sclerosis. They might not be seen in 100% of cases, but in most cases, it is seen in more than half of the MS patients. This means that one of these aspects represents many faces of the disease called multiple sclerosis, which is a multifactorial disease, so this could be one of the factors that we can be working on. We have to understand who has CCSVI, so there is a lot work to do because we do not know this, but we have the methods to find this out.

We can see these things thanks to the interventional radiologist, who will then explain how to do it with a catheter sailing through our veins. It takes a skilled navigator to do this and you can see all of these thin passages where you see the painted arrows. This however is an angiographic examination, you arrive at a second level and it is minimally invasive. This will have to be discussed of course and it will be discussed by who will do this test, but it is indisputable that those who have certain criteria, accessing this type of examination is more likely to see these stenosis.

The stenosis are narrowing. When there are these strictures, we have a system that draws blood to the heart, which is the vascular pump. You can see that, in normal cases, it draws blood from the brain, but when we have this kind of situation, the system that works so well for reasons of gravity or because we have the breath that draws blood to the heart, then we angiographic shows us very different pictures.

Then, in medicine, angiography with selective catheter is the greatest proof that no doctor cannot accept, not a neurologist, not a cardiologist, dermatologist!

Every doctor can see the difference that you see behind my shoulders. You can see the normal jugular (the first one) that is the tube that goes straight and that has to bring the blood from the brain to the heart and you can compare it to the disasters that you see in the other two angiography, where you see the arrows indicate areas with constrictions, where you can see that nature has tried to correct it, has built many bypass, just like a skilled surgeon would do, so many small vessels try to carry the blood through the heart anyway.

This makes the disease very slow to appear, to develop and to evolve, because the blood continues to follow its destiny, but it does it with less efficiency.

The flow of all those little veins that you see here is wonderful, because can still carry the blood, but it does it in unsufficient way: it takes more time than we would want it to take or would like it to take so it can clean the central nervous system, but clean it from what?

Cleans it from toxins, catabolites, carbon dioxide, but also from infections and infectious toxins. That's because the toxins are most harmful infectious. Caused by an opportunistic infection, some people may only get a fever while other people that have such problems become more problematic, perhaps these problems occur in conjunction with another pathology because the cleaning, the drainage is compressed and it is insufficient.

PART TWO

Dr. Zamboni:

We are starting to have some data. You see, we started in our small district of Bologna and Ferrara. Some of you might think that they are late, some are afraid for being late, but no, we are moving really fast!

The publications in the journals of neurology, in which we said that, by combining the doppler angiography, we found the venous insufficiency in 100% of our patients with multiple sclerosis, is not a surprise because at the University Hospital of Ferrara in our computer system, if a person goes to Dr. Galeotti, you can find one case, then another one, then all of the 100% of the people. These are public documents. Our hospital is a public university and you may say "well, I wonder if they are telling the truth".

But what are you saying?? But come on! There is nothing to do, all the people have Chronic Cerebrospinal Venous Insufficiency. There is not hidden data, everything is public!

In the States there is a very important group at the University of Buffalo which is very important for multiple sclerosis. In fact, twenty years ago, Jacobs, a neurologist that worked there, was the person that found the first treatment for this disease. He found the Interferon and remember that before then, there was nothing, He had the great merit to develop something that alliened with that was most identify by the scientific world at the time. And it's not like we are not going to treat this aspect of the disease any more. We simply found another aspect: this is a multifactorial disease. The more we find out about it and the more we can act.

I have found something very interesting that the institute that proposed the interferon and had the curiosity to see that, aside for the immunomodulators factor, there is also a vascular one and neurologists have always had the idea that there is this vascular aspect, so I think they are ready to understand this.

And they have done the first epidemiological study where they found from 56% to 62% and they found some borderline patients and they have tried doing their best, but only with the doppler, not the angiography and they found 62% of their patients. But 62% of this population is very different from what we were about to find with Salvi and Galeotti because they include pediatric cases that I didn't have. They had CSI, which is the Isolated Syndrome that I didn't have in my study. But if we go to see in the mixed population of people with Relapsing Remitting and with Secondary Progressive, that was at the base of our study, they have more than 80% of the patients that were found with the doppler.

They have different data from us in the healthy control group but why did they find one case of CCSVI in five healthy controls? But be careful here: who were our healthy controls?

They were students, people that worked at the hospital, whoever walked by, we were taking them right away, we took them in, gave them the exam and we didn't find the same data. The population of the Buffalo group were family members that were there with the MS patients. It was in a son or a brother that the anomaly was found so they had a control group quite different from ours. Aside from the differences in the data, this study is extremely important because it tells us that there is a huge slice of the population in which no one knew that multiple sclerosis is associated with veins that are malfunctioning. And this is an important thing.

But the most important part is that the studies are now spreading like wildfire on our planet. In the Middle East, where there is a difference in latitude and there is a diverse population, ethnicity and hence genetic background of the Arabs, there was a study that was published last month where 84% of them had multiple sclerosis and chronic venous insufficiency cerebrospinal and there was a 0% in controls.

East-Central Europe gives us 90% of the population which includes Swiss, Germans, Polish and Slovaks. In this ethnic group we have different environmental exposures and many other things that we can put in there and many that we don't know…however 90% of these people had Chronic Cerebrospinal Venous Insufficiency.

When we came out with the study, many neurologists attempted a "technological shortcut" and they started using MRV.

The MRV is nothing other than a magnetic resonance venography and it has the advantage to be non invasive, but doesn't allow us to see these things and sometimes it makes you see them even if they are not there. The panel that I am showing you (the panel C seems to be the easiest for you) where I put an arrow, you can see a stenosis, but there really isn't one. In fact, the jugular had a pretty good flow. This patient underwent the selective venography and he had nothing. What does this mean?

It's telling us that the diagnostic accuracy of the MRI is very poor in both false positives, just like this one, and false negative, just like in this case. Here there isn't a stenosis, for example, so it's very dangerous because if you want to do the angioplasty with Dr. Galeotti or whoever else does the exam for him, he will not find anything, so this test is not recommended. Do not use this method then!

My e-mail inbox is overflowing with messages that I receive from people that believe that I am listening to all of their things all day long and you send me thousands of negative MRV that, what can I tell you? That is not an appropriate test and we never said that it should be done. And this is the proof of that. Luckily, there

is a study that found the gold standard, which is the catheter angiography.The MRV doesn't do anything. So let's try not to forget: the best exams are the ecodoppler done with the right protocol and the selective angiography.

PART FOUR

In this group of people, there is also a neurologist, but you have to find it. I was asked if CCSVI, and you can imagine who asked, is causing changes in the encephalon and so we started a very nice study. Why do I say it was very nice? Well, because there were 24 people, eight of them were healthy and they had to spend hours doing pretty much everything! They understood what type of investigations you are subjected to because of the disease. Sixteen patients had MS, 8 Italians and 8 Americans, but the beauty of this story is that these people were like "twins" and they didn't even know each other. So, with the computer, when the study was better defined by the consortium, Buffalo chose 9,000 people with MS and they chose 8 of them that were born, more or less, on the same day, that had the same type of work, that could have been exposed to the same environmental causes, and have found eight "twins" who did not know the others and they have been studied for a year. These people have made a contribution to science. When they went to check the other "twins" they discovered that nothing had happened.

And they were able to find very precious data, even if the number is quite small.

Now, I'll show you something. This is called magnetic resonance venography and is done with a system called SWI. This system doesn't requires the use of a contrast, but can see the veins where there is no flowing oxygen in the blood, so we can say that the machine has the ability to see the blood without oxygen. And what we found is that the sicker you are, the harder it is to see the cerebral veins. I mean that the blood no longer flows into them. We don't understand why, but we realized that when this happens, the jugular veins and the azygous veins that can be closed and these are veins that are located outside the skull and that determines the venous insufficiency.

Another thing that we found is that when you are closed, there is an accumulation of iron. This is seen with a particular MRI, not a normal MRI. Something tells me that, in the future, the MRI will all be done this way. What you can see right now is a region called Pulvinar Thalamus, which is the deepest part where the venous blood is very difficult to release. The more you see the yellow color, the more iron there is. The iron is in the areas that you see in the healthy control, but you can see how many more yellow spots there are in the person of the same age and that is affected by Chronic Cerebrospinal Venous Insufficiency.

Another thing that we found is that when you are "closed" in the veins that are outside the brain, the cerebrospinal fluid doesn't move, it flows slower and it stops because it's not absorbed since circulation is slower. And this is not a secondary aspect, in my opinion if you think that all the pathological aspects that we know from the biological point of view, comes from a lumbar puncture that is made to analyze the cerebrospinal fluid. This is the condition that allows the researcher and physician neurologist to be aware of the immune and the infectious phenomena and of many others because the spinal fluid shows what they are looking for.

It is important to understand that, if I am closed outside of these veins, the fluid doesn't have a replacement. The fluid is like a refrigerating system, a protection system, which circulates around your brain and the spinal cord and it's really interesting to see that the lack of circulation and lack of reabsorption may create differences in biological diversity that we are aware of, but that we need to work on.

In my opinion this is extremely important. At some point we had done a resonance perfusion. This is not a MRI that is available in all centers but it is possible to have in some Italian regions. This resonance shows you that the more closed you are, the more stasis you have, the lower the cerebral blood flow, the longer the time in transit. Why is this? Because those famous little open paths instead of using the main street, do carry the blood but they do it slower. It would be like me going to Cagliari not passing by the Carlo Felice street, but instead going through Nuoro or taking paths through flocks of sheep. Of course, I am going to get to Cagliari, but when will I? I am going to get there, but not in two hours.

These are the actions that we have taken to see if opening these veins made sense and this is the reason why it was done. Dr. Galeotti will explain this to you quite well. This was done is a conservative and less

risky way because we are still at the stage where we need to understand if this type of treatment makes sense, with who and when, etc.

The first study that we have done is a study that showed us very interesting things so we were the first group to see the stenosis and in the same moment that I saw them, after requesting permission to the ethics committee, I was able to open them. So we had a reduction in the relapses in people that had Relapsing Remitting. The relapses were less than the number of annual recurrences of previous years.

What is very important in my opinion and that no drug can give you, is the improvement in quality of life and improvements that evaluate the efficiency of the legs and arms motor function and also cognitive ability, and above all a function called working memory, which is the recent memory, which is the most useful function.

We had a significantly reduced number of active lesions, which are the ones that light up with the gadolinium in an MRI.

The rate of restenosis with this treatment is quite high, so we have to find something better and we will work on it.

47% of our patients had to liberated again to have better results that would last over time. It's better to have the stenosis in the azygos veins because 96% of the patients didn't have to be touched again. We only checked them.

What I love the most about the study is that it shows us an indisputable fact about the safety. The simple angioplasty is a safe treatment that, in capable hands, gave no complications.

This does not mean it's simple, it means that it is safe in capable hands.

PART FIVE

Dr. Zamboni:

But this study was done while I was doing a diagnostic measure, and therefore is a study that has limitations, even if he has all these good preliminary data that will be explored. So you have to understand that it's ok if the neurologist that is evaluating the study says "yes but we have to work on it" but it is not right to say" It's not true! ". But it is fair for him to say that we have to work on it because this study, scientifically, has some restrictions, and I am one of those who conceived it and that is saying this.

The limitations are that all our patients weren't assessed blind. The physiatrist, the neurologist and me who visited them, were perfectly aware that these patients had multiple sclerosis, so it was a study in which the meter measured with objectivity required by science because we all knew about this.

I must say also say that, on the other hand, if a person was walking 100 meters in 6 minutes and then he walks 600 meters, no one can change the fact that the person walked more but from a scientific perspective it is not expected to do it this way, even if the actual differences, you have seen, were very important. It wasn't the correct scientific way to do it, so now we will do the study with these criteria.

Then, our MRI protocol on people where one person lived in Ancona, one lived in Padova, one lived in Bologna, were going to receive the test with different tools. In this case, the data was blinded because the neuroradiologist did not know we had done the liberation, but even this can be challenged as scientific methodology, not as a result, but we say that we absolutely have to work to get stronger confirmation, more extended, more secure about the effects of the treatment.

In the group that you saw before, of the three families and the eight twins, at one point they said "ok, now that you found the stenosis, do the liberation". And we did this with criteria: it was a small study and I can't make you see all the results but we did it and, in a couple of months, this study will give us independent statistical results, and from there we will have additional important data for you.

PART SIX

Dr. Zamboni

In this trial, eight were liberated, the other ones weren't liberated for six months. The other half made themselves available to wait and it is very important to be available at this stage because if you are willing to help, we can understand things faster. If everyone thinks for himself and believes to be clever and goes when he wants to go, the neurologist will stop the work and nothing will get done! Then, if something happens where do you go?

Now, let's follow the example of these young people. The eight that were chosen randomly got liberated right away. The other ones played the game with the dice because for six months they weren't operated and we had the opportunity of measuring everything that was changing and that I showed you, even the advanced in their brain, when the blood flows normally and when it doesn't. They have provided valuable data, and these valuable data, I am sure, will convince the neurologist to work with the radiologist and with the expert in vascular diseases, with what you need.

Of course, I have never seen all these parameters because the measurements are blinded, are taken with code numbers and they are now in the hands of an indipendent statistician that is going to evaluate them and will give them out so that there will be no doubt and no shadow on our work.

What I can tell you is that we had one American girl who, for emotional reasons, felt like fainting and it was probably because we brought a handsome surgeon to see how she was feeling but everything was safe. Even this study showed that the simple angioplasty, in capable hands, is a safe treatment. But it doesn't make you lose anything, you don't have any foreign body inside of you, your veins are simply dilated and they are still the same veins, they can close again and they can be redilated. There is nothing that is compromised, and this is a very important aspect when you access something that was not there before and that wasn't available.

This must be a tool that we can use together with all the ones that we already have and it has to be a safe one. We can't be like cowboys and try new things on other people's skins before it was experimented safely, so I insisted that, if the treatment has to be done, they should be done by a group that have a program, with their proper neurologist and with a conservative regimen.

Here it is, you can see everyone that are greeting you because, by myself, I woudn't have done anything. This is the main group that I worked with and there are more people that I am not showing here. At the end, I am always the one that gets the compliments, but without them, I wouldn't have been able to do anything, so please, I ask you to accept the appreciation of all the people that worked with me.

I believe that I am here to aswer the many questions that you have and I believe that many questions you have inside of you can also be answered by Galeotti and Salvi. I suggest you listen to the other reports and then we will answer to all of your questions. I would listen to other things too probably because there are many aspects that I have not touched that are of relevance and therefore they will have the opportunity to respond to other questions. Then, if we weren't clear, we will be here and we will have a discussion together. Well, now here is Galeotti.

Dr. Galeotti:

Thanks. Good morning. As you have heard, I am a radiologist, not a neuro radiologist, that is called interventional radiologist, but a vascular interventional radiologist. To approach this type of therapy program with prof. Zamboni, I didn't have to learn anything new in the sense that there is a branch called venous interventional radiology.

Interventional radiology is a discipline in which the radiologist, who looks inside the human body using x-ray machines, can make diagnosis, can see where the diseases are and it can act for certain things that can be solved in this manner.

The interventional radiologist enters the human body through small punctures, which enter the venous system, using the femoral vein catheters and with them goes inside and moves around to treat certain medical conditions.

In the venous field there are two types of treatment, one that closes the vein; having a young audience over here that can normally carry the treatment of vericocele. This is the kind where, in medicine, veins can

be sacrificed. And then there is the angioplasty. Angioplasty means dilating a vein using a balloon. This type of angioplasty is similar to coronary angioplasty in which the arteries are dilated and in this case, we speak of the arterial system that connects the heart and is of great importance.

What you see now is a gonadal vein that gives problems in the vericocele and this has been simply treated by closing the vein of spirals, see? If we close the vein, the blood will find a better way of reflux. In venous angioplasty there isn't a lot of information and directions like we have in the arterial field. The classic example is given to us by people that are suffering of renal failure and they have to do dialysis, the so-called limb arteriovenous fistula in the arms where the blood passes from the arteries to veins.

These veins may experience stenosis. This vein that you see is very substantial and when it arrives in the chest, in the vena cava, it's restricted. The end result is what you see. The arm is swollen, and this is an arm that can no longer be used because it cannot withstand the flow of dialysis and it creates problems.

Here in this case, as I said, we arrive at this restriction by using small puntures with a balloon catheter.

Here there are the balloons, they are little tubes that have the expandable part outside.

Here you can see that it expands causing an opening of the restriction. It gets there in a very precise and controlled manner and this is the end result, there is no longer the restriction.

PART SEVEN

Galeotti

Here you see that the arm is not swollen any more and the person can be on dialysis again.

I hope I won't get too technical, but now I will show you another vein condition. This is the inferior vena cava, a vein in the abdomen of a patient affected by cancer. You can see how it's restricted and it has collateral circulation, as you see on this side. We can solve the problem with the use of a balloon and by placing a stent that is like a wire mesh and, as you see there is no longer the restriction and we were able to solve the problem with a minimally invasive procedure. This procedure is not experimental or innovative, there is nothing new in what we do, and now we can apply this procedure, this therapeutic approach, to the disease that has been described by Professor Zamboni and that is called CCSVI, Chronic Cerebrospinal Venous Insufficiency.

As you have seen this is characterized by the fact that the veins that carry blood away from the spine and the brain are blocked, they have blocked segments.

In vascular surgery, our job is to help diagnose the problem, so we have to use the catheter and draw the veins and confirmed the stenosis and, as you just saw, through the use of baloons, we can also resolve them. This is a pattern that makes you see that these little blue tubes are the cerebral veins that go to all the main channels of output. The venous return of the brain is represented by the internal jugular vein, and partly by the vertebral system.

I would say that the internal jugular vein is the main drainage when we're lying down while when are standing, much of the blood takes the path through the veins that are called condylar and that are found behind the jaw, the vertebral system uses a venous cerebrospinal system and the main ways of the runoff are represented by the jugular and the vertebral veins.

The venous system of the spinal cord is more complicated. Here we see a vertebra, a cutaway, and see inside the medullary channel, you see this groove where inside there is the bone marrow, there is a very complicated network of veins that, seen in a front projection from the sacral to the cervical level, via the thoracic and lumbar area, they are all connected to each other. It looks like a little ladder. They are very important veins that reach the main circle to get to the heart, through the extra spinal pathways that are represented at the individual levels of the so-called sacral veins, the ascending lumbar veins, the intercostal veins and the vertebral veins.

In a vision that seems generally complicated, the veins that are the intercostal veins, the lumbar veins and sacral veins, represent the roots of a main and strange, curved vein that is called azygos, a vein that looks like the handle of an umbrella, very little known in medicine. We can say that it's very little used in any medical

discipline and there is little news about it in radiology, but we know that its function is to collects all of this complex venous system and it brings it with this arch, as you can see, to the level of the superior vena cava.

So, in this type of venous disease that has been described as CCSVI, we have to look and possibly going to solve the blocks that have developed inside the jugular veins and in the arch of the azygos vein, which is the end point of the route of the venous drainage of the spinal veins.

These are veins that can, quite frequently, for anatomical reasons, be compressed: the renal vein by an artery called mesenteric and the iliac vein by the arterial iliac.

In some patients these veins may be crushed and the blood that cannot longer circulate well any more, deviates and goes to the spinal level and rises to the level of the lumbar vein, goes back in the azygos vein and then goes into the left renal vein. This vein is called lumbar-azygos and it can go back to the level of the azygous vein.

These veins can cause problems too in the spinal venous system because there can be a hampered exit and a potential overload, an increase in carriage for reasons that are not normal.

For this reason, we do the procedure and we try to watch all these complex clusters that you see there in the list and, luckily, we manage it with one single access is the femoral vein of the left vein of the left groin. The patient is awake and under local anesthesia. It is a routine that we do for most of our procedures, it is not a painful and the local anesthesia allows us to make the puncture, to enter into this femoral vein, put this small catheter in and from this point we go up with our catheters and we look at all the systems that I talked to you about.

This is the normal iliac vein and this is the study of the lumbar plexus, a very complicated network of veins, which represents the venous system of the lower spine and is the root of the azygos vein.

After this you see the left renal vein, we see that our small catheter is inside, here, and you can see that it’s very thin. We then inject the contrast that has to leave the renal vein and go straight to the vena cava.

This is what I told you before: it’s the azygous vein, that sort of umbrella handle that represents the endpoint of the venous course of the venous cord.

This is what we thought and what we were able to verify. This is its normal appearance because there is no document in the previous scientific literature that tell us how it was. No one had ever thought of studying it because there was no clinical indication to do so.

The normal appearance (we were helped by books and from normal human anatomy) is a vein that is about eight millimeters in diameter, it’s constant and drains into the vena cava, which is the main one that has valves that are more or less developed internally. These are always the common aspects.

The azygous vein is anastomosed, connected with the left renal vein. You can see the study below of the left renal vein, which has this little valve that allows the passage of blood coming down from the azygos vein in renal vein, but not vice versa. When this renal vein is not functioning properly, this valve is forced and causes this overhead.

Then, we go back up to the jugular veins, which we have seen as the main passage of venous blood to the brain, at least in a patient that was in the supine position. Then we saw how well we can study them. In the study of the eco doppler with the first images that the professor showed you, you can see the valves. It shows you how are these valves and how they work and this is something that not even the angiography allows you to see well.

These are cases of normal angiography and even in this case, there were very few indications of other studies and there is little previous literature.

It is like a pipe of a fairly constant size, you can see that not all veins have this constant caliber. They can also change depending on the number of our breaths and they expand and they close. You can see above at the area where it enters the chest and becomes the so-called brachiocephalic vein that has a diameter of about eight to ten millimeters. They might have valves. Indeed there are cusps of valves with two leaflets. This is the appearance of a normal valve.

This species of valves that look like the wings of a sea gull represent the valves that prevent blood from going back into the jugular, they are the so-called anti reflux valves. The blood must go from the jugular into the heart and not vice versa.

PART EIGHT

And this is what we consider normal. In addition to this we investigated the small veins that are called vertebral veins and that pass close to these ones. Having anticipated the way our approach could be, I can show you quickly the results of a prospective study of our patients that we did about two years ago, whose results were mentioned to you by Professor Zamboni. First, I will show you the result of our drip charts: what did we find?

The phlebography happens when injecting liquid contrast with the catheter into the vein and draw the content of it, then see if it is normal, as in the cases that I showed you, and to see if there are any changes.

This is the list where you see many strange names. I have a ring, a septum and hypoplasia we have a vein that is undeveloped. In all these patients we found something that were, more or less, distributed in individual veins. I would say that the most striking example to see is the so-called ring, a small ring. We hypothesize that this is a congenital alteration, we don't know yet of what nature, but we can see that a point in a large vein has a constriction and this is the point where a vein should download the blood at the level of the thoracic venous system. Here, I see three veins in a row. You see this event here on the right where it seems to be an eccentric septum, a kind of small membrane that goes inwards.

Things are different when we talk about valve malfunction that can be seen very well by the ultrasound. You saw that the valve did not open. It's not this way with the angiograph in which these changes, which we already knew about thanks to the Doppler, we are just speculating about.

We can see the malformation of the valves and they are a little fat. Here we see a sector that is in a transverse position, a valve that looks almost like a septum within the vein.

I can tell you that the patients were treated with the balloon dilation, thanks to the guidance given to us by the ultrasound. In this case, a radiologist would tell you that the vein would look normal without the guidance of the ecography and I tell you the importance of the interdisciplinarity of the study just like the professor said before. These tests must be designed and used together and the preliminary doppler test of the jugular is important because this is what gives us the indication for the treatment.

This is called hypoplasia and it happens when the veins develop very little. This jugular vein is very small, especially at this level, and you can see the presence of parallel channels, where a vein doesn't work, other veins develop, they dilate to try to support the collateral circulation.

Here you see another jugular that is very thin, and the contrast, which is the black liquid drawing the veins around the lattice, is not normal. These circles are trying to compensate for the vein that is too small, and normally, the arteries and the veins are able to compensate, but at some point they are in trouble, they don't have the same strength as the main vein.

Again, look how small is the jugular vein. Do you see how very thin it is?

And this is what happens in the collateral veins.

We tried to provide the topography of the jugular vein that you can see here colored in pink. At low level, which emerges in the thoracic area, it develops the changes that we saw and you see that almost 90% of the cases that we found were at the lower level. It is natural that it is where the vein needs to complete the flow that the stenosis forms and leads to difficulties.

We found lesions associated with low, medium and high levels. Only in the 9% of cases, as in this case, you see a narrowing in the lower area, you see a narrowing a bit higher, and in 0.6 % of cases, you see them in the medium-high area.

Here you see a compression of the jugular vein in the highest section and this compression is comparable to the one that the professor showed you. The thin vein was seen in the MRI. We consider this physiological and abnormal for the carotid artery bulb that rests upon it.

It is for this reason that I like to show this. If you go on the internet unfortunately you will find operators that would put metal stents at this level to treat it. It seems a bit premature and a little risky for me right now to go and treat injuries that are not injuries and that, in our experience, have a very low incidence.

Going down, we went to investigate the azygos vein, the vein that looks like an arch, and in some cases we went inside at the point where it arches.

We have always found that these structures are valves and you can draw them with the contrast and they look like they are not done very well.

This is a bicuspid valve with two valve leaflets that has a narrow course that is a bit eccentric.

We don't know what the normal appearance of the azygos valve is, but assuming that these valves could give problems, all patients who had this kind of feedback, and there were about 70%, we have expanded them with the balloon.

I'll show you some other examples. Here is a patient who has mono valve in the valve cusp, entering with the catheter and injecting there is a significant reflux of the contrast and of the blood at the venous and lumbar spine level.

Even more evident in about half of the arch path, a retrograde case came to a certain point where there is a small sect, a small obstruction that has struggled to pass, we have found here the so-called hypoplasia, reduced development You see, at this level of azygos tube it is also very restricted in terms of its collateral vein, the so-called emiazygos where we found some small points.

We also found a pathology, something that we have defined as twisting, a so-called candy wrapper, a vein that is twisted around itself and understand that at this level there is the reduction of the load and there is also a difficult passage for the blood. Here there are two examples in the azygos that, frankly, we had never seen before in any other vein.

We also found something known as agenesis, especially in patients with major diseases, as would be the primary progressive cases. We have found, particularly at the lumbar venous plexus, the veins can't be seen well, they look like spider legs. At these levels they look like small sausages, they are not well developed and, at this point, we are just assuming and we are totally lost because we saw only ten cases of this type of patients where the veins were not well developed, so this needs work and further study.

We studied the potential routes of hyper influx, we just mentioned the iliac and the renal vein. Here are two cases where you see the left iliac vein, it's like a tube where, at a certain point, there is a compression, the blood doesn't flow well for several collateral circles and this is the same for the left renal vein.

The injected contrast doesn't show it, but refluxes into the lumbar plexus that are these veins over here.

So this is another potential route of engorgement of the venous system. We obviously wanted to study all of them and, in most cases, we found these changes in the jugular and the azygous vein and in the influx of the hyper point only in smaller percentages. We assume this to be only the second of concomitant injuries, probably with an impact, we do not know, similar to those of the normal population, but it is always a causal factor. We assume that a dilated jugular vein could probably be a contributory cause to have this and it is therefore appropriate to investigate, it is right to have this kind of completeness.

We also classified them as a type of association, as a purely statistical value, depending on how this kind of obstruction or stenosis are single or are more or less associated with each other.

And I come to tell you, and I will end with this, that we decided to show you how to treat this when we are already inside the patients with our femoral access and we were already through the stenosis. We thought of expanding these strictures, obviously in the least invasive way possible, as it is done in medicine for many other veins. We didn't want to use patients as guinea pigs and we didn't want to do any damage, but we wanted to solve a venous problem and this is still our view about it. Patients are treated with the angioplasty, with the balloons. Here you see them swollen, but when these balloons are carried through the veins they are completely deflated and have the diameter of the catheter. The inflation of the balloon happens with the outside pump, and we used balloons with low pressure, that does less possible damage. Here I show you what happens when a low pressure balloon meets an important stenosis and it fails to dilate.

Only in these cases we passed to use a second balloon, so-called non-compliant, which is a balloon that has more force to add pressure to the stricture.

PART NINE

GALEOTTI:

Here I show you some fairly intuitive images, easy to understand. You can see the narrowing at this level, the balloon was dilated and the shrinkage is much less evident the day after. These are annular-type of lesions and these are the ones that respond better to expansion. You still see the balloon centered at the level of this stenosis and the shrinkage and the day after you see that there is a significant recovery of the caliber. Even at this level (the cases are very similar), you see the narrowing of the vein, the big balloon and this is the vein after the expansion occurred.

Here I quickly tell you that we tried to expand these malformed valves. You see there's passage, but the Doppler was telling us that the valve was not working well and see what the immediate result has been.

I must say that, especially in these patients, we had the restenosis, a recurrence. We don’t think that it was a true recurrence, but it was probably the same balloon that didn’t make an effective expansion, that probably there wasn’t the immediate result and that the valve probably returned to be deficient.

This is an idea that is shared by some of our colleagues and that says that a malfunctioning valve can be treated well with a stent. I will show you that a stent is a metal mesh that keeps the valve to the wall. But we have some doubts about using the stent because it is a method that, especially with regard to life expectancy and the evolution of its function, gives us some doubts.

Here are more examples. This malformed valve causes a narrowing of the jugular vein. After it is dilated, you see that there is a good result. We know that there might be a recurrence, as in this case. Here you see that the contrast doesn’t even go through, that the valve is almost deflated, you can see that the edges are not doing well and the blood doesn’t go down after the expansion.

This is the image of a transverse septum at the level of the jugular vein. Most of the times, these ones go well because there is a thin membrane that, with the simple expansion of the balloon, as you see, disappears and this results in an improvement of the flow. We also tried to dilate the hypoplastic veins, which are underdeveloped, with much smaller balloons.

You see this undeveloped vein with its collateral circle; we tried to dilate and we had a fair result.

Here I show you the possible complications, you can see this small crack, a small crack that is built on a vein, because the structures of the veins that don’t have high capacity don’t create major problems, as closing an artery during the angioplasty could create problems. Here we are dealing with veins.

We also tried to dilate the azygous vein.

Here we have a septum, sometimes the wire that guides us has trouble passing through this section, but we can break through it, we bring the balloon inside and we dilate. This is the pre post control and there isn’t the septum any more.

Let me quickly show you other cases. This one here is a valve that was closing completely or at least we hypothesized this. This is the control after the expansion and these are the valves that are open just like a small gate.

Here again you see the before and after. There is a valve septum at this level, then there isn’t any more and there is less reflux, which means that the blood goes down less.

Do you see the valve with three cusps?

At this level, we bring the balloon, we dilate it to spread it along the wall and now you see it before and after the procedure.

Again, you see an undeveloped vein, you see this section, here it’s irregular, here it’s normal, up here is not right and it’s a little jagged. We dilate it with the balloon and next time you see it, it has recovered a good flow.

Here we have more examples that are very similar. Here there is a very thin vein, this is the before and this is after the expansion.

You see the vein in the final control that is a channel that is a little clearer. Look at this level: here there is a emiazygos vein. Here is the balloon and the vein that has recovered a good gauge.

We also tried to expand the so-called twisting, or torsions, and you see that the result is not bad after taking the balloon inside. The vein probably has an inflammatory fibrotic component, inside it has recovered a good caliber and we tried to expand the concomitant veins which is the left renal vein that we couldn’t see and where the circulation of blood was going in the paraspinal, lumbar, gonadal, venous circle.

After the expansion we found a good path.

These are the veins that are probably compressed. We can’t hypothesize that this treatment can last over time, but from here to suggest that we put a stent in it for the moment is still a stretch.

Quickly, I can tell you that we also expanded this one in one case. We never found spinal stenosis in the vertebral veins, but this vein had a valve that was a little 'dysmorphic” with this cervical spinal venous opacification within the bone. After the dilation it regained a good caliber. We also expanded the so-called brachiocephalic vein, we saw this notch in the vein of the chest further down in the jugular vein, we also found stenosis at the level of jugular valve. We used the balloon in the brachiocephalic vein and the jugular vein and this is the result: you can see the disappearance of the notch.

This is something that we tried in a patient who had the compression of the iliac vein, where the blood coming up from the leg, was flooding the lower vertebral circle. We closed this vein, just like I showed you that we had closed the varicocele vein, with some spirals, some metal springs, to try to close, put a dam in the passage of the blood. It is a case, it is clear that we need a much more realistic number of examples of this.

These are vascular outcomes. I am not speaking of neurological outcomes of the expansions that we have done, certainly less invasive, there are minimally invasive. What results have they given us?

We have measured the venous pressure of the treated vein before and after, the incidence of complications that this could create, and the percentage of how long these veins were staying open over time.

Well, the pressure is always better. This chart tells us that the pressure after the expansion is lower we always reduced the pressure which is the force that moves the blood on the inside. We have had no complications, at least no major complications or thrombosis, the closure of the vein, the rupture of the vein, we had two small bruises, two small bruises in the femoral region and two dissections, a little bit of headache during the procedure, two times the balloon broke, but it wasn’t a problem because we changed it with no major complications.

Professor Zamboni already mentioned about the patency rate and its excellent distance with regards to the azygos.

We did check ups and doing a check up means doing the doppler, we don’t do a new phlebography for checking.

In the azygos veins we saw that after 18 months, 96% remained open with only a 4% relapse rate, so all in all, this is a comforting result, but as you see, in the jugular veins after 18 months, 47% showed a return of the stenosis. I had partly explained that the annular stricture are those that respond better, but we find them in 45% of patients while the remaining patients have a malfunctioning valve. We give them a hand with the balloon but this tends to recur. Despite this, we treated the patients again, this is still ongoing and we are still evaluating these patients.

We don’t like these results and I repeat that the alternative may be to put a stent, the wire mesh, but we still have a lot of doubts about this treatment.

I end by saying that the angioplasty, this PTA that means angioplasty, is certainly safe and well tolerated, the patient barely feels the balloon when it is inflated, there is just a feeling of light discomfort. This is a procedure that is done in about an hour and this is only because it is a long process and we have to see many veins. The patient is awake and after only four hours can be discharged, go out on his own feet because it is a venous puncture that doesn't give big problems.

The results are very promising in the azygous area, as I said 96% patency is certainly very promising, and I must say that we found the restenosis only in patients who had the twisting, the candy wrapper and only in these patients we included a stent in the second instance. Here you see it, it's a small metal mesh and here we see the results and how it holds this open.

This is because, in fact, a twisted vein is a closed vein. However even if this stent were to encounter a thrombosis or it would close, it would not change the situation, mainly because the azygous vein is inside the chest, behind the heart, behind the esophagus, among the lungs, for which surgery is not feasible at this level because it's very invasive and I think that there isn't a justification. However, we have inserted the stent only in this case.

PART TEN

Galeotti

About the jugular, we said that 47% of the patients recurred after 18 months and we don't like this. In these patients, we have redone the dilation, however we have redone the expansion using different things, using balloons that can give increased pressure, we tried to use the so-called cutting balloons, which are balloons that have small metal plates that cut these veins and the valves a little, and an alternative to this could be surgery of the jugular veins.

I must say that, in our experience, after the second expansion occured some of the patients were sent to the surgeon. This could also be opportunity for discussion with professor Zamboni.

Venous surgery is a surgery that vascular surgeons don't like because of technical difficulties and it has a high complication rate. This is because the veins are susceptible and tend to close again and have thrombosis. This could be a good idea if done with good hands particularly with the jugular, the idea would be to put a stent there but it is still a question mark. We didn't put anything in the jugular veins and, at this time is not my intention to put anything. There are small and flexible metal tubes that can be dilated inside the vein that are carried up with an operation similar to angioplasty. They keep the vein open, particularly at the valves level, they keep these valves open and avoid them flickering and then closing.

But we have our doubts because while there are immediate concerns, the stent is not like a venous arterial stent. It has a high percentage of immediate dislocation, it may migrate, if it does take off it doesn't move to the outskirts, but it moves centrally, it can go in the lung, in the heart, and it is very dangerous from this point of view.

With the jugular veins, we don't know what the stent would do it's not yet sufficiently tested long-term. Here you see that these are examples of multiple stents that had been put in the femoral artery of a leg, you see that they are closed and there is a collateral circulation that compensates. And what you see at a distance is the stent that can break; here you see there is a break in the structure in the mesh of the stent. They are little stents that can break. As you can see here, this is a coronary stent, in this case its very low incidence, a very rare complication, but in our experience we have seen them break inside a liver, in a bile duct, a tube that carries bile and that can be affected by cancer. It's treated with a stent and as you can see here, it is fractured.

So we think that in a jugular vein, which is a very superficial vein that is subject to the continuous movements of the neck in a patient who has several decades of life expectancy, twenty are also very rare, but this for example, is a stent in the liver that broke after six months. In a coronary artery it can occur after a year while in the superficial femoral artery it can happen after a year.

We don’t know what these stents will do in a patient who has sixty years of life expectancy. If a stent breaks it can create a thrombosis. A stent could make a decubitus and this means that it can pierce the wall of the vein and pierce the carotid artery that runs near it. And, I say this on a small note because, on the Internet you can see some centers that take hundreds of patients with this type of pathology while we do not know if CCSVI is truly associated with multiple sclerosis. We still have to prove it. We still have to have more scientific backing so we can say "ok, we must treat this vein at all costs” then we start working with a stent, but we cannot expose the patient to this type of risk.

I end with this. Thank you.