

## **Appendix 1**

### **Data collection, processing and storage**

#### *Non-imaging data*

Non-imaging data are collected using paper clinical rating forms according to standard operating procedures designed for the Heart-Brain Study. After pseudo-anonymization, non-imaging data are stored in a central database (OpenClinica, LLC, Waltham, Massachusetts, USA). Data are entered, inspected, and signed off by a local investigator. Data are monitored at site and study level by a data-manager.

#### *Biomarkers*

Blood samples are stored at local biobanks. Cerebrospinal fluid (CSF) samples are stored and processed centrally.

#### *Imaging data*

We set up a data storage and analysis platform for imaging data (Figure 1). Images and derived data are stored centrally using the Extensible Neuroimaging Archive Toolkit (XNAT) [1], hosted by Translational Research IT (TraIT) [2]. MRI scans are anonymized locally at the four data acquisition sites using the Clinical Trial Processor (CTP). Derived imaging markers are stored next to the original MRI scans on XNAT. Image data quality is automatically monitored with a quality assessment (QA) report that summarizes the data consistency between Open Clinica and XNAT and agreement with the scanning protocol. Quality of scans is reviewed visually by neuroradiologists (brain MRI) and cardiologists (cardiac MRI).

Quantitative imaging biomarkers from cardiac and brain MRI are computed. Brain MRI scans are processed with two automated pipelines implemented in the Fastr workflow method [3]. First, a brain tissue (Figure 2a) and white matter hyperintensity segmentation (Figure 2b) method developed by Quantib B.V., based on [4], is applied to the T1-weighted and fluid attenuation inversion recovery (FLAIR) scans. From these segmentations, the following parameters are computed: volumes in milliliters (mL) of total brain gray matter (GM), white matter (WM), CSF, and white matter hyperintensities (WMH). Second, a region-of-interest (ROI) segmentation method and arterial spin labelling (ASL) quantification method is applied [5–7]. The ROI segmentation uses GM and WM

segmentation (SPM8, London, UK) [8], and multi-atlas registration of 30 atlases with 83 structural brain regions [9,10] based on the T1-weighted scans (Figure 2c-d). Quantification of ASL data into cerebral blood flow (CBF) maps (Figure 3) includes motion-correction of the raw ASL data [11] and partial volume correction [12]. This pipeline results in the following imaging biomarkers: total brain volume (mL), GM and WM volume of 83 brain structures (mL), and average (and standard deviation) CBF in the GM brain regions (mL/100g/min). In addition to the automatic processing, manual annotation of microbleeds and segmentation of infarcts is based on susceptibility-weighted imaging (SWI) and FLAIR scans respectively. The total CBF (mL/min) is quantified based on phase-contrast flow scans in the cerebropetal arteries. The basilar artery and internal carotid arteries are manually contoured using the flow analysis tool of Mass software (Division of Image Processing, Department of Radiology, Leiden University Medical Center, Leiden, NL) (Figure 4).

For cardiac MRI post-processing, an automatic pipeline for epicardium and endocardium contour detection on the two chamber and four chamber (2KLV and 4K) cardiac MR cine scans is developed (Figure 5). The contour detection uses multi-atlas-based segmentation and an image-registration-based model. The detected contours are used to segment the diastolic and systolic phases on two orthogonal views, and to process short-axis scans for volumetric parameters, i.e. end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV) and ejection fraction (EF). In addition, diastolic function is assessed from the mitral inflow pattern derived from phase-contrast MRI.

## References

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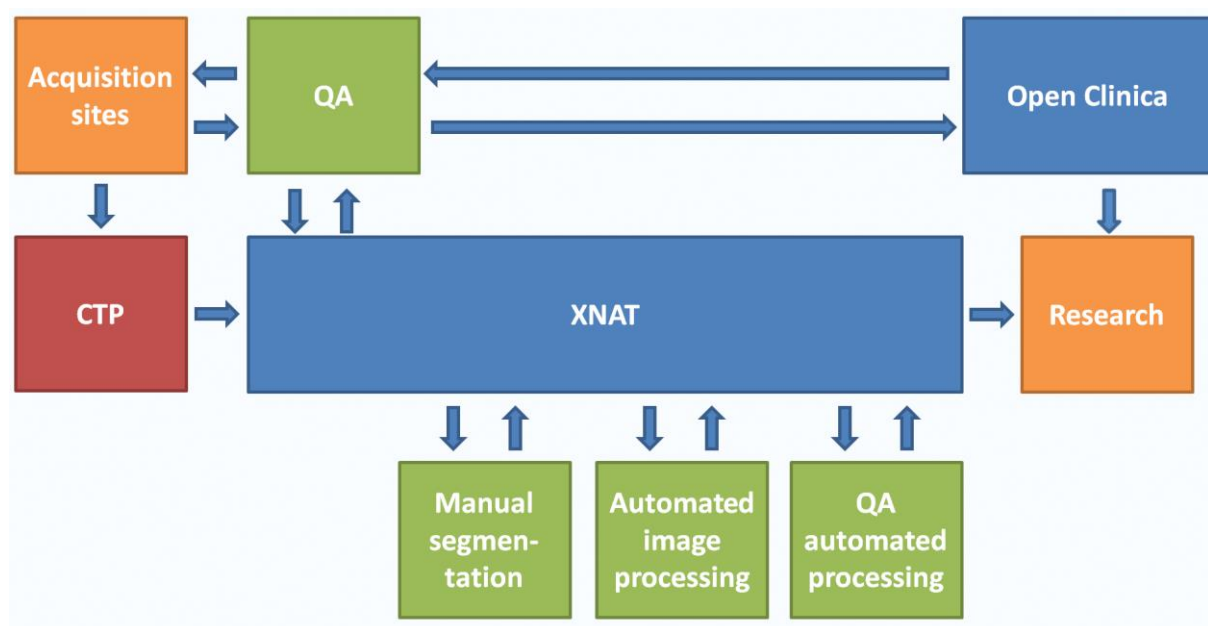


Fig. 1. Overview of the data storage and analysis platform and data flow. MRI scans are uploaded from the four data acquisition sites to Extensible Neuroimaging Archive Toolkit (XNAT). For anonymization of the scans, data is sent via a Clinical Trial Processor (CTP). The consistency of the data in XNAT and their correspondence with the clinical data in OpenClinica is assessed weekly with an automated quality assessment (QA) procedure. In addition, scans are downloaded from XNAT for manual and automatic processing, and for visual QA of the scans and the automated processing results. Results of all steps are uploaded back to XNAT. Finally, derived image data are downloaded from XNAT and clinical data are downloaded from OpenClinica. For analysis, downloaded data are combined into appropriate software formats.

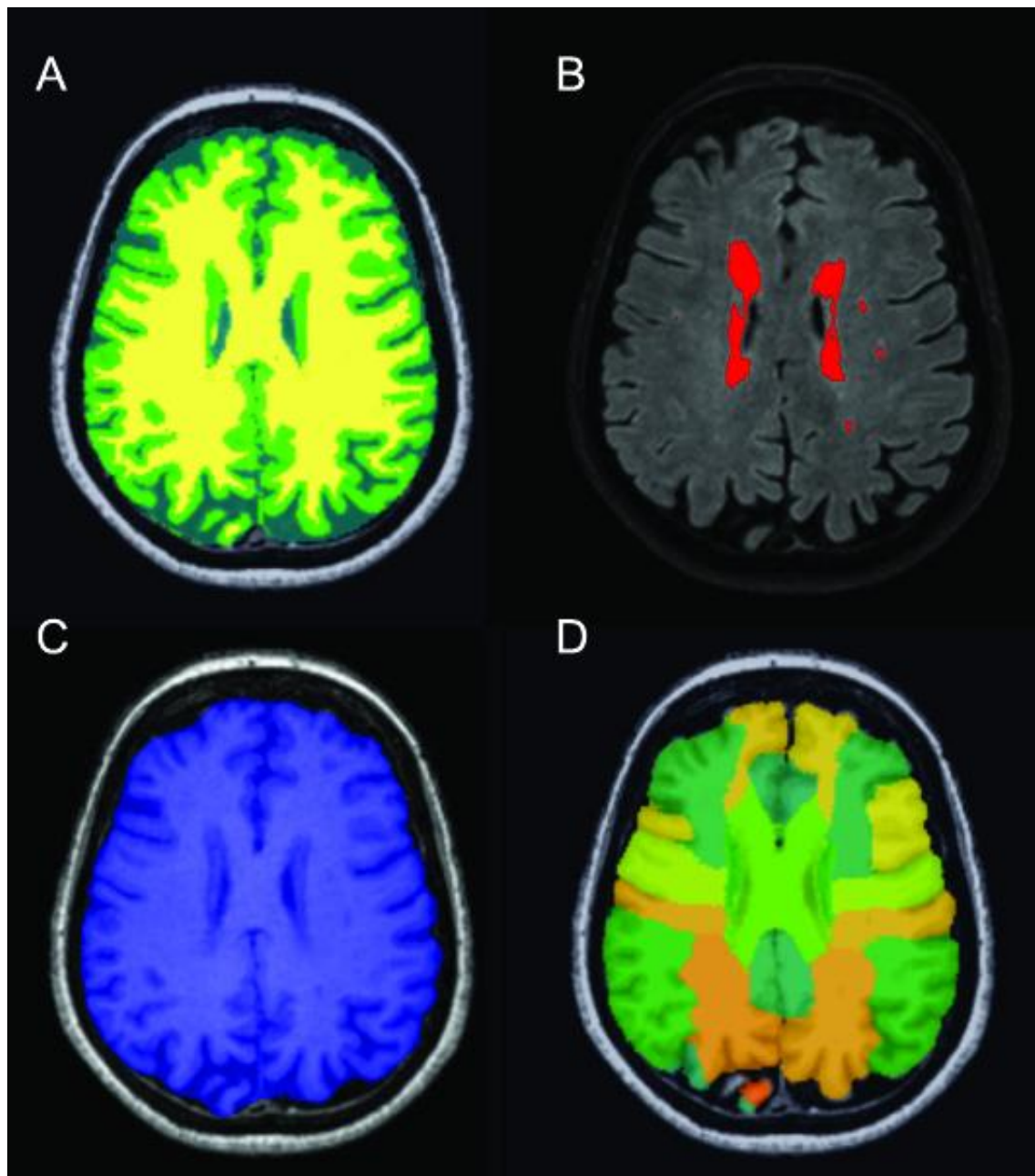


Fig. 2. Imaging biomarkers of the structural brain scan of the Heart-Brain Study: A) brain tissue segmentation (yellow = white matter (WM), green = gray matter (GM), blue = cerebrospinal fluid (CSF), B) red = white matter hyperintensities (WMH), C) brain mask, D) 83 regions-of-interest.

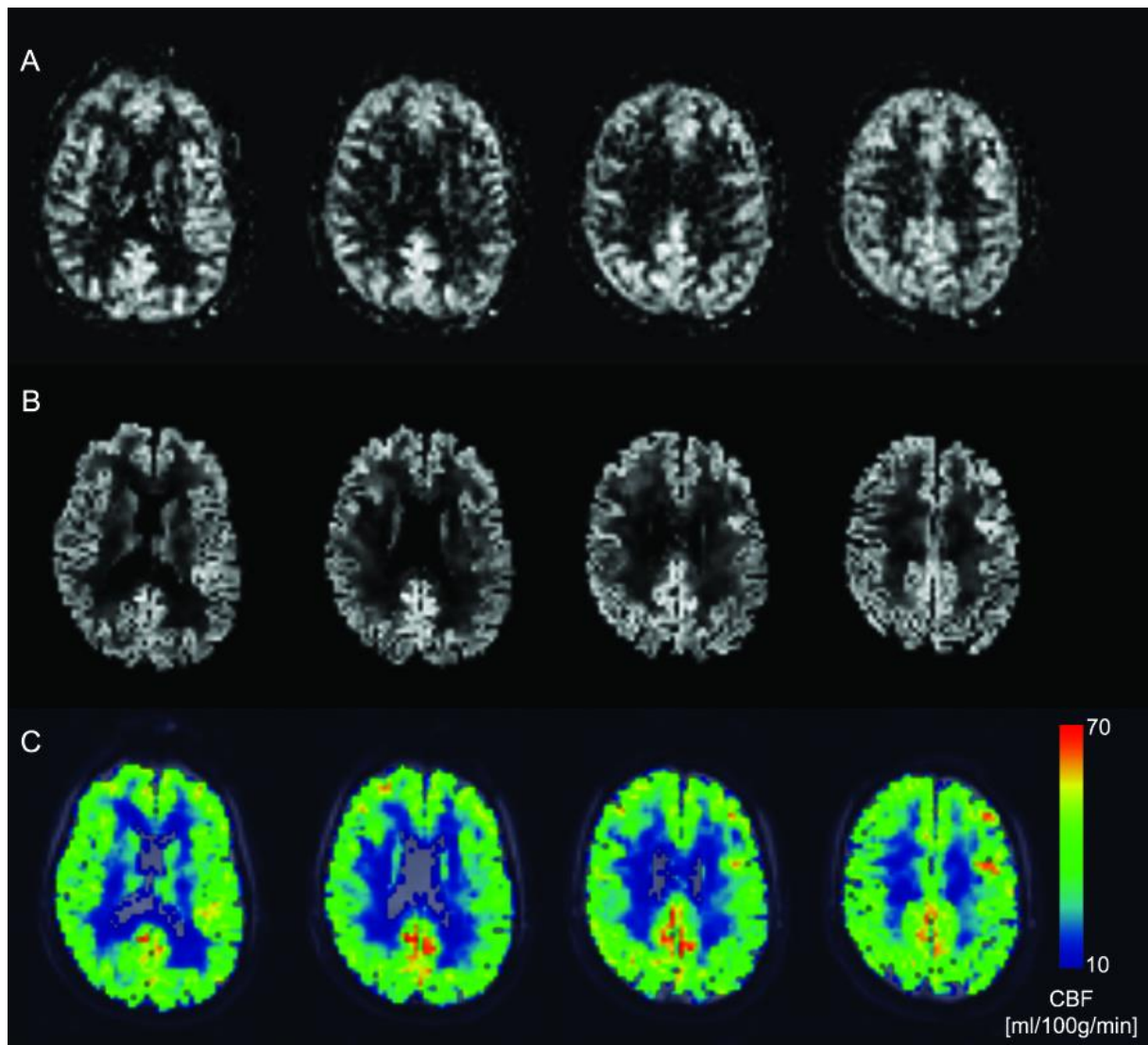


Fig. 3. Arterial spin labeling (ASL) scans for one Heart-Brain Study participant, four axial slices are shown. A) Perfusion-weighted ASL images after motion correction, B) cerebral blood flow (CBF) map, C) CBF map as color-overlay with M0 normalization image as background.

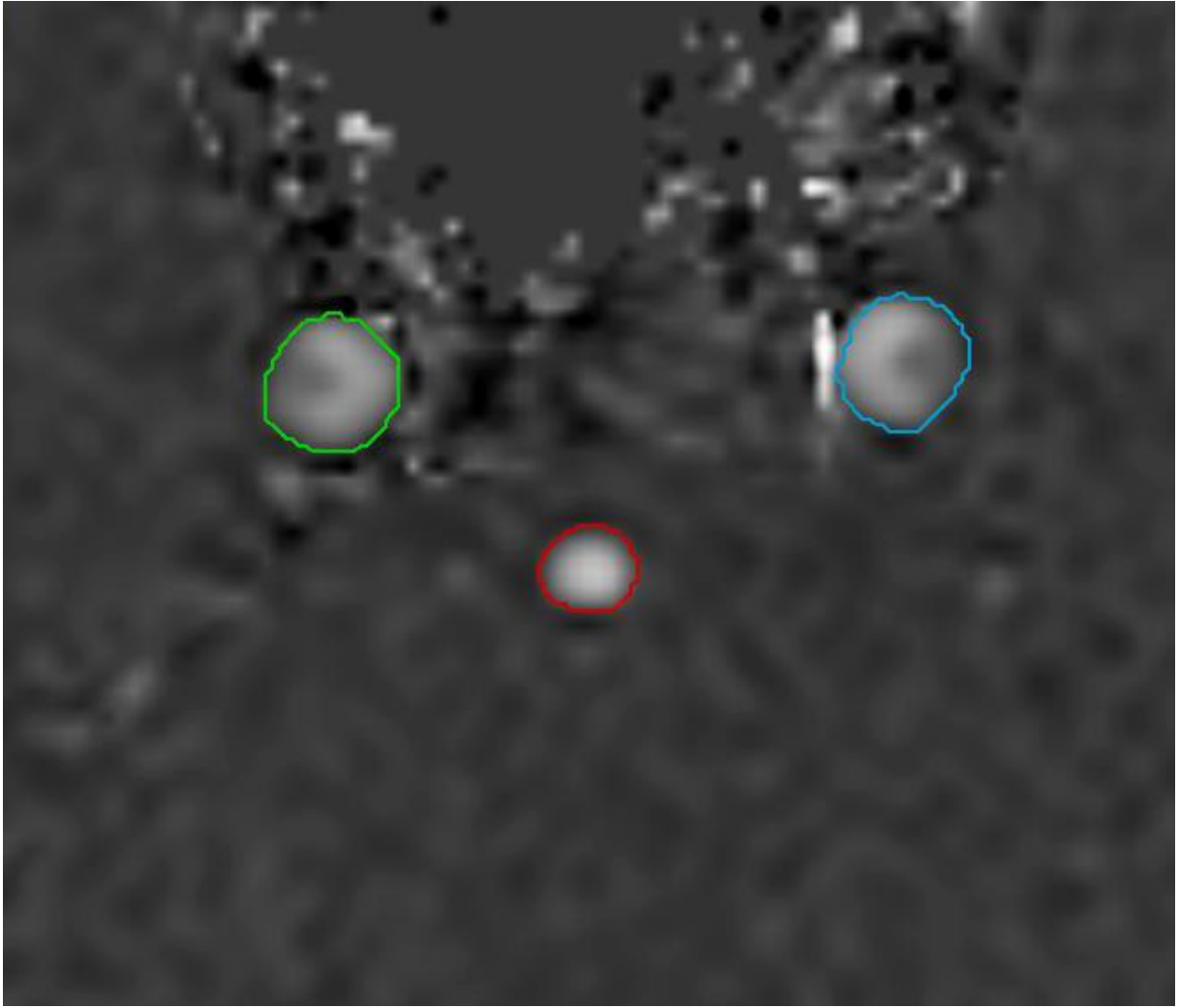


Fig. 4. Q-flow pipeline; manual segmentation of left and right carotid artery and basilar artery.



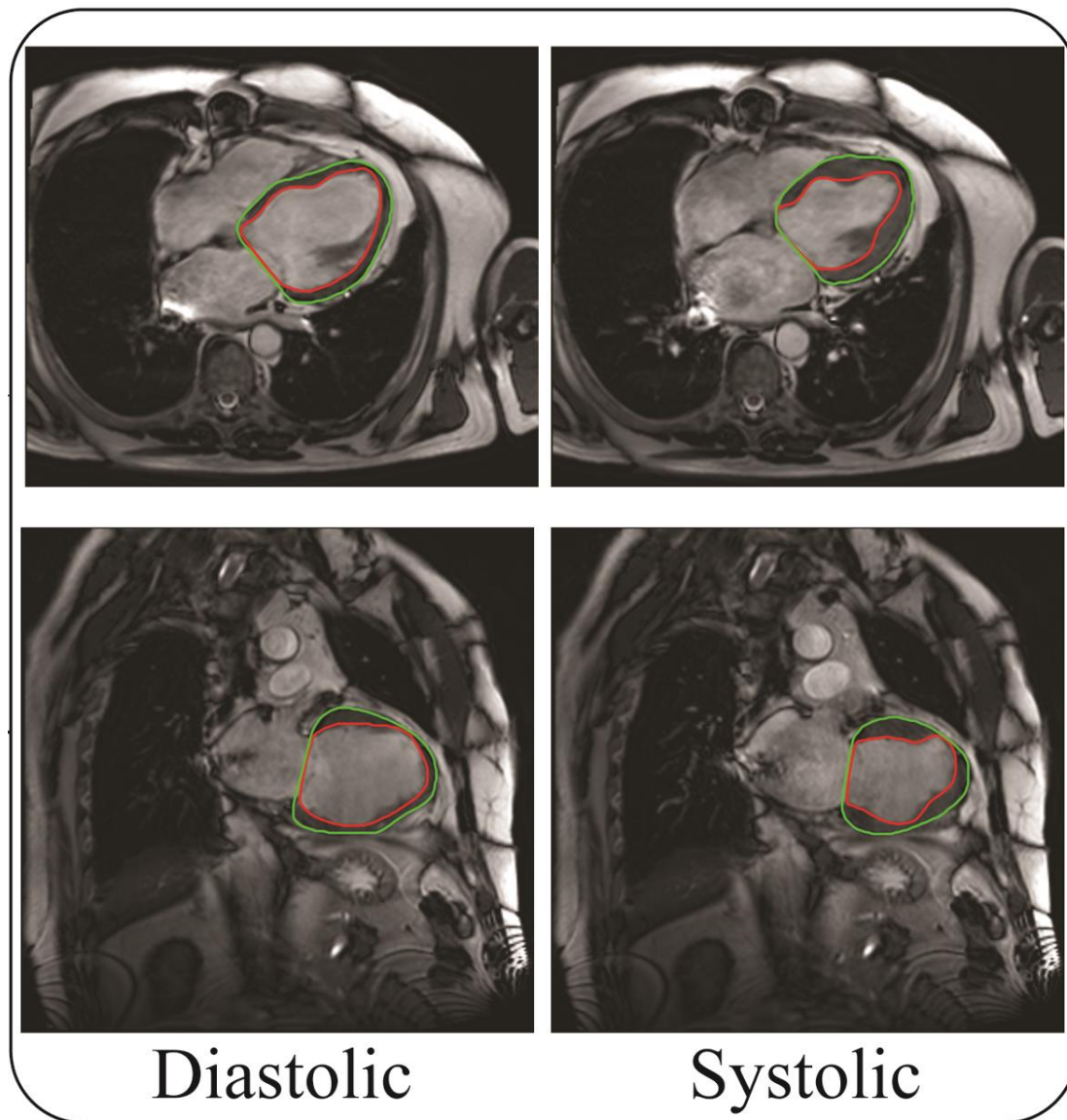


Fig. 5. Examples of MR cardiac parameters that are extracted through automated cardiac post-processing. An automatic pipeline for epicardium and endocardium contour detection on the two chamber (below) and four chamber (above) cardiac MR cine scans. The proposed pipeline uses multi-atlas-based segmentation and an image registration based model for the contour detection. These contours are used to process short-axis scans for true volumetric parameters.