UPDATE IN RADIOLOGY

A practical introduction to the hemodynamic analysis of the cardiovascular system with 4D Flow MRI

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Abstract The 4D Flow MRI technique provides a three-dimensional representation of blood flow over time, making it possible to evaluate the hemodynamics of the cardiovascular system both qualitatively and quantitatively. In this article, we describe the application of the 4D Flow technique in a 3 T scanner; in addition to the technical parameters, we discuss the advantages and limitations of the technique and its possible clinical applications. We used 4D Flow MRI to study different body areas (chest, abdomen, neck, and head) in 10 volunteers. We obtained 3D representations of the patterns of flow and quantitative hemodynamic measurements. The technique makes it possible to evaluate the pattern of blood flow in large and midsize vessels without the need for exogenous contrast agents.

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Introducción práctica al análisis hemodinámico del sistema cardiovascular mediante la técnica «4D Flow»

Resumen La técnica de resonancia magnética 4D Flow permite evaluar cualitativa y cuantitativamente la hemodinámica del sistema cardiovascular representando en tres dimensiones los patrones de flujo sanguíneo en el tiempo y cuantificando variables hemodinámicas. En este trabajo describimos la técnica 4D Flow en un equipo de resonancia de 3 T y adicionalmente se exponen, además de los parámetros técnicos, las ventajas, las limitaciones y las posibles aplicaciones clínicas. Para esto estudiamos a diez voluntarios con la técnica 4D Flow en diferentes áreas corporales (tórax, abdomen, cuello y cráneo) con la que obtuvimos representaciones...

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tridimensionales de los patrones del flujo y medidas cuantitativas hemodinámicas. La técnica permite evaluar los patrones de flujo sanguíneo en vasos grandes y medianos sin la necesidad de contrastes exógenos.
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Introduction

During the last years we have seen important innovations in magnetic resonance images (MRI), especially in the field of cardiovascular imaging; this means that today not only the anatomic study but also the functional study of heart and vessels is possible. The very first maps of in vivo vascular velocities were reported back in the early 1980s and since then angiography sequences like phase contrast angiography (PCA) consisting of 2D retrospective acquisitions with the cardiac cycle (2D cine PCA) are available in most MRI equipments. This sequence is essential for the functional evaluation of the cardiovascular system and it can be acquired during one apnea only.

The time-resolved three-dimensional flow-sensitive MRI with three-directional velocity encoding (4D Flow) modality consists of MRI acquired though a phase contrast angiography that acquires blood flow data in three (3) spatial directions (3D) during the whole cardiac cycle for the qualitative and quantitative evaluation of vascular hemodynamics. In this case acquisition lasts more (5–20 min) and it is necessary to synchronize it with breathing. With 4D Flow data we can both see and analyze quantitatively blood flow patterns in heart and large vessels through 3D cine representations during the whole cardiac cycle by means of pathlines, streamlines, vector graphics and 3D velocities. It also allows us to perform hemodynamic measurements of mid, peak and minimum velocities, ejection volumes, vessel wall shear forces and pressure gradients. Given it is a 3D modality among the multiples advantages of 4D Flow the possibility of quantifying the flow in any interesting views and vessels by postprocessing images is included when the patient is no longer in the resonance equipment without the need for any more sequences in other views as it happens with the 2D cine PCA. Also 4D Flow is a modality that does not use any ionizing radiation or contrast media. Its clinical potential is enormous because it allows us to perform the anatomic and hemodynamic evaluation of the patient’s vessels with cardiac or cardiovascular diseases like: congenital heart diseases, heart failure, arteriovenous malformations, aneurysms, fistulas or stenoses in blood vessels, among others.

In this review we will describe the 4D Flow modality in ten (10) volunteers through a 3T MRI and we will be discussing the advantages, limitations and possible clinical alterations.

Principles of the 2D cine PCA

The 2D cine PCA is an MRI modality synchronized with the electrocardiogram (ECG) that delivers phase contrast images velocity-sensitive. 2D cine PCA images are acquired in different stages of the cardiac cycle (retrospective acquisition) and they can be seen dynamically. Their main goal is to evaluate hemodynamic parameters like flows, volumes, and velocities.

Flow is quantified by measuring spin-echo transverse magnetization in two (2) different time frames after applying one bipolar pulsed magnetic field gradient with a positive «lobe» followed by a negative one of the same magnitude but different direction. The coding of blood velocity in any spatial directions is based on the phase difference between the moving spin transverse magnetization vector and static spins. This is possible due to the fact that the static spins do not accumulate phase difference because when they experience the positive gradient they rotate to a certain angle and when they experience the negative gradient they rotate to the same angle but in a different direction. This means that the net phase displacement is zero. However, moving spins accumulate phase difference due to the fact that the intensity experienced by the positive and negative gradients is not the same due to movement and change of position (Fig. 1). The phase difference angle is directly proportional to both the velocity and movement of the spins.

It is important to highlight that the maximum velocity detected is determined by the Velocity Encoding parameter—expressed in cm/s. Blood flow velocities beyond this parameter are coded erroneously, so aliasing occurs. With the data acquired magnitude and phase images are built (Fig. 2) through the complex difference and the phase difference of the transverse magnetization vectors.

4D Flow

The 2D cine PCA modality can be extended to the 3D spatial acquisition in an effort to code the blood flow in the three (3) directions of Cartesian coordinate system in different phases of the cardiac cycle. Because we need three (3) directions for flow coding we need four (4) sequences—three (3) that are sensitive to velocity and one (1) reference sequence the total acquisition time is longer than with 2D modality. This modality is known as 4D Flow since it is named after four (4) dimensions—three (3) spatial dimensions plus a 4th temporal dimension.

4D Flow images allow us to quantitatively evaluate the regional and global dynamics of blood flow through hemodynamic measurements like the average, maximum and minimum velocities, the average beat flow, regurgitant and progressive flows, ejection volumes and mathematical approximations to pressure gradients and shear forces in the vessel walls. It also allows us to analyze quantitatively the temporal evolution of the complex patterns...
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Figure 1  Velocity coding principle in 2D cine PCA images. In time 1 a positive gradient is applied resulting in a phase displacement that is the same both for the static (circle without asterisk) and mobile spin (circle with asterisk). In time 2 a gradient of the same magnitude but different opposed to the 1st one is applied. It is now that the mobile spin has been displaced from its original position while perceiving a different gradient magnitude from the static spin. After the application of the bipolar gradient the result is that static spin phase between time 1 and time 2 is zero; however, the mobile spin rotates different angles in two (2) times and consequently accumulates a phase proportional to the velocity and distance gone by.

of blood flow through streamlines, pathlines, 3D velocity charts, and vectors; representations that describe blood trajectory across the cardiovascular system.12–14

At the beginning this modality was known thanks to its capacity to give qualitative information through the 3D representation of cardiovascular flow. However, recently with 4D Flow some methods have been developed for the quantitative analysis of blood flow. Also the new technological advancements in both hardware and software allow us to reduce the sequence time of acquisition and apply it in the clinical setting.13

Technique of acquisition

For the gathering of time-based volumetric data combined with velocity coding data in the three (3) spatial directions we use k-space segmentation methods synchronized

Figure 2  2D cine PCA axial images at the level of the pulmonary artery bifurcation. (A) Magnitude image. Blood vessel anatomic information. (B) Phase image. Blood velocity is coded through the intensity of pixels—bright color meaning flow coming out of the image and dark color meaning flow coming in.
with the ECG signal—for a total description the reader can use the quote. The Cartesian segmentation method uses the $k$-space with its three (3) perpendicular axes ($kx$, $ky$, $kz$) and divides it into a 3D matrix ($Nx$, $Ny$, $Nz$). Then during each beat of the heart it acquires a set of single-cut $k$-space lines ($Nseg$) for all phases of the cardiac cycle. If $Ny$ represents the lines all across the phase image ($ky$-axis) and $Nz$ represents the cuts ($kz$-axis) the acquisition of the whole 3D volume will last for a certain number of beats equal to $NyNz/Nseg$ and a time equal to $T_{adc}$ = $(NyNz/Nseg)T_{ECG}$, where $T_{adc}$ is the duration of all acquisition and $T_{ECG}$ is the duration of a single beat. For every line of $k$-space four (4) different data need to be gathered: one reference acquisition and three (3) velocity codifications resulting from the application of bipolar gradients in the $x$, $y$, $z$ directions. After the gathering of the data the 3D images are reconstructed—including one (1) anatomic or magnitude image and three (3) phase images representing blood velocity in the three (3) axes of the coordinate system (Fig. 3).

**Image acquisition**

We studied 10 volunteers (9 healthy ones and one with a transplanted kidney) using a Philips Ingenia 3T kit (Philips Healthcare, Eindhoven, The Netherlands) with 4D Flow in some of the following body areas: chest, abdomen, neck and skull. Acquisition parameters can be seen in Table 1. We proceeded with free breathing, electrocardiographic synchronization and a chest, head, or neck cardiac coil based on the examination area. Also in certain volunteers 2D cine PCA with parameters of temporal resolution similar to those of 4D Flow were acquired.

**Image processing**

Obtained data were extracted in RAR-REC format and postprocessing was performed using the GTFlow software (Gyrotools LLC, Zurich, Switzerland) that allowed us to estimate each point, blood velocity in the three (3) spatial
directions and in all phases of cardiac cycle. Postprocess is detailed in the three (3) simplified steps shown in Fig. 4.

Additionally the following hemodynamic variables were estimated in different vessels: ejected volume, average velocity, maximum and minimum velocity by picking out 2D regions of interest from one (1) automatic edge detection algorithm.

### Methods of representation

4D Flow data are commonly viewed as streamlines, pathlines, vector charts and 3D meshes that allow us to represent 3D blood flow patters in time. In Fig. 5 the different kinds of 3D representation that can be obtained through this modality can be seen.

1. **Streamlines.** Streamlines are curves that connect elements (particles) of a fluid in space with the characteristic that the curve is tangential to the velocity vector of several particles in a given time. This is why streamlines give us a general view of the flow pattern described by a fluid element in the cardiac cycle.

2. **Pathlines.** Pathlines indicate the trajectory followed by one particle of fluid. This representation can be regarded as the pathway followed by one fluid element within the flow at a given time. Pathlines are used to analyze the temporal evolution of blood flow patterns during the cardiac cycle. They can be coded with colors representing flow velocity too.

3. **Vector charts and meshes.** For every particle vectors charts associate one vector with the magnitude and direction of flow velocity at that point so that for every point the evolution of the flow velocity pattern can be observed through time. You can also draw regions of interest in any vessels in order to analyze the behavior of blood flow through any of the aforementioned methods. You can also build 3D meshes to get profile information of blood flow velocity on one vessel or region if interest.

### Artifacts and difficulties

Phase contrast images are susceptible to errors induced by eddy currents and other heterogeneities of the magnetic field that have a tendency to increase as the studied region moves away from the magnetic isocenter. Aliasing can occur since the velocity encoding (Venc) sampling is lower than blood velocity. It is important to correct data when these artifacts show up in order to guarantee the vision and quantification of flow. To prevent these artifacts from happening due to aliasing the use of one 2D cine PCA sequence is recommended and based on the estimated peak blood velocity the picking of the most adequate value for Venc in the 4D Flow

| Table 1 Acquisition parameters for the 4D Flow modality based on the area of study. |
|--------------------------------|--------------------|----------------|
| Field of view (mm)           | 350 × 350 × 120    | 350 × 350 × 120 | 270 × 270 × 70 |
| Voxel size (mm)              | 2.5 × 2.5 × 5      | 2.5 × 2.5 × 5   | 1.5 × 1.5 × 1.5 |
| Images                       | 48–56              | 40–50           | 40–60          |
| RT (ms)/ET (ms)              | 4/2.1              | 4/2.1           | 4/2.1          |
| Venc (cm/s)                  | 200–150            | 100             | 110–160        |
| SENSE (factor)               | 2                  | 2               | 2              |
| Angle of inclination (°)     | 6                  | 6               | 6              |
| Phases                       | 16                 | 20              | 16             |

ET, echo time; RT, repetition time; Venc, velocity encoding.

Figure 4 4D Flow image postprocessing. Firstly the vascular structures in the magnitude image were segmented by choosing an appropriate intensity threshold and secondly a 3D isosurface was created based on the maximum velocity data included in the segmentation. Finally the vessel isosurface was used to generate a certain number of seeds (particles) inside the isosurface that were used to estimate the streamlines, the pathlines and the 3D vector charts and meshes.
acquisition always bearing in mind that a high Venc eliminates artifacts due to aliasing but it also limits the low velocity-flow sensitivity.\textsuperscript{12,21} When it comes to artifacts caused by respiratory motion there are several compensation modalities by using sensors (navigators) capable of detecting the patient’s respiration through the diaphragmatic motion while synchronizing such respiration with 4D Flow acquisition.\textsuperscript{4,7,24,25}

The main setback of 4D Flow is the duration of 4D Flow acquisition sequences–time especially increases when more spatial and temporal resolution is needed or simply when the acquired volume is increased. To solve this problem there are speed-up methods including parallel images, sampling strategies exploring the correlations in the space–time domain and radial acquisitions of k-space.\textsuperscript{26–28} These modalities can produce overlapping artifacts or reduce the temporal resolution of images. Some of these strategies are currently under investigations and validation.

The difficulty of clinically applying 4D Flow is due to both the time of sequence acquisition and its complexity. However, both scientific investigation and the interest of the industry on MRIs predict a bright future for this modality.

**Applications of the 4D Flow modality**

The 4D Flow modality allows us to assess blood flow both quantitatively and qualitatively in any vessels of interest and without any means of contrast. It allows us to assess the heart large vessels, its ventricles and valves in systole and diastole in one acquisition only. Also thanks to 3D acquisition it allows us to select within the acquired volume 2D views through any angles. Similarly and based on the area of interest abdominal, neck, and skull vessels can be assessed among other vascular structures.\textsuperscript{29–31}
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Figure 6  4D Flow images in large vessels and heart. (A) Segmentation of aorta and representation of blood flow through pathlines. (B) View of blood trajectory in the aortic arch and the pulmonary artery in one healthy volunteer. (C) Heart ventricular filling in diastole.

To better illustrate the capacity of quantitative analysis this modality has the videos that can be seen in files 4D Flow 1 and 4D Flow 2.

1. Aorta and heart (Fig. 6). One of the various potential clinical applications of 4D Flow is the study of flow in the ascending aorta. Hope et al. evaluated one subgroup of patients with bivalve aortas and found within this group an eccentric abnormal blood flow associated with major shear forces in the vessel walls as well as a greater risk of aneurysms. Consequently the risk of aneurysm in patients with bivalve aorta can be stratified by quantifying the shear forces obtained through 4D Flow, which allows more objectivity both in the diagnosis and possible interventions in the ascending aorta of these patients. Also possibly though 4D Flow we will be able to quantify both the abnormal flow and the hemodynamic load; define the risk of vascular diseases like aneurysms or dissections before developing symptoms.

The 4D Flow modality will possibly be useful in numerous clinical situations associated with congenital thoracic cardiovascular anomalies like persistent arterial ductus, conotruncal anomalies like the Fallot tetralogy, partial or total anomalous pulmonary venous returns and in patients with left-to-right shunting. Also with this modality we can identify patients at risk of pulmonary hypertension and further development of Eisenmenger syndrome. Similarly the MRI is the postoperative chosen modality since it allows us to assess both anatomic and functionally the cardiac cavities and the integrity and functionality of surgical corrections like interatrial baffles, outflow septostomies and Fontan conduits, among others. This is why 4D Flow images have a greater clinical value because they give us information of both intra and extra cardiac blood flow patterns in these situations.

2. Abdomen. The Doppler ultrasound has been the less invasive modality for the study of blood flows and the quantification of hemodynamic parameters in the vena cava, the portal system and vascular diseases (Fig. 7). However, it can be greatly affected by factors such as obesity, intestinal air or edema. This is why the MR-angiography is more and more important—because it does an excellent anatomical evaluation. Markl et al. published their results showing the potentiality of the 4D Flow modality both for the quantification and characterization of blood flow of the different intra-abdominal vascular structures and in some pathological situations like portal hypertension.

In patients with renal transplant the MRIs can be very useful because they give us important information like perfusion defects, tumors, post-transplant proliferative conditions and collections, among others. Through the 4D Flow modality we will be able to evaluate the size, orientation and relation to other abdominal organs and integrity of the intra-renal vascular structures. It is also possible to evaluate the anastomoses of the renal artery to the iliac artery and of the renal vein to the iliac vein while watching and quantifying blood flow through these anastomoses (Fig. 7).

3. Carotid and cerebral arteries. The digital subtraction angiography is the chosen method to evaluate neck and intra-cranial arteries but it is also an invasive method requiring iodinated contrast media. Thus techniques like CT-angiography (with iodinated contrast too though) and MR-angiography are more and more important for the study of carotid and cerebral arteries. The carotid Doppler is a very valuable low cost-tool thanks to its great accuracy for the study of carotid bifurcations yet, it is limited to small fields, it depends on the operator and is sensitive to a poor acoustic window. The 4D Flow modality has all the characteristics of the aforementioned methods while giving us anatomic and hemodynamic information (Fig. 8). It allows us to assess the vascular structures of the neck and the distribution of the carotid walls shear forces, find carotid stenoses and quantify blood velocity in the common carotid artery and the carotid bifurcation. It is also useful to evaluate and quantify both flow and velocity patterns in aneurysms and intra- and extra-cranial arteriovenous malformations. Studies performed in 7T ultra-high magnetic field resonance imaging devices have shown that smaller caliber-vessels can adequately be assessed (e.g. the posterior cerebral artery) and their pulsatility
Figure 7  4D Flow images in abdominal vessels and in one patient with a renal transplant. (A) Healthy volunteer. Abdominal aorta, main efferent branches and main intra-abdominal venous structures. (B) Detail from the origin of the celiac trunk, the superior mesenteric artery and the portal vein. (C) Sagittal image with anatomic reference of the abdominal aorta and some of its main branches. (D) Patients with a renal transplant. Coronal view where 3D streamlines of the vascular structures irrigating the transplanted kidney can be seen. (E) Detail of the arterial (caudal vessel) and venous flow (celiac vessel) and blood velocity coded based on a scale of colors. (F) Pathlines of former case.

Figure 8  Blood flow patterns at the main cerebral arteries and neck. (A) 4D Flow of the carotid and vertebrobasilar system of one healthy volunteer performed in 3T. Color patterns are coded according to velocity. (B) View through pathlines at the bifurcation of the right carotid and vertebral arteries. (C) Velocity patterns at the right carotid vertebral arteries showing greater peak velocity in the carotid artery. Note the parabolic profiles so characteristic of laminar flow in both arteries.
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4D Flow and 2D cine PCA

Today 2D cine PCA is widely used for the study of blood flow in cardiovascular MRIs. However, its main setback is that it uses 2D cut views that need to be selected during the examination and require a highly skilled operator managing the resonance equipment. In contrast, the 4D Flow modality with its whole heart 3D volume-study, so the planning of the sequence is greatly simplified without contribution from the operator (Fig. 9). However, the greater advantage of the 4D Flow modality lies in its capacity to perform multiplanar image analyses in the postprocessing since it allows the quantification of blood flow in any arbitrary views and angles without the need for acquiring new images. Other than measuring flow and velocity it also allows us to estimate hemodynamic biomarkers such as shear stress in the blood vessel walls, pressure gradients and pulse wave velocity without the use of any venous contrast media.

Some studies have confirmed that the 4D Flow measurements of flow and velocity strongly correlate to that of 2D cine PCA. On the other hand these modalities have a tendency to underestimate 20–25% of the maximum velocity or average systolic peak observed through Doppler ultrasound. However, we need to understand that in the MRIs velocity is always averaged since both multiple cardiac beats and a greater voxel size are needed to be able to obtain 3D images which in turn translates into a lower temporal and spatial resolution than that of Doppler ultrasound. When the resolution of the 4D Flow sequence is very high only those voxels displaying the fastest velocity will show values more proximal to that of Doppler ultrasound.

Figure 9 4D Flow and 2D PCA. (A) Quantification of the average velocity of flow in the ascending aorta through the 2D cine PCA modality. To the left we can see flow direction for every vessel and to the right the chart of velocity values in the cardiac cycle. (B) The same quantification was performed with 4D Flow. Note the similarity of values of the average velocity of blood measured through 2D cine PCA and 4D Flow modalities (B). (C) Selection of the ascending aorta and the pulmonary artery in one single 4D Flow study. The charts of average velocity of aorta (up) and pulmonary artery blood (down) are shown here as well. In charts A and B y-axis is blood velocity (cm/s) while x-axis is time (s). However, in chart C x-axis represents the cardiac cycle divided into sixteen (16) different phases.

Conclusion

In this review the 4D Flow modality is shown to be valid, non-invasive and allowing us to perform quantitative and qualitative analyses of blood flow in large and medium-size vessels without the need for exogenous contrasts. This modality has a great clinical potential since it gives us complete morphologic and anatomical information on the cardiovascular system by estimating hemodynamic biomarkers and visualizing blood flow patterns.

Conflict of interests
The authors reported no conflicts of interests.

Ethical responsibilities

Protection of people and animals. Authors confirm that no experiments have been performed on human beings or animals.

Data confidentiality. Authors confirm that the protocols of their centers have been followed on matters concerning the publishing of data from patients. They also confirm that all patients included in this study have been given enough information and handed over their written informed consent for their participation in this study.

Right to privacy and informed consent. Authors confirm that in this report there are no personal data of patients.
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Appendix A. Supplementary data

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