MR Imaging with the CCSVI or Haacke protocol

Reports from the Haacke protocol are often made available to the patients. The report consists of four major components: 1. anatomical images of major neck and brain vessels as well as the azygous vein; 2. flow quantification of major neck vessels, major brain dural venous sinuses and the azygous vein; 3. conventional anatomical MRI sequences showing brain structures and, when present, examples of MS lesions; 4. susceptibility weighted imaging (SWI) showing the small venous structure of the brain, iron lesions in the brain white matter and measuring iron content in the major deep grey matter nucleus.

Section 1: Basic information.

This section contains the demographic information of the patient, the institution where the MRI scan took place, whether the patient has received the complete CCSVI MRI protocol and, if not, what MRI sequences the patient's data includes.

Section 2: Anatomical Information

In this section, two MRI sequences are used to evaluate the anatomical information of the major neck vessels and azygous vein. One is called 3D dynamic contrast enhanced (CE) MRAV or TRICKs, the other is 2D time-of-flight (TOF) MRV.

In the 3D CE MRAV sequence, a contrast agent is injected into the right or left medial cubital vein through a power injector. While the contrast agent passes through; the major neck arteries, brain arteries, brain capillary system, brain venous system and major neck veins, the MRI scanner takes snapshots (images acquired every 5 to 15 seconds) of the head and neck at different time points continuously for several minutes until most of the contrast agent washes out of the vascular system (or reaches equilibrium in the body). Each snapshot consists of a 3D slab containing as many as 96 images (a set of very thin slices covering the head and neck). Each group of images is given a series number. All series contain the same number of slices and cover the neck coronally from the anterior to posterior where the major vessels reside. This method is used to show the anatomy of the vessels and in particular whether the major veins are present or not. As long as the contrast agent can go through, regardless of the blood flow's speed, the vessels will be seen in this set of images. ***The first set of images*** in this section is

composed of three images which are chosen to represent the arterial phase, the early venous phase and then a late venous phase. The arterial phase will only show the major arteries including common carotid arteries, internal carotid arteries, vertebral arteries and major cerebral arteries. This method has been used in clinics for many years to image disease on the arterial side, such as artherosclerosis and stenoses of the arteries. Usually the later phases are discarded since the venous side was not considered as relevant. The early venous phase shows the major cerebral sinuses and large neck veins with fast flow, such as the normal healthy internal jugular veins and subclavian veins. The later venous phase tends to show veins with very slow flow, such as the subcutaneous veins (external jugular veins) and the vertebral venous plexus. For the vertebral venous system or external jugular veins, depending how large the vein is or how fast the flow is in that vessel, it can show up in the early venous phase or later venous phase. For instance, some MS patients develop very large vertebral veins; they can show up even earlier than the stenosed internal jugular veins. When the veins are shown, the arteries are still bright. This overlapping of arteries and veins makes it difficult to show veins clearly. In order to eliminate arteries, we do a subtraction of the arterial phase from the venous phase of interest. After this process, a set of subtracted images with veins only is generated. It is crucial to acquire high quality arterial images in order to obtain good venous-only images.

Since the snapshot is acquired in a 3D slab, we can do a projection from any angle to get the best view to see the narrowest part of the vessel. These images are referred to as the 3D rotation of the subtracted images, which composes ***the second set of images*** in this section. In this picture, the existence, caliber, stenosis, and connection with other venous systems related to the internal jugular veins are discussed. Generally, colored arrows point to areas of interest on the images to demarcate individual vessels or abnormal areas. ***The third set of images*** focuses on vertebral venous system, usually including three images; one is the whole slab showing the entire vertebral venous system which is followed by two images with a thinner projection. The goal is to show the vertebral veins and deep cervical veins separately. Depending on which phase shows the strongest vertebral venous signal, an early or late venous phase is chosen as the first image. The thinner slab is usually from the same series, but we choose the slices encompassing only the vertebral venous system to avoid overlapping with the internal jugular veins. *In summary, the first three sets of images from our report are from 3D CE MRV data. The first picture shows the dynamic changes of contrast agent going through the vascular system, the second picture shows the internal jugular veins and the third picture shows the vertebral venous system.*

2D TOF MRV does not require a contrast agent. The contrast is attained through suppression of the stationary tissue signal in the 2D slice and enhancement of the inflowing blood signal (also referred to as time-of-flight effect). The arterial system is also purposely suppressed as described below so the vessels that are seen will be veins only. Since the blood is constantly moving, part or all of the saturated blood moves out of the 2D imaging slice and is replaced with fresh blood (not saturated) that is flowing into the imaging slice. Thus the signal from the blood vessels will be much higher than the stationary tissue. If we are only interested in the venous flow, then we can add another saturation pulse under the imaging slice toward the heart, which will saturate all the arterial blood that will be flowing into the slice. This way, only the venous blood gets refreshed with unsaturated blood. The result is a 2D TOF MR image with high signal in veins and low signal in both arteries and stationary tissues. For efficiency purposes, the 3D CE MRV is usually acquired in the coronal orientation view in order to cover a larger region in a short time period. However, the 2D TOF MRV is best acquired in a transverse (sometimes called axial view) which is perpendicular to the direction of flow in the major neck vessels in order to get the best venous signal. So 3D CE MRV shows one whole vessel in the coronal projection, while 2D TOF shows only a cross-section of the vessel at different levels. This makes 2D TOF MRV complimentary to the 3D CE MRV. Also, the in-plane resolution of the 2D TOF is four times higher than the equivalent reformatted 3D CE MRV view in the same place. In summary, the 3D CE MRV helps to localize where the abnormalities take place and the 2D TOF MRV shows the cross-section of the stenosed region. In this view we can then determine whether the cross section looks normal, is pancaked or uniformly stenosed. So the ***fourth set of images*** in this anatomic section consists of 3 to 5 different slices showing the cross-section of the neck vessels at different levels. We tend to choose the slices where the narrowest caliber of the vessel or pancaking takes place and the slices below and above the stenosis with normal caliber so that the changes of the vessel diameter can be observed from these sequential but not continuous slices from the lower to the upper level of the neck. The 3D CE MRV image is used as reference; the localization of each slice from 2D TOF MRV is marked as a red line (numbered) on the reference image. In this way, we have a good idea where the cross-section of the vessel from the 2D TOF MRV located. Another complimentary piece of information which can be derived from the 2D TOF MRV is an indirect assessment of the flow information. Usually findings from 2D MRV agree with that of 3D CE MRV. When there is disagreement, both methods are compared. For example, when 3D CE MRV shows the vessel is present, while the there is no signal from the 2D TOF MRV, this indicates that the flow speed is very slow and that

the signal inside the vessel is saturated in the 2D TOF MRV just the same as the background tissue. When there is inhomogeneous signal inside the vessel, it usually indicates unsteady or non-uniform flow (this could be turbulent or vortex flow).

The fifth set of images in this section represents the anatomical information of the azygos vein. Most sites that use the CCSVI protocol use the 2D TOF method to image the azygos vein. The cross-section of azygous vein is shown on multiple continuous slices; we choose the slices that best show narrowing or pinching and also some slices above and below the narrowing with normal caliber. The transverse 2D TOF data is then reformatted to a sagittal view where the azygos vein can be shown in one single slice to see if there is a general narrowing trend. This data is often hampered by breathing artifacts so the best images are the transverse images. Owing to the breathing artifacts and some other technical limitations, the azygos vein is not always clearly seen even on the transverse view.

Section 3: Flow information

Flow quantification is performed using a special MRI sequence by encoding the flow inside the blood vessels. This sequence generates two sets of images: a magnitude image and a phase image. The magnitude image shows the vessel anatomy and the phase image can be used to quantitatively measure the velocity and direction of the blood flow. The phase image contains the phase values of each voxel, which are proportional to the velocity of the blood flow at that voxel location, For a Siemens MRI scanner; if the phase appears dark this implies flow towards the heart. The darker the phase, the faster it flows toward the heart. If the phase appears bright, this implies flow towards the brain. The brighter the phase, the faster it flows toward the brain. If the data is from a GE scanner, dark means flow towards the brain, bright means towards the heart. We have developed our own software to process the flow data and to define a number of physiological flow measures to represent these findings.

First the user segments the vessels by drawing contours on the vessel boundaries. Then the software reads in the phase values inside each vessel contour. The software can decode the phase values to get the flow velocity of the blood flow through each voxel. Then the following parameters are calculated: integrated flow, volume flow rate, positive volume flow rate, negative

volume flow rate, positive flow volume, average velocity, peak positive velocity, peak negative velocity, peak to average velocity ratio, average positive velocity and average negative velocity. The first five parameters have been chosen as most clinically relevent at this time although many other measures are also available and stored for each patient.

Currently, most sites measure the flow at four different locations: *1) the upper neck level, 2) lower neck level, 3) straight and sagittal sinus, and 4) azygos vein.* In each subsection (i.e., for each anatomical region), ***the first set of flow images*** contains one magnitude image, 1 to 3 phase images, and an anatomical reference image showing where the flow quantification takes place. In the magnitude and phase images, major vessels are shown and indicated by colored arrows. ***Five graphs are shown*** including; total integrated flow per cardiac cycle, flow rates in the form of total, positive and negative, and average speed coincide with the magnitude and phase images. These allow us to determine if there are abnormal flow patterns such as no flow, reverse or reflux flow, and circulatory flow patterns (often the case for widened bulbous lower levels in the internal jugular veins). If the flow curves for a given vein fall through zero and change direction, then we refer to this as reflux flow. However, on occasion the vessel shows flow in both directions at any given time. This we refer to as circulatory flow.

The flow quantification at the upper neck level usually takes place at the second cervical vertebrae level (C2). The lower neck level is at the sixth vertebrae level (C6). These two different levels helps us to get a flavor for the flow coming immediately out of the brain and the flow at the lower level of the neck just above the confluence of the internal jugular veins with their corresponding subclavians before the blood goes back to the heart. The lower part is perhaps the most important because that is what represents most of the venous blood escaping from the entire head/neck system. The major vessels we can see for the neck include: internal jugular vein, common (internal) carotid artery, vertebral artery, vertebral vein, external jugular vein, anterior jugular vein, deep cervical vein, as well as the anterior and posterior vertebral venous plexus. In some cases, we can only visualize some of the vessels, and in other cases, we can see multiple vessels of the same name (such as two right external jugular veins).

This part of the report closes with a table of flow measurements both per cardiac cycle and then translated into flow per second. Data is given for both the left and right sides separately. If there is much more blood flow in the arteries than the veins, this suggests that the vertebral plexus

may be carrying that missing load. Azygos flow is also shown along with its own quantitative flow table.

Section 4: Conventional data

There are a number of conventional data sets that are collected. These include: T1 weighted images (T1WI), T2 weighted images (T2WI), FLAIR (Fluid attenuation inversion recovery) images and post contrast T1WI images. These constitute part of the standard MRI protocol used to image MS patients clinically for many years. In this section, ***the first set of images*** represents the FLAIR data. FLAIR is very sensitive to MS lesions, which appear as hyperintense or hypointense signal in the white matter. We tend to choose 4 to 6 images at representative brain levels to show the MS lesions. The ***second series of images*** in this section is a comparison of the pre-contrast and post-contrast T1WI. If lesions appear enhanced post contrast, they are thought to represent acute lesions and these are then highlighted in the images with arrows.

Section 5: Susceptibility weighted imaging results

In this section, ***the first series of images*** are SWI phase images where lesions with high iron can be clearly seen. They can be MS lesions or hemorrhages. MS iron lesions can appear as a solid round,patchy dark,or ring-like dark signal inside the white matter. We tend to put the FLAIR images of the same brain level beside the SWI phase to compare the iron lesions on SWI and the hyper-or hypo-intense lesions on FLAIR image. For most cases, we can find corresponding lesions on FLAIR when iron lesions are visible, but not always. ***The second series of images*** in this section are MIPs of the SWI data where small venous structures of the brain, such as medullary veins, deep cerebral veins, and peripheral veins, can be shown . Dark areas representing iron in the basal ganglia are also shown. This set of images can tell whether the patient has diminished or engorged venous structures. ***The third series of images and plots*** represent iron quantification in the deep grey matter structures. There are seven structures in which we measure iron including: 1) caudate nucleus (CN), 2) globus pallidus (GP), 3) putamen (PUT), 4) pulvinar thalamus (PT), 5) red nucleus (RN), 6) substantia niagra (SN), and 7) thalamus (THA). We have acquired SWI phase data on 122 normal subjects. After measuring the iron content of the 7 stuctures for each of the normal subjects, we have created a baseline of normal iron content in each nucleus. On the phase images from the MS patient, we draw the boundary of the structure of interest (usually following the contour of the nucleus). The software

will generate the graph where data from the MS patient fits into the baseline graph. The region of interest (nucleus) is divided into two regions; one region includes those pixels with a phase value above a threshold value which indicates high iron deposition (Region II). The parameters we use include: 1) average iron of the total region (TR-AI), 2) total iron of region II (RII-TI), 3): average iron of region II (RII-AI), and 4) normalized region II area (RII-NA).

In this section, the table contains a list of the 7 structures and the four relevant iron measurement parameters. A check mark is placed in the box for that structure when there is abnormal iron content. If there is a check mark, the phase image and the graph will usually be shown. In this graph, the solid line is the regression line of the normal subjects. The outer dashed lines represent the 95% prediction intervals of the regression. We use the 95% prediction intervals to represent the normal iron deposition. Any patient beyond these intervals is assumed to have abnormal iron deposition in the structure plotted. The hollow square (left hemisphere) and triangle (right hemisphere) represent the measured result for the MS patient.

Why is all this important?

Having an MR scan prior to treatment is crucial for a number of reasons. First, it gives you a baseline of the brain tissue, MS lesions, vascular anatomy, flow characteristics, small veins, possibly perfusion if that is eventually added to the protocol, iron content, and the presence of any microbleeds or thrombus. Apart from the critical issue of acting as a treatment planning guide for the interventional radiologist or vascular surgeon, this information is the baseline from which you can judge what happens in the future. For example, do lesions go away, does blood flow improve, does iron content stay the same or reduce? Furthermore, if complications develop this baseline scan can help determine where the problem lies. All this is not possible if you do not have the initial scan run with the CCSVI protocol.