

User's Guide

# PMOD Cardiac PET Modeling (PCARDP)

Version 3.9



PMOD Technologies

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# PMOD Cardiac PET Modeling Tool (PCARDP)

The PCARDP tool represents a flexible environment for the quantification and analysis of myocardial PET studies. Particularly, the following analysis scenarios are supported:

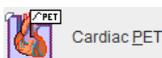
- ▶▶ Processing of dynamic PET studies of the heart with a broad range of tracers. Depending on the tracer, the results represent myocardial blood flow (MBF) or a metabolic turnover such as the metabolic rate of glucose (MRGlu).
- ▶▶ Processing of static PET studies. The results consist in polar uptake map and a corresponding numeric table.
- ▶▶ Processing of gated PET studies to assess LV function. The results represent various functional metrics like LV volume/time curve, ED (end-diastolic) volume, ES (end-systolic) volume, SV (stroke volume), EF (ejection fraction) as well as segmental uptake.

Parallel processing of paired stress and rest studies for a side-by-side comparison is supported for all the above scenarios.

# User Interface

## Starting the PCARDP Tool

The PCARDP tool is started with the **Cardiac PET** button from the PMOD ToolBox



or by directly dragging image files onto the above button.

## Organization of the PCARDP User Interface

The user interface of PCARDP consists of four pages which can be selected by tabs. The color layout and pages name change based on the analysis scenario.

Particularly we have a common interface for the dynamic and static PET analysis as illustrated below:



**DB Load** page: This page for loading the data is only available when the use of PMOD databases is enabled.

**Reorientation** page: This page serves for the spatial reorientation of the data to the standard short axis orientation and the definition of the myocardial segments.

**Kinetic Modeling** page: This page deals with the kinetic modeling of the segmental TACs, the parametric mapping and the exploration of the results.

**Compare** page: This page allows comparing the stress and rest outcome as well as the comparison with a normal database, if one is available.

The interface slightly changes for the gated analysis:



1) **DB Load** page: This page for loading the data is only available when the use of PMOD databases is enabled.

**Reorientation** page: This page serves for the spatial reorientation of the data to the standard short axis orientation and the definition of the myocardial segments.

**GATED Analysis:** This page allows exploration of the results and deals with the gated analysis.

**Compare** page: This page allows comparing various stress and rest gated analysis outcomes.

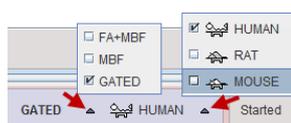
## Step-Wise Processing

Data processing is organized by a stepwise progression from one page to the next towards the end result. On each processing stage the user has to take some action such as data

loading, alignment inspection or parameter configuration, and then start the next processing step with the action button located in the lower right. As soon as the result is calculated, it will be shown on a new page representing the new processing stage. To repeat a calculation with modified parameters, the action button in the lower right has to be activated again.

### Processing Mode

The main switch between the different processing mode is located at the window bottom, offering the selections **FA+MBF** (for water PET), **MBF** (perfusion tracers and FDG), and **GATED**. The second switch between **HUMAN**, **RAT** and **MOUSE** initializes the configuration settings to values optimized for the corresponding species.



### Convenience Buttons

In some places the following buttons appear:

-  Hide some of the user interface elements to free some space. With the panel hidden, the icon changes to . When this button is activated, the panel is shown again. This functionality may be helpful with small computer displays.
-  Reset the parameters to their default values.
-  Display help information.

### Clearing Studies

When new data is loaded, the previous data and results are cleared. However, it is also possible to explicitly reset the tool closing all image series in the PCARDP tool with **Close all studies**  button available on the lateral taskbar. Alternatively, this can be done selectively for STRESS and REST series by selecting the **X** button to the right of the image.

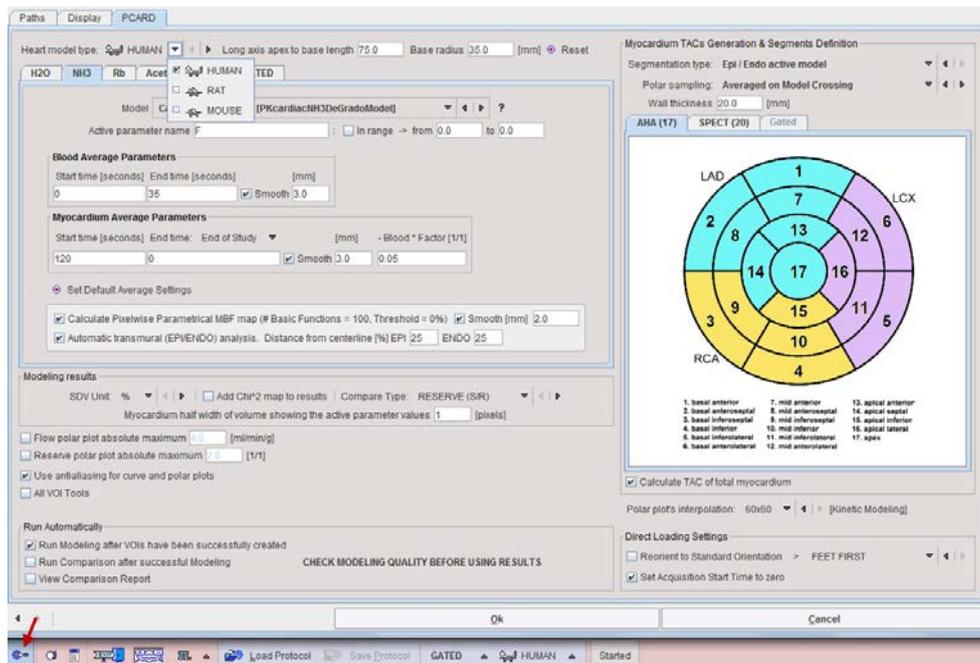


# Configuration Settings

If PCARDP is used to process different study types, like dynamic and gated studies, the configuration needs to be adjusted before a new study. The configuration dialog can be opened using

- ▶▶ the ALT+S key,
- ▶▶ the  button in the lower left, or
- ▶▶ the **Settings/Modify** entry in the **Cardio PET** menu.

The following window appears with the processing settings on the **PCARDP** tab.

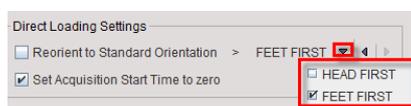


The **Heart model type** list serves for selecting the species: **HUMAN**, **RAT** or **MOUSE**. The default geometry parameters such as **Long axis apex to base length**, **Base radius** and **Wall thickness** values are adjusting accordingly. The values can be changed in the corresponding number fields for optimizing the automatic definition of the myocardium. The default values for the selected species can be restored with the **Reset** button.

The specific dynamic and gated configurations are described separately in dedicated sections.

## Configuration for Image Loading

There are two image-related configuration options:



For the data processing it is important that the images appear in the HFS orientation. If this is not the case, either the **HEAD FIRST** or **FEET FIRST** option of **Reorient to Standard**

**Orientation** should solve the problem. If not, please activate the **with Operation button** button during image loading and use the **Assistance** button to correctly HFS orient the PET study.

If the **Set Acquisition Start Time to zero** option is enabled, the start time of the first selected acquisition is set to zero, and the other frame times adjusted accordingly. This setting is highly recommended because due to DICOM compatibility issues the whole data may be shifted in time. In such a case, kinetic modeling will most likely not result in valid estimates.

## Saving and Retrieving Configurations

If different types of studies are analyzed with the same PCARDP installation it is recommended to proceed as follows:

For each study type

- ▶▶ Configure the different settings as described above.
- ▶▶ Perform a successful processing.
- ▶▶ Save the successful configuration using the **Settings/Save** entry in the **Cardio PET** menu and name it suggestively, eg "Ammonia 1-Compartment".

Later, when PCARDP is started to process a particular study, **Load** the appropriate configuration using the **Settings/Retrieve** entry in the **Cardio PET** menu. This restores all configurations, and processing can be begun without going into the configuration details again.

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**Note:** Loading a settings file restores all configurations of the entire PCARDP tool. For instance, the configurations related to all tracers are restored, not only of the currently active one.

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When PCARDP is closed, all configuration settings are stored as the initial PCARDP settings. They are loaded again the next time PCARDP is started with the same PMOD login. Therefore, explicit loading of a settings file is not required if only a single study type is processed. This behavior can be exploited as an alternative to using different settings files. To do so define a separate PMOD login for each study type, eg. "Cardiac NH3" and "Cardiac H2O". These logins can then be used to process ammonia and water studies, respectively.

## Additional Documentation

The PCARDP tool is based on a range of functionalities from the PMOD environment which are not explained in this documentation. Please refer to the

- ▶▶ *PMOD Base Functionality Guide* for information related to data loading, image viewing, volume-of-interest (VOI) definition.
- ▶▶ *Cardiac PET Workbook* for further recommendations and trouble-shooting hints.
- ▶▶ *PMOD 3D Rendering Tool Users Guide* for rendering-related information.
- ▶▶ *PMOD Fusion Tool Users Guide* for fusion related information.
- ▶▶ *PMOD Kinetic Modeling Users Guide* for kinetic modelling related information.

## Chapter 1

# Dynamic Data Processing

PCARDP implements the following features for data processing of dynamic PET data:

- ▶▶ Calculation of anatomical images representing blood volume (BV) and myocardium (MYO) from the dynamic uptake series. Depending on the tracer, early and late images are averaged, or alternatively a factor analysis can be applied (water only).
- ▶▶ Calculation of time-activity curves (TAC) from the left ventricle (LV), the right ventricle (RV), as well as from different segments of the myocardium.
- ▶▶ Fitting of adequate kinetic models to the segmental TACs to quantify the tissue parameters such as perfusion or glucose consumption.
- ▶▶ Calculation of parametric perfusion maps (for  $\text{NH}_3$  data only). Use of the perfusion maps to perform an analysis of the transmural perfusion gradient.
- ▶▶ Combination of the results to quantify myocardium function in well-defined sectors specified by the American Society of Nuclear Cardiology (*ASNC* <http://www.asnc.org>) and the American Heart Association (*AHA* <http://www.americanheart.org>).
- ▶▶ Generation of a normals database from a set of quantification results obtained from a cohort of healthy volunteers. Patient results can then be compared against the normal database to quantify deviations in terms of z-scores.

## In This Chapter

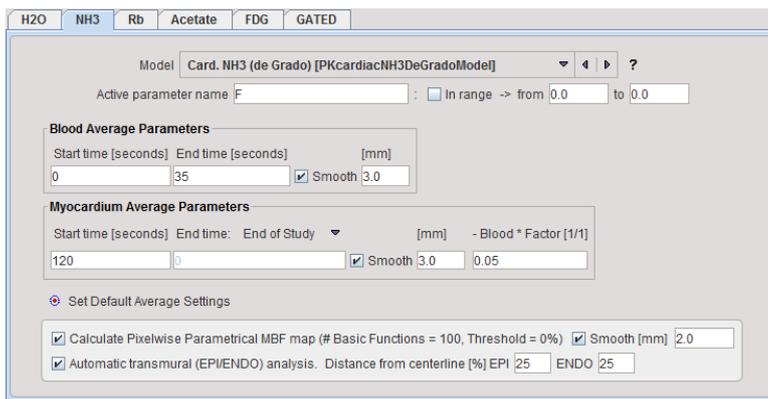
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## Processing Configuration

Access the configuration with the  button in the status line, close to the **Cardio PET** menu. To begin please start selecting the appropriate **Heart model type**. Proceed with the characteristic settings for dynamic PET analysis as described in the *Analysis Selection* (on page 11).

## Analysis Selection

Note the tabs labeled with the different PET tracers and GATED.



Please select the tab corresponding to the data to determine the processing method, the tracer name in case of dynamic data. The tracer-specific processing settings are then accessible in the panel and may be adjusted.

- ▶▶ **Model:** the list selection offers all kinetic models suitable for the selected tracer. The ? button shows a summary description of the currently selected model.
- ▶▶ **Active parameter name:** The cardiac tool has the capability to disregard a parameter value in the statistics when it is clearly outside the physiological range. The string entered in the **Active parameter name** text field defines which parameter is undergoing this restriction. The allowed range needs then to be configured in **In range from .. to**.

There are two sections for defining the defaults for the averaging strategy. The idea is to calculate images showing sufficient anatomical information by a weighted combination of some of the dynamic acquisitions as described in *Generation of Blood Volume and Myocardium Images* (on page 94).

- ▶▶ **Blood Average Parameters:** The definition has a **Start time**, and **End time**, and an optional **Smooth** parameter. In the example above all frames between 0 and 35 seconds (frame start times) will be averaged, and then smoothed with a 3D Gaussian filter of 3mm full-width at half maximum. The result is assumed to represent an anatomical image of the blood volume.
- ▶▶ **Myocardium Average Parameters:** Similar to **Blood**, the **Myocardium** image is generated by averaging the frames between the **Start** and **End** time specified underneath. As there may exist some activity in the cavities, a fraction of the blood

volume image can be subtracted to improve the contrast. In the example above a fraction of 0.05 of the image generated by the **Blood** configuration will be subtracted.

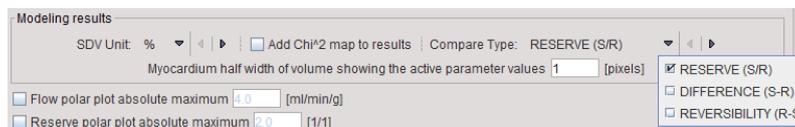
### MBF Special Cases

- 1) In the case of the **NH3** tracer there is a box **Calculate Pixelwise Parametrical MBF Map**. If it is checked a MBF map will be calculated within the area of the left ventricle using a *basis function method* (on page 100). Based on the MBF map, the perfusion across the heart wall can be analyzed. This functionality is enabled with the **Automatic transmural analysis** box.

The **H2O** tracer has as an additional choice **Factor analysis**. Please refer to *Pre-Processing Steps with Factor Analysis (Water only)* (on page 59) for more information how a factor analysis can be employed for the generation of blood volume and myocardium images.

## Modeling Results

This section contains some options with respect to the modeling results:



- ▶▶ **SDV unit:** The kinetic model not only returns the fitted parameter values, but also estimates of their standard error. The standard error can be expressed in absolute units (1/1 configuration), or in percent of the parameter value (% configuration, coefficient of variation).
- ▶▶ **Compare Type:** When a patient has been scanned at rest and stress, the results can be compared in three ways. With the **RESERVE (S/R)** choice the perfusion reserve is calculated by dividing the segmental perfusion values at stress by the corresponding values at rest. With the **DIFFERENCE (S-R)** choice the difference is calculated instead. This latter approach avoids the problem of dividing by a small number which may for instance arise in scar tissue. The **REVERSIBILITY (R-S)** is defined as the inverse difference.
- ▶▶ **Myocardium half width of volume showing the active parameter values:** The cardiac tool constructs a new image data set which shows the calculated parameter value (usually the MBF) in the pixels which were used for calculating the segmental TACs. Usually, these will be pixels along the myocardium centerline, resulting in images showing segments that are much thinner than the myocardium itself. To make the segments look thicker, pixels on both sides of the centerline can be added. For example a value of 2 would add two pixels to the inner and to the outer of the centerline. Images with increased segment thickness may be an advantage for fusion purposes, especially for a 3D fusion with an angio CT data set. The settings has no effect when the Endo/Epi myocardium outline procedure is selected.
- ▶▶ **Add Chi^2 map to results:** When this box is checked the Chi square value of the kinetic model fit is also returned to PCARDP and assembled in an additional polar map.

## Optional Settings

- ▶ **Flow polar plot absolute maximum:** Allows setting a fixed color table maximum value for the flow polar plot display.
- ▶ **Reserve polar plot absolute maximum:** Allows setting a fixed color table maximum value for the reserve polar plot display.
- ▶ **Use antialiasing for curve and polar plots:** Controls whether lines and points are drawn antialiased or not. With the checkbox enabled graphics look smoother.
- ▶ **All VOI Tools:** Allows accessing all VOI tools when manual adjustment is to be performed after automatic VOI outlining.

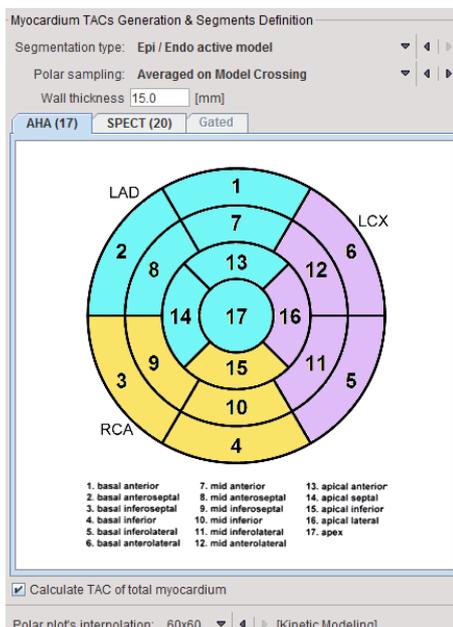
## Flow of Processing

The section **Run Automatically** contains three boxes. If they are checked, a processing will be started as soon the data for it is available:

- ▶ **Run Modeling...** If this box is checked, TACs are calculated and the modeling performed as soon as a complete set of VOIs has been defined.
- ▶ **Run Comparison ..** : If this box is checked, the results of kinetic modeling analysis are automatically transferred to the comparison page. Note that it is advised to inspect the results of kinetic modeling before relying on the generated report.
- ▶ **View Comparison Report:** If this box is checked, the report page is shown each time data is transferred to the comparison page.

## Contouring and Segmentation

The area on the right side of the configuration window defines the heart segmentation model applied as well as the sampling method within the segments.



## Heart Segmentation Type

PCARDP supports different segmentation models. Currently, the standard *AHA 17-segment model* (on page 89) is available, as well as the *ASNC 20-segment model* (on page 92) which is often used with SPECT data.

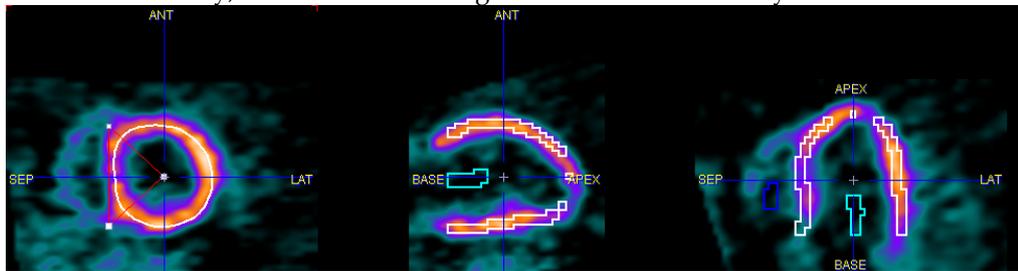
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**CAUTION:** A single segmentation must be employed in order to create a normal database, and when comparing patient data against such a database.

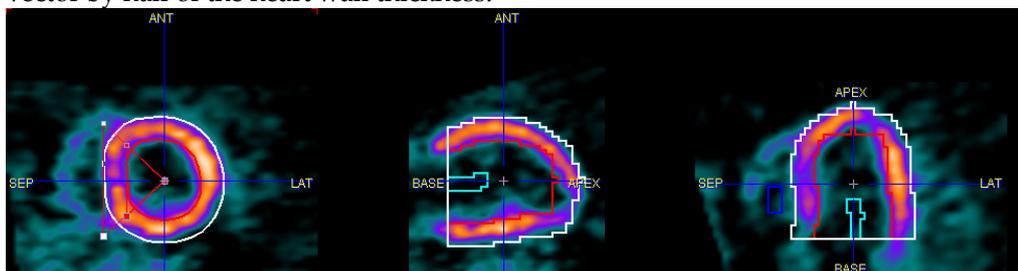
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There are two options available for the myocardium detection procedure:

- 1) **Myocardium center line:** the myocardium centerline detection is done by fitting a geometric model of the left ventricle to the MYOCARDIUM images and then adjust it locally according to the tracer uptake pattern. The resulting outlines are shown as contour lines in the SA image. Note that this procedure should work reasonably with images showing most parts of the myocardium, but may result in a distorted shape in the case of severe defects. Generally, it is recommended to try improving the automatic result interactively, rather than outlining the center lines in a fully manual fashion.

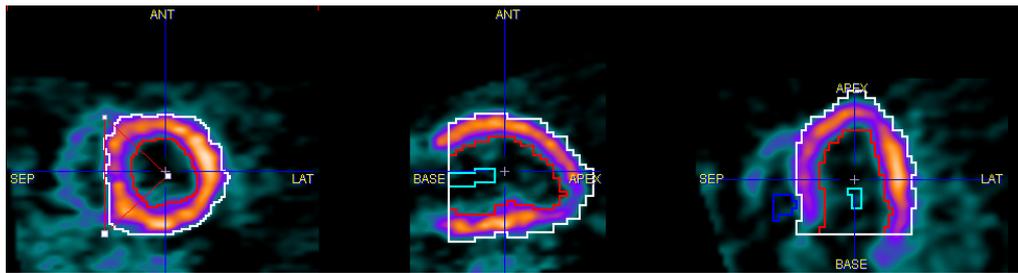


- EPI/ENDO outline:** the myocardium center line is used to generate Epi/Endo contours. Initially, a normal vector is calculated for each vertex of the myocardium center line. Finally, the point belonging to the myocardium center line is translated along the normal vector by half of the heart wall thickness.



The advantage of the EPI/ENDO definition is that the sampling boundary is very clear and that both contours can individually be adjusted.

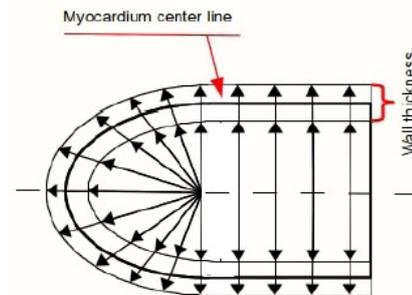
- EPI/ENDO active model:** This approach performs first the **EPI/ENDO outline**, and then adjusts the contours to the local image intensity using an active model (pseudosnake) algorithm.



**Polar Sampling**

The **Polar Sampling** selection defines how voxels are sampled within the outlines and used for the segment TAC calculation. PCARDP interpolates the axial range defined by the myocardium model into 22 slices. For each of the base and mid slices a radial sampling is performed every 10°, and a conical sampling in the apical slices. There are different ways how the myocardium samples are detected:

| METHOD                            | MYOCARDIUM center line                                                                                                                               | EPI/ENDO outline and EPI/ENDO active model                                                              |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| <b>Radial Maximum</b>             | Using the maximum value on the radial profile. The <b>Wall thickness</b> determines the range from the model within which the maximum is determined. | The maximum value is determined along the radial profile between the Epi and Endo profiles.             |
| <b>Model Crossing</b>             | Using the value at the intersection of the radial profile with the myocardial model.                                                                 | Using the value in the middle between the Epi and Endo shapes.                                          |
| <b>Averaged on Model Crossing</b> | Using a neighborhood of 4 voxels at the intersection of the radial profile with the myocardial model.                                                | Using a neighborhood of 4 voxels in the middle between the Endo and Epi shapes.                         |
| <b>Averaged on Radial Maximum</b> | Using a neighborhood of 4 voxels around the determined profile maximum.                                                                              | Using a neighborhood of 4 voxels around the determined profile maximum between the Endo and Epi shapes. |



The sampling locations found are not strict pixel locations, but geometrical coordinates. Correspondingly, the program will calculate the image values at the sampling points by interpolation from the neighboring pixels. Radial Maximum is recommended if there is reasonable uptake in tissue, while Model Crossing allows the user to tightly control the sampling, at the cost of having to exactly define the contours.

With the “Averaged on ..” variants more than a single sampling point is determined: the left/right and the inner/outer neighbors will also be included. The suitability of averaging is very depending on the pixel size: if the pixel size is large, the outer/inner samples might add information which is actually outside the myocardium. Therefore, averaging should only be applied with pixel sizes in the range of 2mm.

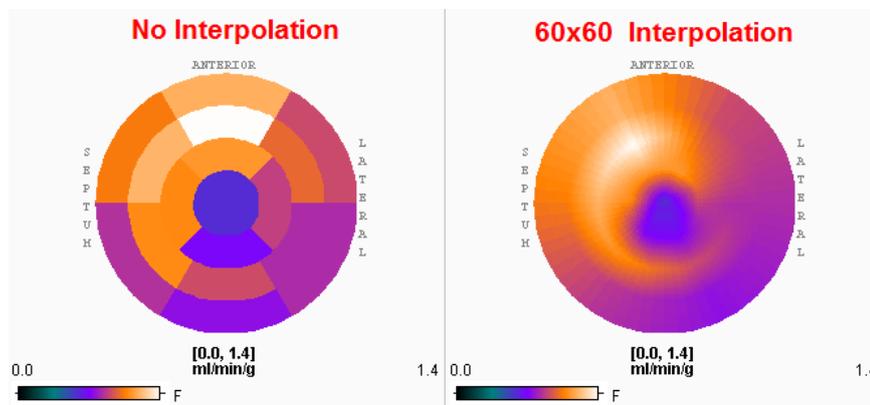
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**Note:** the exact sampling points found by a prescribed sampling scheme can be visualized as spheres in a 3D rendering scene (see *Examining the Results* (on page 42))

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As a means to get a robust global result PCARDP allows averaging the TAC signals from all segments into a single TAC **TOTAL MYOCARD**. This TAC is only generated, if the box **Calculate TAC of total myocardium** is checked.

The **Polar plot interpolation** choice defines how the information calculated in the segments is presented in the polar plots. If it is set to **NO**, the segment structure is clearly visible. If set to **48x48**, values at 48 radial distances and 48 angular increments are interpolated, and similarly with the **60x60** setting. The effect is illustrated in the example below. While the raw polar plot represents the true numbers, the values are smeared by the interpolation filtering.



## Data Processing Steps

Processing a dynamic myocardial study with PCARDP consists of the following steps:

- 1) Configuration of the appropriate kinetic model and the segment model of the myocardium.

Loading of the dynamic studies. If data was acquired in different conditions (Rest/Stress), they can be loaded in a single operation.

Generation of anatomical images showing the myocardium and the blood volume as clearly as possible. This is achieved by averaging appropriate frames as described in the section *Generation of Blood Volume and Myocardium Images* (on page 94).

Determination of the left ventricular long axis to bring the data sets into standard short axis orientation, as described in *Standard Reorientation of the Heart* (on page 89). An automatic procedure is available. If it fails, the orientation must be manually adjusted by the user.

Definition of the volumes-of-interest (VOI) in the short axis view. The VOIs are required to calculate the TACs of the right ventricle, the left ventricle, and the different myocardium segments. An automatic procedure is available. If it fails, the VOIs must be manually corrected or outlined by the user.

Calculation of the time-activity curves. The number of myocardial TACs depends on the selected segment model (see *Myocardium Segment Models* (on page 89)).

Transfer of the TACs to the kinetic modeling tool. The LV TAC serves as the input curve, the RV TAC is applied for spillover correction in the septal segments, and the myocardium TACs are fitted with the selected model (see *Kinetic Models* (on page 95)). The result is a set of model parameters for each TAC.

The result parameters are returned to the cardiac tool for the assembly of the results. They are displayed as polar plots, and compiled into report pages.

If one of the ammonia tracers is applied, a parametric MBF map is additionally calculated using a basis function method.

Different types of reports can be generated and printed.

A normal database can be compiled from the results of normal volunteers. It can be used to find and quantify the deviations found in patient studies.

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**Note:** These steps are performed for all flow studies, except if the factor analysis methodology is applied to water studies. In that case, different preprocessing steps are applied which are described separately in *Pre-Processing Steps with Factor Analysis (Water only)* (on page 59).

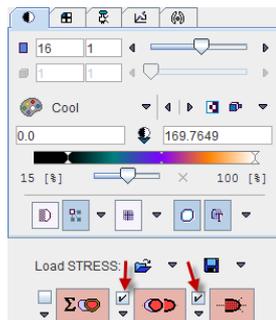
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### Automatic Procedures

On the **Reorientation** page there are check boxes for enabling automatic procedures as described below. They are located to the left of the red action buttons:

-  Button to start the cropping/averaging process for calculating the BLOOD (average of some early frames while the tracer arrives in the left and right ventricles) and the MYOCARDIUM images.
-  Button to start detection of the Short Axis (SA) orientation based on the BLOOD and the MYOCARDIUM images.
-  Button to start detection of the myocardial centerline or the epi/endo boundaries. This is done by fitting a smooth model of the left ventricle (LV) shape to the MYOCARDIUM image and adjusting locally to the uptake pattern. The results are shown as contour lines in the SA images.

The recommended setting is enabling the automatic boxes of the SA reorientation and myocardium contouring. In this way the procedures will run, whenever the time averaging definition is changed.

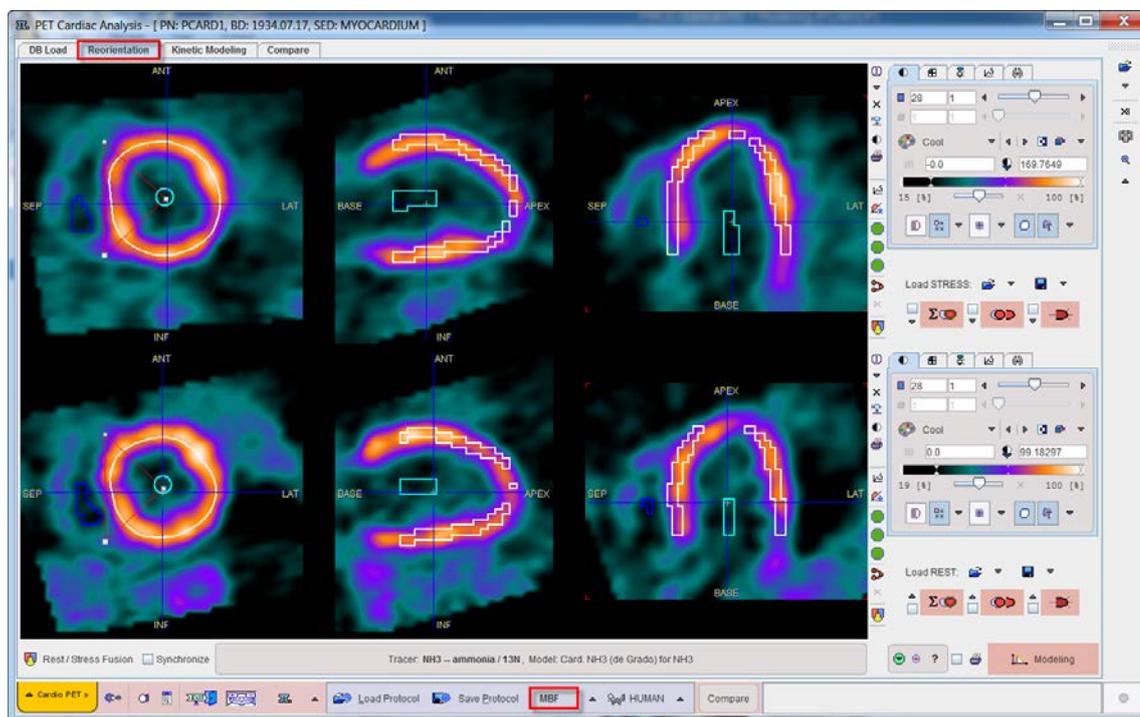


## Data Loading

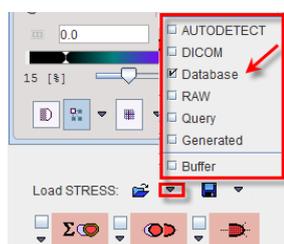
The layout of PCARDP is designed for processing the stress study in the upper half of the window, and the rest study in the lower half. Otherwise the results will be labeled incorrectly and the comparison will be wrong. If only one study is processed, it should be loaded into that part which is more appropriate for labeling. Note that if two studies are selected for loading on the **DB Load** page, *the first one will be considered as stress, and the second one as rest*. When loading DICOM data, PCARDP will analyze the encoded information and show warnings if the model selection seems inappropriate or rest and stress series seem interchanged.

### Loading from the Reorientation Page

On the **Reorientation** page data are loaded using the load buttons in the [STRESS] and [REST] area, respectively. Additionally, the page supports standard short axis orientation of the data and the definition of the myocardial segments.

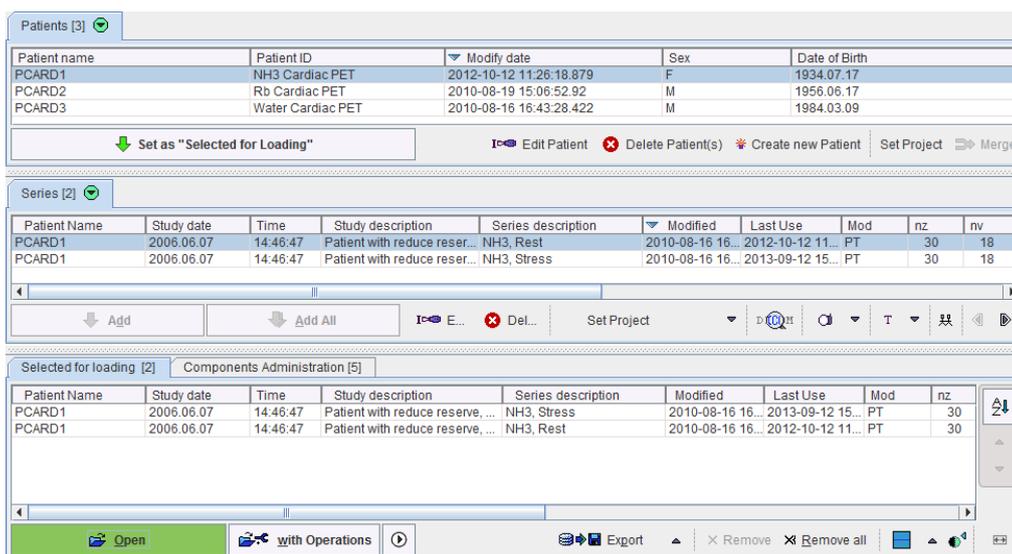


Note the triangle button to the right of the loading button. It allows selecting the data format of the studies, in the example above **Database**. Activating the button opens an image data selection window for selecting and loading the images.



### Loading from the DB Load Page

If the database functionality is enabled, the user interface shows an additional tab **DB Load**. On this page, both the rest and the stress studies should be selected for loading, with the stress study on top as illustrated below.



Alternatively, images can be loaded via the lateral taskbar:



-  Load image. The format can be selected with the small down arrow below the button.
-  Close all image series in the PCARDP tool, including any image results.
-  Allows aggregating PCARDP results for statistical analysis
-  Allows visualizing the saved results.
-  Allows opening and sending the aggregation results to the R interface for further statistic analysis.

### Direct Loading

When selecting image series for loading, activate the **Open** button. In this case, the loading dialog window will not be shown and the images will be loaded with the corrections enabled in the *configuration* (on page 6). If adjustments of the orientation or the timing are required, please use **with Operations**.

## Generating Blood Volume and Myocardium Images by Averaging

### Cropping and Time Averaging

Depending on the field-of-view of the scanner and the reconstruction settings, the heart may only cover a small fraction of the image volume. In order to ease processing it is

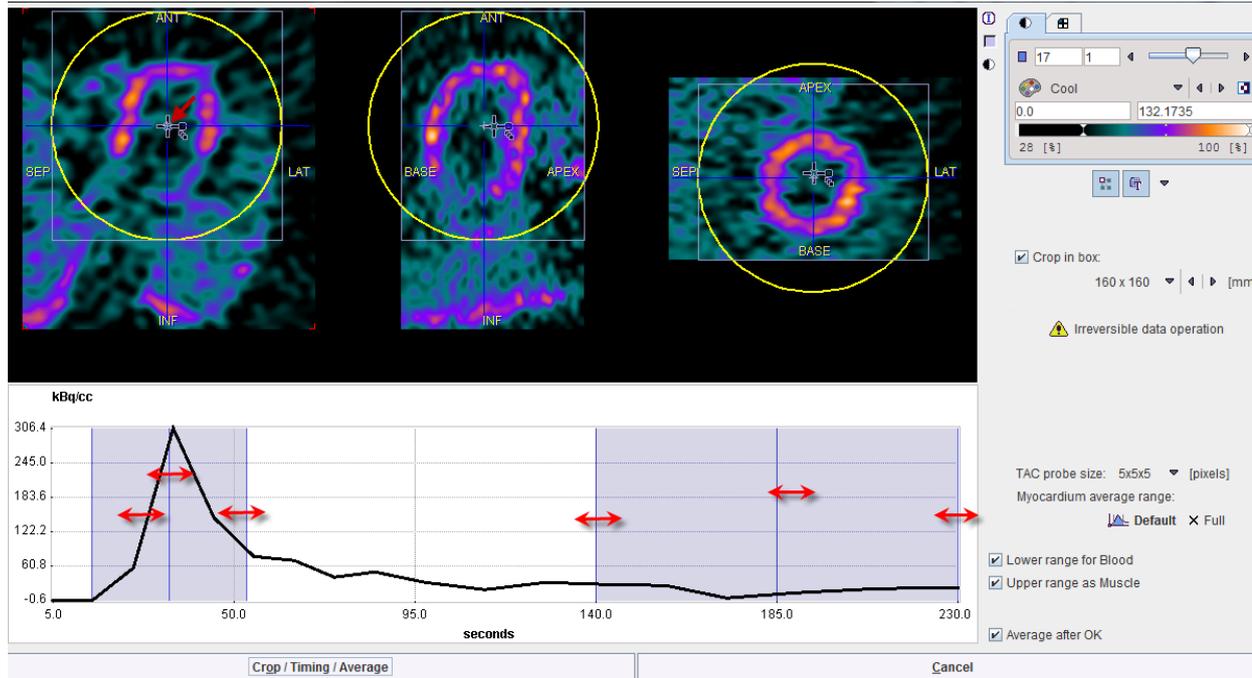
recommended using a cropping procedure for restricting the image volume to the heart. Ideally, cardiac PET images should already be reconstructed with limited field-of-view centered at the heart, and with pixel sizes in the order of 2 mm.

The purpose of averaging the early (BLOOD) and the late frames (MYOCARDIUM) is to obtain images with optimal anatomical information to be used for the SA reorientation and myocardium detection. Their quality has a direct impact on the automatic procedures, and manual adjustments are also easier with clear images. There are various reasons why the images calculated with the default averaging settings may not be optimal:

- ▶▶ Low injected activity, resulting in noisy images. Because of the dilution effect the tracer is not well seen in the cavity of the left ventricle (LV).
- ▶▶ Delayed appearance of the bolus so that too much background is included in the calculation of the BLOOD images.
- ▶▶ Poor tissue perfusion making the LV anatomy unclear. There is no real solution to overcome the problem. A workaround is using the BLOOD image as an additional guidance in outlining.
- ▶▶ Patient or heart motion causing a blurring of the MYOCARDIUM image.

The following procedure is recommended to generate optimal BLOOD and MYOCARDIUM images:

- ▶▶ Compare the Stress and Rest series and decide, which images have better quality. Work on these images towards a satisfactory solution.
- ▶▶ Select the button  for the averaging process. A dialog window appears which allows to interactively specify a cropping window as well as the averaging ranges. The upper part of the window shows the average images. If the **Crop in box** check is enabled, a cropping volume is also indicated by yellow sphere. The center of this sphere can be placed by dragging the indicated handle. Its size can be changed with the list selection. Before proceeding, the sphere should be placed such that the whole heart is included in the box and that enough margin is allowed for the SA reorientation. With each click an average time-activity curve (TAC) is calculated and shown in the lower curve panel. The sampling is performed by signal averaging around the triangulation mark with a configurable **TAC probe size**. The two shaded areas overlaid on the TAC represent the time ranges for frame averaging. First click into the blood pool of the LV. The TAC curve should show a clear initial peak. Adjust the left area by dragging with the mouse so that the peak is enclosed. Next click into the LV wall to generate a myocardium TAC. Adjust the right shaded area to cover the relevant portion of the late uptake. Activating the **Default** button the average range of the myocardium is set according to the configuration. If modeling only uses 4 min of the data, the myocardium averaging should not extend past 4 min to avoid motion mismatch.



The action button to continue is located in the lower left. It changes the naming according to the enabled options. With all options enabled (recommended) the button is labeled **Crop/Timing/Average**.

- ▶▶ Cropping is an irreversible operation. Therefore an explicit confirmation is requested before it is executed. Note that cropping is only supported once. Thereafter, only changing of the time-averaging definition will be possible.
- ▶▶ Before time-averaging is performed, a dialog window is opened which shows the frame ranges together with the smoothing filter settings based on the default configuration. If needed, they parameters may be modified.

Do you want to create Blood and Myocardium STRESS images?

| Blood         |             |                                            |      |  |
|---------------|-------------|--------------------------------------------|------|--|
| Start [frame] | End [frame] |                                            | [mm] |  |
| 5             | 10          | <input checked="" type="checkbox"/> Smooth | 6.0  |  |

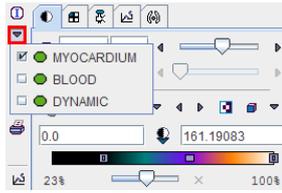
| Myocardium    |             |                                            |      |                        |
|---------------|-------------|--------------------------------------------|------|------------------------|
| Start [frame] | End [frame] |                                            | [mm] | - Blood * Factor [1/1] |
| 21            | 24          | <input checked="" type="checkbox"/> Smooth | 6.0  | 0.05                   |

Upon confirmation, the averaging is performed as prescribed.

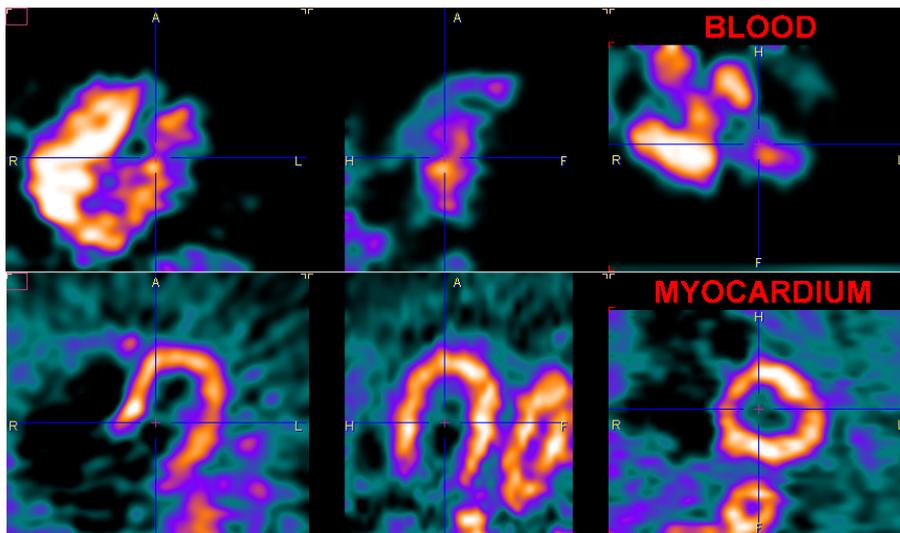
- ▶▶ If the "automatic" checks for the SA reorientation and contouring are on, those two steps are also immediately performed.

### Arrangement of the Result Images

Each time the time-averaging is performed, two new image series - **BLOOD** and **MYOCARDIUM** - are calculated, and the display is switched to **MYOCARDIUM**. The user can switch between the original study and the averaging results by the study selection as illustrated below.



The clearer the anatomy in the images is, the better will the automatic procedures work, and the easier will the analysis be. However, typically images of the following quality can be obtained. Due to the increasing dispersion of the bolus it is often difficult to get a well delineated LV blood pool.



### Potential Problems

Note that there are various reasons why the images calculated with the default averaging settings may not be optimal:

- ▶▶ Low injected activity, resulting in noisy images. Because of the dilution effect the tracer is not well seen in the cavity of the left ventricle (LV).
- ▶▶ Delayed appearance of the bolus so that too much background is included in the calculation of the BLOOD images.
- ▶▶ Poor tissue perfusion making the LV anatomy unclear. There is no real solution to overcome the problem. A workaround is using the BLOOD image as an additional guidance in outlining.
- ▶▶ Patient or heart motion causing a blurring of the MYOCARDIUM image.

## Transforming Images into Standard Short Axis Orientation

The next step is to rotate the images into the standard short axis orientation, see *Standard Reorientation of the Heart* (on page 89). An automatic procedure is available, but when it fails a manual interaction is required.

### Automatic Reslicing

The PCARDP tool offers an automatic procedure for the short axis reorientation. As soon as the button indicated below is activated the procedure is started.

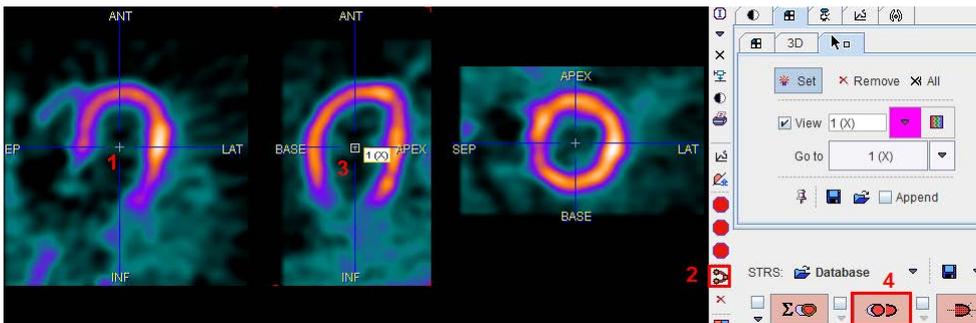


The images are reoriented, and the resulting parameters shown in the reslicing tab. The box next to the reorientation button is for enabling the automatic mode. If it is checked, the reorientation process is started as soon as anatomical images are generated or loaded.

The arrow below the box can be used to copy the short axis transformation from rest to stress, and vice versa. If the transformation is copied, the target images are immediately resliced. Note that due to patient motion between the studies the copied transformation may not be fully adequate. In this case please fine-tune manually using the handles as described in Manual Reslicing below.

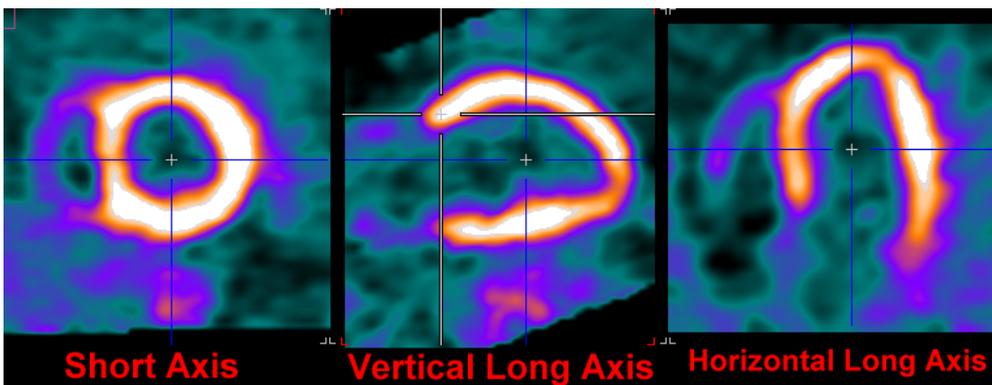
If the automatic reorientation returns an inadequate result, it can be supported by manually indicating the center of the left ventricle using a marker. Please proceed as follows:

- ▶▶ Reset the orientation using the  button indicated above.
- ▶▶ Click into the images until the orthogonal planes intersect in the LV center.
- ▶▶ Select the  button, and click into the LV. A marker appears as illustrated below.
- ▶▶ Activate the automatic reorientation button  again.

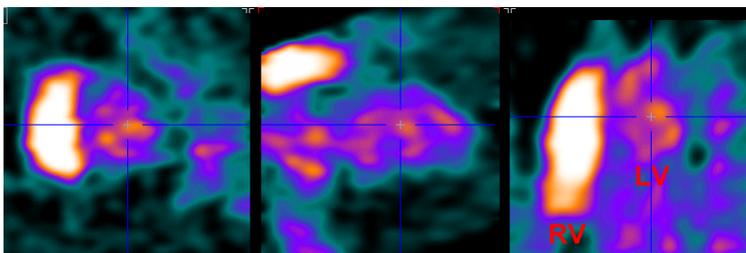


### Correct Short Axis Orientation after Reslicing

Please verify, that after the automatic and/or manual reorientation the images are oriented as illustrated below:

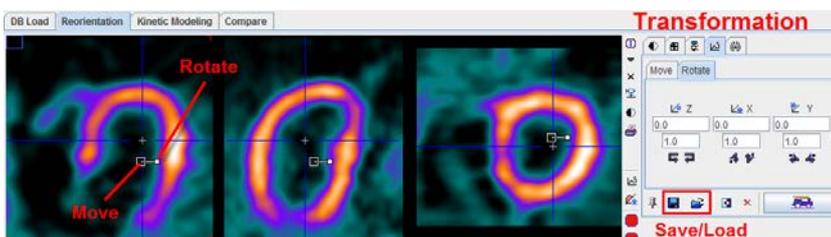


For the automatic contouring and the subsequent segmentation it is very important that the septum appears to the left in the SA slice. This can be verified by checking the right ventricle in the BLOOD images, which are shown with the same transformation parameters. For the automatic contouring it is helpful if the heart is centered in the center of the image volume.



### Manual Reslicing

After the averaging process has completed, the display shows the MYOCARDIUM images in *reslicing mode*.



The button  provides a quick way to bring the images into an approximate short-axis orientation. The fine-adjustment can then be done using the handles which are shown in each of the orthogonal slices:

- ▶▶ The large open rectangle in the image center serves for shifting the images along the axes: click the left mouse button into the rectangle and drag the image into the desired direction.
- ▶▶ The small closed rectangle connected to the image center allows rotating the images: click the left mouse button onto the rectangle and drag around the center.

As an alternative to the mouse-operated reslicing numerical values can be entered on the **Move** and **Rotate** tabs. If anything goes wrong the transformation can be reset with the  button.

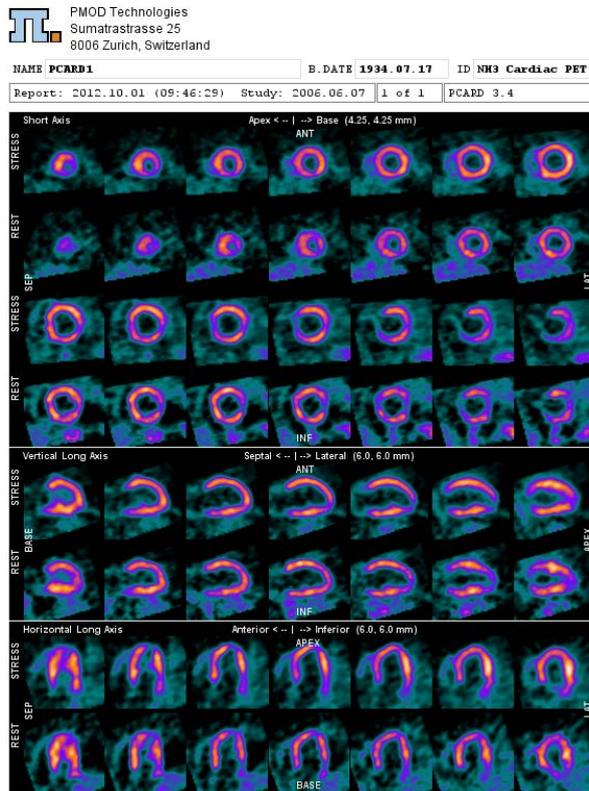
Once the right orientation has been found it is recommended to quit the reslicing mode in order to avoid inadvertent orientation changes. To this end, select any other tab such as the image presentation tab .

### Standard Cardiological Report Page

After the images are properly SA reoriented, a myocardium Stress-Rest comparison report can be generated using the report button located left to the **Modelling TACs** button.



The report layout is organized in three main sections: the upper section shows 14 slices in SA orientation of the Stress study and the corresponding slices of the Rest study; the middle section displays 7 Stress and Rest slices in vertical long axis orientation; the bottom section shows 7 Stress and the corresponding Rest slices in the horizontal long axes orientation.



As usual, the report can be annotated, printed or captured in different formats and sizes.

## Myocardium Outlining by Volumes-of-Interest (VOIs)

After the images have been brought into standard short axis orientation the next task is definition of the myocardium model by VOIs. Again, there is an automatic procedure. However, the contours found by the procedure might sometimes require adjustments or even fully manual outlining.

The next sections describe how the VOIs can be created within PCARDP. For general information about VOI creation and manipulation please refer to the *PMOD Base Functionality Guide*.

### Automatic VOI Definition

Select the contouring button indicated below



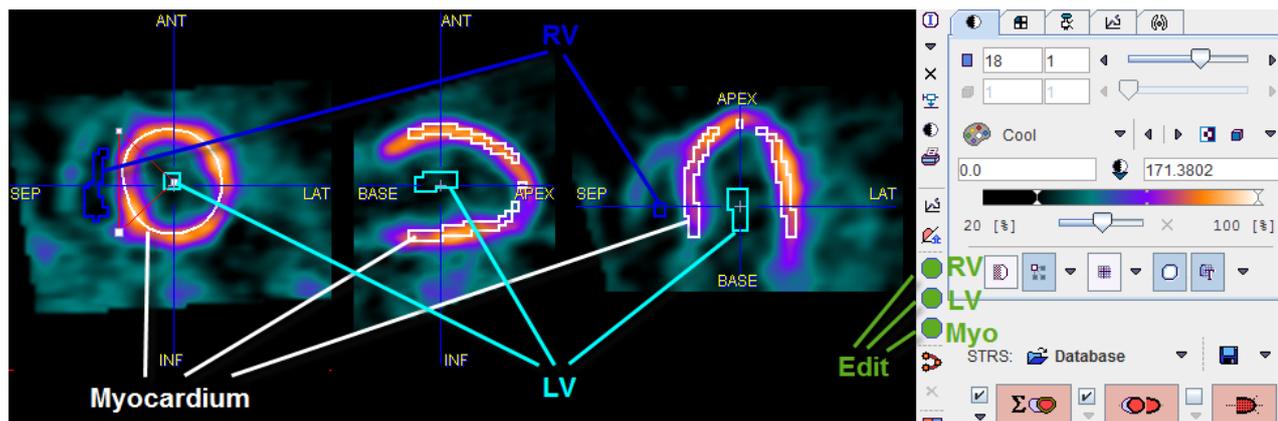
to start the automatic outlining process. The program tries to find a VOI in the right cavity (RV VOI), in the left cavity (LV VOI), and the centerline of the myocardium (Myocard VOI).

The box left to the contouring button is for enabling the automatic mode. If it is checked, the contouring process is started as soon as an automatic SA reorientation completes.

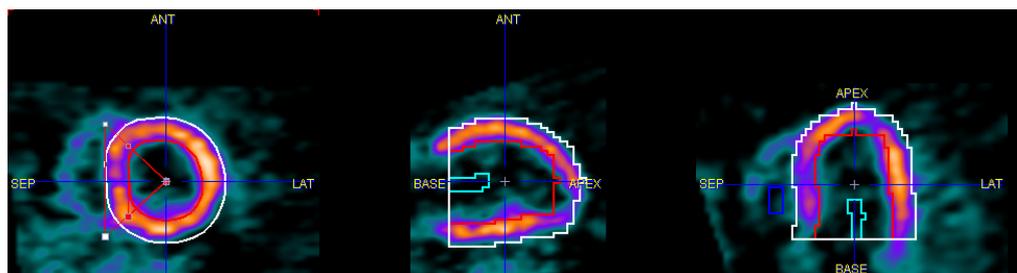
The arrow below the box can be used to copy the VOIs from rest to stress, and vice versa. Note that due to patient motion between the studies and different physiologic conditions, the copied VOIs may not be fully adequate and therefore may need adjustments.

### Inspecting the Result VOIs

The user is notified if automatic contouring fails. Otherwise, the VOIs resulting from automatic contouring are shown as an overlay in the images. The illustration below explains the different elements in the display.



In the case of an Epi/Endo definition the Myocardium consists of two contours:



The green buttons indicate that VOIs have been found for all three structures. It is recommended to check the results before proceeding to the quantification. Crucial locations are

- ▶▶ the base: only that part of the base should be included which shows myocardium in the full 360°;
- ▶▶ the apex: the activity is often reduced towards the apical tip, making the auto-contouring difficult;
- ▶▶ lesions: the program tries to define a smooth centerline, but gross defects can compromise the results.

The easiest way to check the VOI placement is scrolling through the slices as follows:

- 1) Select the image presentation tab and adjust the lower/upper thresholds so that the color allows to clearly see the contour lines. Hereby the reslicing mode is also disabled, so that the images are not unintentionally moved.

Click into one of the orthogonal images, then scroll through the slices using the mouse wheel.

As an alternative click anywhere into the images to get new orthogonal slices at that triangulation point.

If necessary, the VOIs can be adjusted. Use the green buttons open the VOI construction dialog with a corresponding VOI preselected. The VOI definition and correction is explained in the next section.

---

**CAUTION:** When scrolling through the slices you will note that the most apical contour essentially consists of a point. Please *DO NOT DELETE THIS POINT*, because it is essential for the polar plot generation.

---

## Marker Guidance

The automatic myocardium detection can be difficult, especially if the image quality is poor, if there are area of reduced uptake, or if there is no clear separation between myocardium and liver. To make the automatic outlining more robust, the user can specify markers in the myocardium.

## Marker Interpretation

The program will interpret the markers as follows:

- 1) If only 3 markers are placed they are considered to define the *bounding box* of the left ventricle.

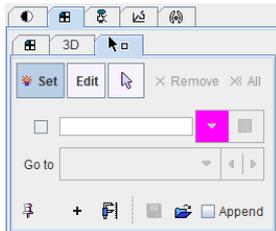
With more markers the algorithm works on a SA-slice basis. Whenever it finds more than 2 markers in a slice, it will fit in a first stage a circle to the markers, and in a second stage the circle to the intensity. In a third stage the information is propagated to slices without markers and used to fit the maximal intensity. Finally, the found contours are smoothed in all directions.

## Placement of Markers

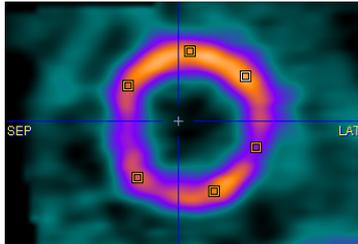
The following procedure is recommended for the actual placement of the markers.

- 1) Navigate the images by clicking into the LV center until the LV extremes are visible.

Select the  button. The tabs in the image controls area are switched to the **Markers** tab.

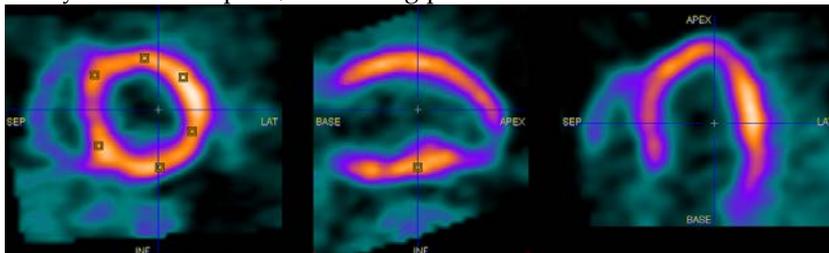


Use the mouse wheel over SA images to locate the first slice showing myocardium uptake as a full circle. Place 4-6 markers by clicking into the center of myocardial wall.

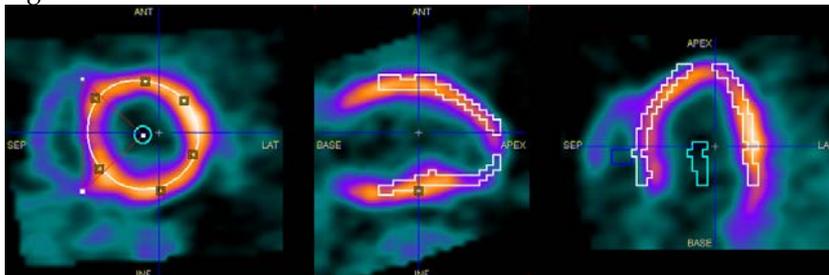


Note that a marker is placed whenever clicking into the image as long as the **Set** toggle button in the **Markers** tab is on. Activate the arrow button to go to the plain triangulation mode. Alternatively, the `Ctrl+Shift` keyboard keys can be hold to avoid marker setting

Repeat this marker placement in some other slices down to the apex, particularly at mid-cavity and in the apical, narrowing part.



Finally select the contouring button  to restart the automatic contour detection algorithm.



If the outlining result is not satisfactory, just add new marker points and repeat, or enter the procedure for manually editing of the VOIs.

### Manual VOI Definition and Editing of Automatic VOIs

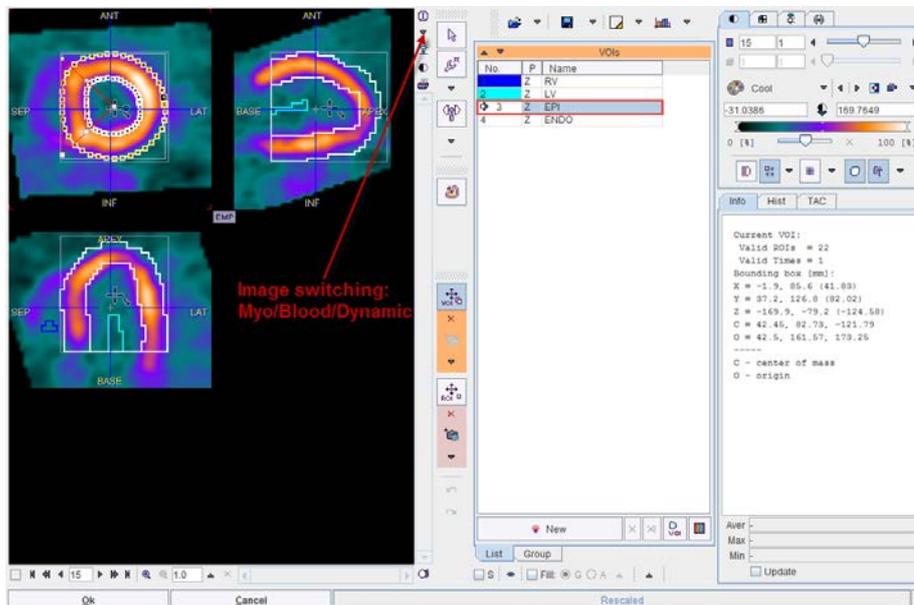
As a last resort VOIs can also be created and edited using the standard PMOD VOI tool. It can be started using the three buttons



which are red as long as the VOI definition is empty, and become green afterwards.

## Definition of Myocardium

It is recommended to start the VOI definition with myocardium. Selecting the button indicated above opens the VOI definition dialog, showing the MYOCARDIUM short axis images in the axial mode.



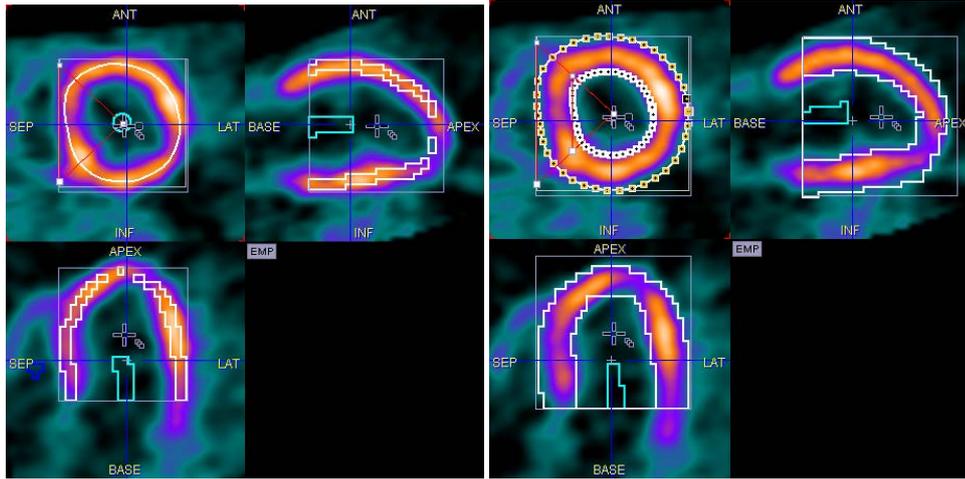
Note that all three images (DYNAMIC, BLOOD, MYOCARDIUM) are available during the VOI outlining process. Use the selection indicated above to switch between the images. The availability of the different information has several advantages:

- ▶▶ The BLOOD images are helpful for defining the RV VOI.
- ▶▶ Switching back and forth between MYOCARDIUM and BLOOD helps to verify whether the contour definition is adequate in myocardium parts with defects.
- ▶▶ The DYNAMIC images can be used to check whether there was significant patient motion during the scan. After completing the outlining, simply step through all the acquisitions and look for the relative movement between the contour and the myocardium.

Note also that the relevant VOIs **RV**, **LV**, and **EPI/ENDO** or **Myocard** are predefined in the **VOI(s)** list. We recommend using the output from the automatic VOI generation and adjusting the contours rather than outlining fully manually.

### Adjustment of the automatically created Myocard Centerline

- 1) To inspect the contours switch to the orthogonal view. In each slice the centerline is represented by a circular region-of-interest (ROI) which has a 60° angle indicating the septum location.



Select the **Myocard** VOI (or **EPI**, or **ENDO**) in the list.

To perform global adjustments like shifting and/or scaling a VOI select the **VOI Action** button



Drag the VOI with the handle in the center, and scale it by dragging the edges of the VOI bounding box.

To reduce the number of contours at the base click into the short axis images, scroll with the mouse wheel to the slices where the myocardium appears in less than a 360°, and then remove the region-of-interest in that slice by selecting the **ROI Remove** button indicated below.

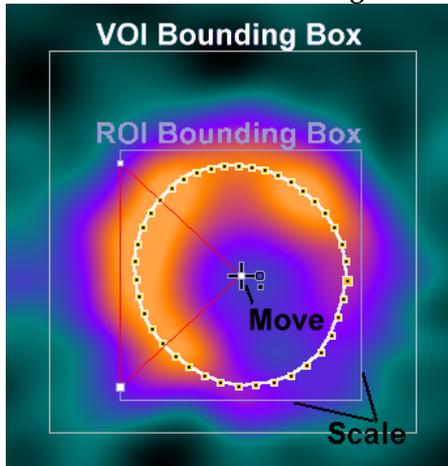


Note that this function is only available if the axial plane is active.

To adjust the shape of the contours in individual slices scroll to a slices where the contour needs correction. A global adjustment can be obtained by scaling and moving the ROI. To this end select the **ROI Action** button



As a result the **ROI Bounding Box** is shown in the image.

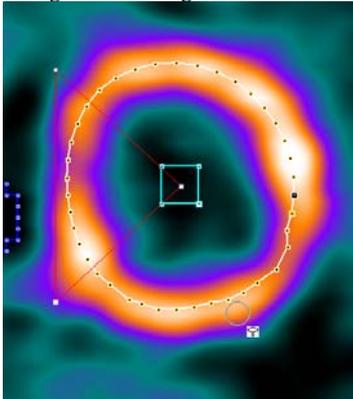


Now the ROI can be scaled by dragging the edges of the bounding box, and moved by dragging the center handle as indicated above. Fine adjustments can be done with a

different tool, the Hammer tool



Drag the tool against the contour points to push them.



After such adjustments have been done in all slices, the myocardium centerline is ready for further processing.

In the case of unsuccessful operations use the undo button



to go back to the previous state of VOI definition.

### **Creating the Myocard Centerline VOI Fully Manually**

To build the centerline **Myocard** VOI fully manually:

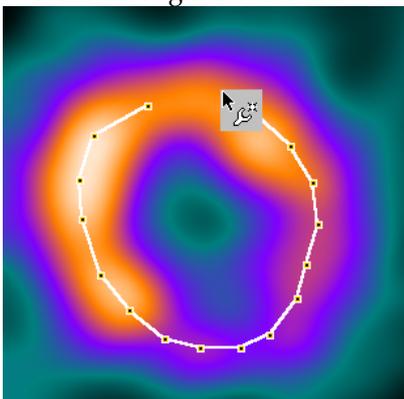
- 1) Select the **Myocard** VOI in the list.

Scroll through the short axis slices until the last basal slice with 360° myocardium is shown.

Select the **ROI Edit** tool



and click along the centerline

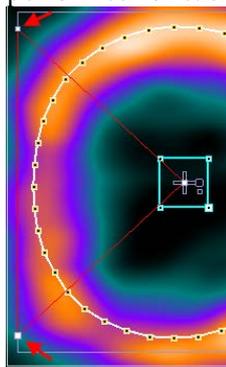


closing the contour by clicking at the first point or selecting the **Finish** button.

Immediately, the septal 60° angle is shown.

Ensure that the septal angle points to the left where the RV should be located. To be able to adjust the angles, select the **ROI** action tab, so that the bounding box of the ROI is visible. Then, drag the connection of the septal angle with the bounding box as indicated below so that a 60° angle is enclosed as indicated below. This adjustment must be

performed for each slice separately.



Scroll to the next slice towards the apex with the mouse wheel, perform the outlining process, and repeat until the centerline is defined in all relevant slices.

---

**CAUTION:** Polar sampling is currently only supported when the number of vertices is identical for all contours. If this is not the case, the polar plot of the dynamic data can not be shown, and the sector TACs are calculated by averaging the activities of voxels alongside the contour.

---

The VOIs in the right and left ventricular cavities are much easier to define.

### *Creating the LV VOI Manually*

- 1) To navigate to the location of the left ventricle make sure the display shows the orthogonal slices.

Adjust the colors so that the location of minimal activity in the left ventricle becomes dark.

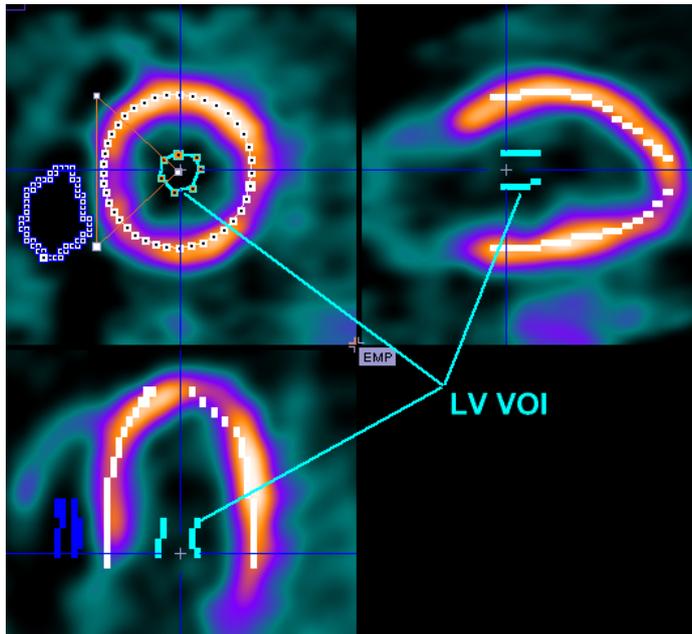
Select LV in the VOIs list. If the myocardium VOI is still selected, it will be overwritten by the following actions.

Select the cold Iso-contour tool 

In the SA images scroll to a slice showing minimal activity in the LV.

Click into the dark area of the LV. An iso-contour ROI is drawn. Make sure it stays in the center of the cavity to minimize the spillover from myocardial activity.

Repeat this process in some of the neighboring slices, until a representative VOI has been defined towards the base:



**CAUTION:** The activity concentration calculated in the LV serves as the input curve during the quantification process. Any underestimation of the input curve will directly translate into an overestimation of the calculated flow in all segments. Therefore, an accurate placement of the LV is of utmost importance!

### *Creating the RV VOI Manually*

- 1) To navigate to the location of the right ventricle make sure the display shows the orthogonal slices.

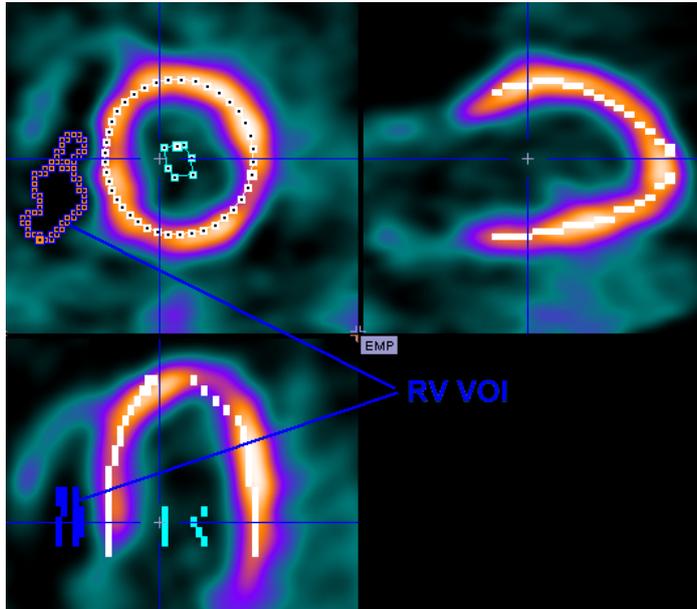
Select **RV** in the VOIs list. If the myocardium VOI is still selected, it will be overwritten by the following actions.

Select the cold Iso-contour tool .

In the SA images scroll to a slice showing the the RV clearly.

Click into the dark area of the RV. An iso-contour ROI is drawn. Make sure it is not too close to the septum to minimize the spillover from myocardial activity.

Repeat this procedure in some neighboring slices, until a representative VOI has been defined:



To check the location of the VOI, switch the display to the BLOOD images.

### VOI Saving

The saving button

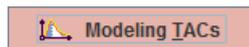


in the VOI tool allows to explicitly save the current VOI definitions in a file. However, the VOIs will also be part of a saved protocol.

After all VOI definitions have been completed, select the **Ok** button of the VOI dialog window to return to the cardiac tool and continue the analysis.

## Calculation of the Time-activity Curves

After the VOIs have been defined the



button becomes active. When it is selected the following processing steps are performed:

- ▶▶ The full DYNAMIC study is resliced into the short axis orientation and interpolated, so that the range from the apex to the base is covered by 22 slices. At the same time, the data set is truncated to a box enclosing only the heart. These operations are also applied to the BLOOD and the MYOCARDIUM data sets.
- ▶▶ The blood time activity curves are calculated in the LV and RV VOIs.
- ▶▶ The time-activity curves in the different myocardial sectors are calculated according to the segmentation model defined in the configuration.

---

**Note:** If complete data is available in the **Rest** and **Stress** rows, the above processing is performed for both of them.

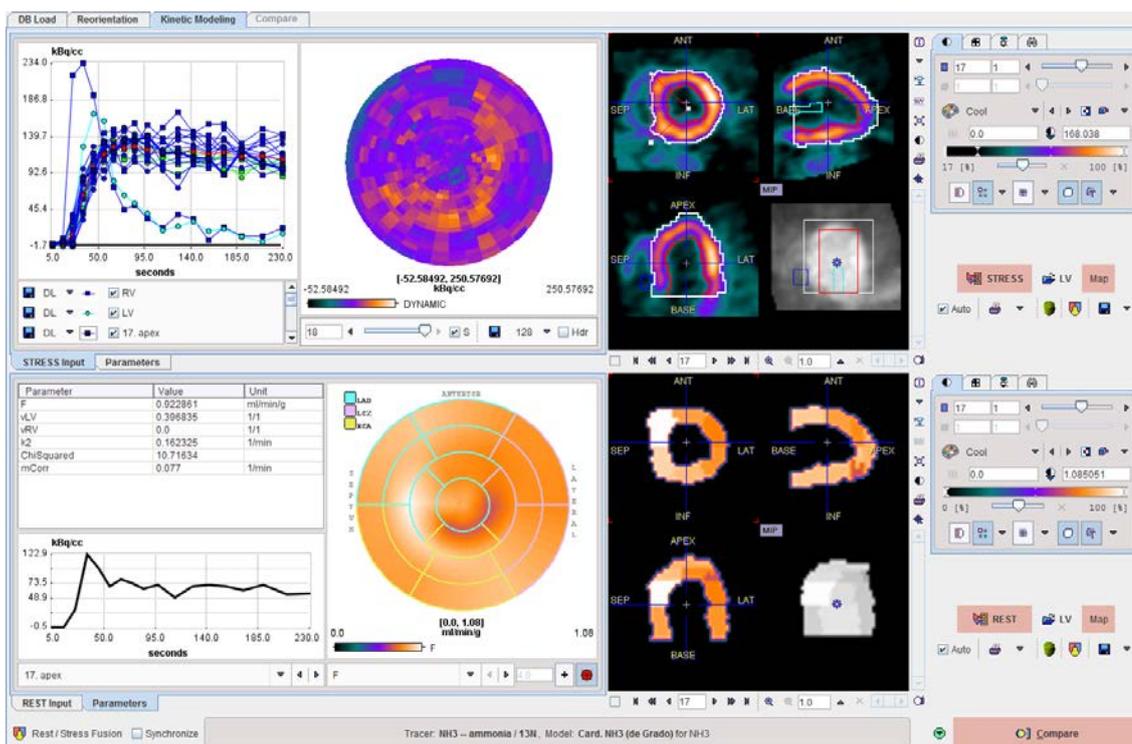
---

## Kinetic Modeling

The behavior after completion of the TAC-calculations depends on the configuration of the **KM** buttons on the **Kinetic Modeling** page:

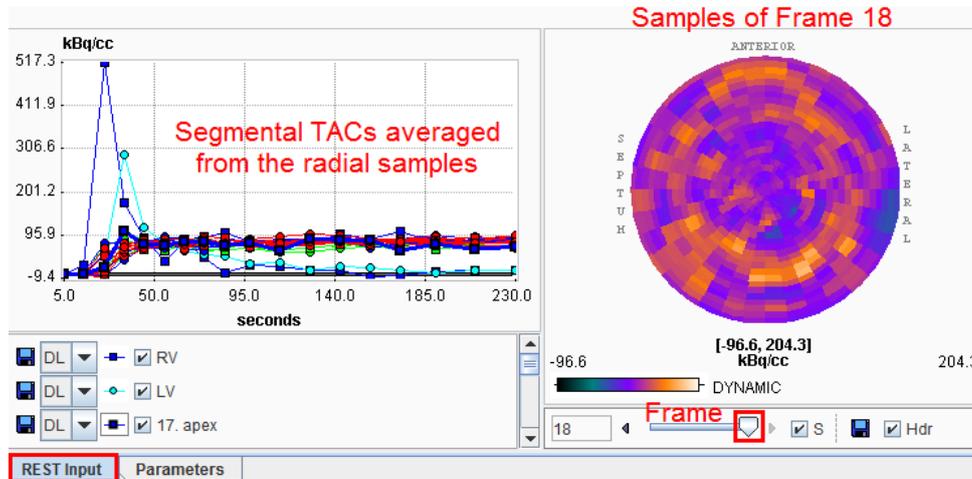
-  With this *manual* configuration the PCARDP tool just switches to the **Kinetic Modeling** page and shows the calculated TACs.
-  With this *automatic* configuration the PCARDP starts modeling of the calculated TACs with the configured model immediately in the background (recommended). The model is fitted to each of the TACs, the results are returned and then shown on the **Kinetic Modeling** page for inspection.

The data and the fitting results are organized on the **Kinetic Modeling** page.



## Polar Plots of Dynamic Data

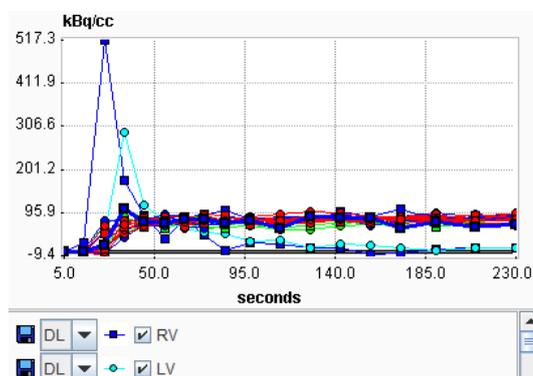
The result of radial sampling is visualized on the **REST Input** or **Stress Input** tab of the **Kinetic Modeling** page. The frame selection allows scrolling through the uptake times and monitor the concentration in the sampled tissue voxels. Note that the polar plot is only available with the automatically outlined myocardium VOI.



The **S** checkbox allows synchronizing the polar and image display frames. The dynamic polar map can be saved activating the **Save** icon, either as an **Image**, or as a **Text (tabulated)** file. Optionally, the header can be appended during the text saving procedure by enabling the **Hdr** checkbox. After saving, numeric data can be analyzed in the PMOD-R interface or outside the PMOD software, and the image data by a parametric mapping approach.

## Sampling Inspection

It is recommended to briefly inspect the TACs. They are shown in the **REST Input** or **STRESS Input** tabs on the **Kinetic Modeling** page.



The following should be checked:

- ▶▶ The RV TAC appears first and typically shows the highest peak of all curves.
- ▶▶ The LV TAC shows a clear peak and then drops below the myocardial activity. Note that the curve shapes depend on the speed of the bolus injection and the heart activity.
- ▶▶ If some of the myocardial TACs have a very similar shape as the LV TAC this indicates that their VOIs include too high a fraction of the LV blood pool.
- ▶▶ Make sure that the timing is right; if it is not correct for some reason (eg. processing data which does not include the timing information), kinetic modeling will fail or return invalid results!

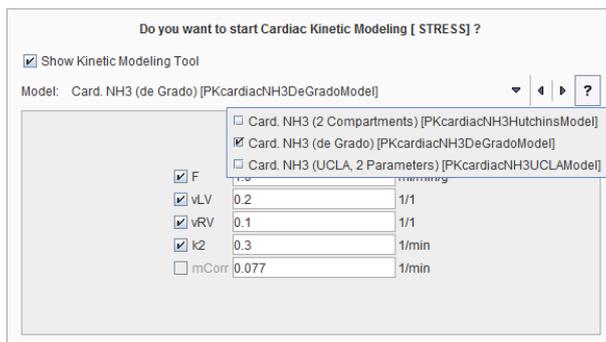
Note that for a closer inspection of the curve shapes you can zoom into the curve display by dragging a rectangle using the left mouse button. An alternative is to click with the right mouse button into the curve area and then select the **View in Separate Window** entry of the context menu.

*If the data is not convincing, please return to the VOI outlining step and correct. A problem occasionally seen and difficult to correct is, that a patient moved, so that in the early frames the VOIs are not aligned with the myocardial position throughout the whole acquisition.*

## Interactive Kinetic Modeling

If modeling needs to be repeated in order to investigate the fitting results, or if background fitting was not enabled, please select the

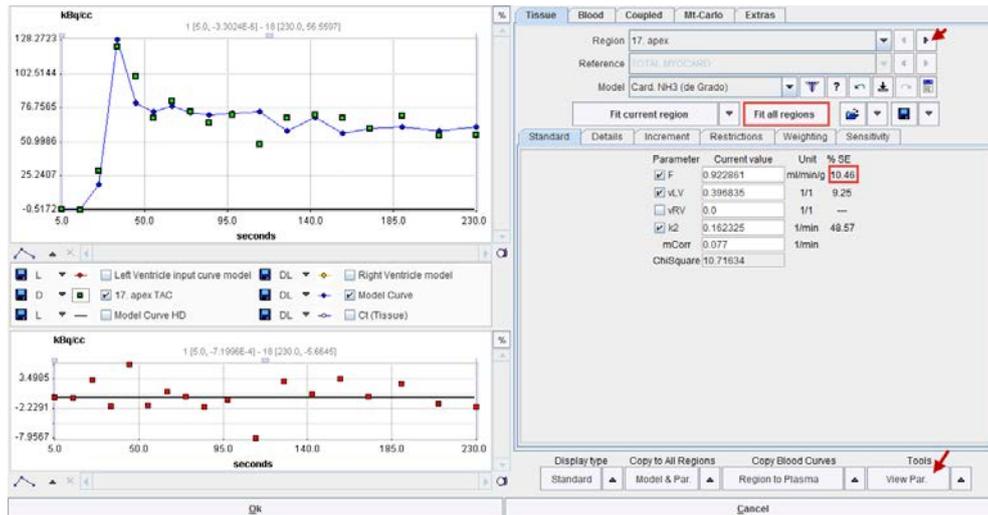
  or the corresponding **REST** button to start kinetic modeling of the TACs. A dialog box comes up showing the currently configured model with the starting parameter values, for example



If needed, the model can be switched to a different model applicable for the tracer. Also, the starting parameters can be adjusted. For modeling stress data one would probably double or triple the initial flow value.

As soon as the user confirms with **Yes** the data are loaded into the PKIN kinetic modeling tool. If the **Show Kinetic Modeling Tool** box is not checked, the model is regionally fitted in the background and the results returned. Otherwise, the kinetic modeling tool PKIN is opened in a separate window with the data loaded (see below). This is the recommended way of operation, because the fitting process can be precisely monitored and adjusted if needed.

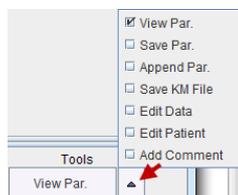
### Model Fitting



The PKIN dialog window initially shows the first TAC in the curve display as green **Measured** points, and the **Model Curve** with the default model parameters in blue. Use the **Fit all regions** button to fit the model to the TACs of all myocardial segments. The **Parameters** and the **Model Curves** are updated accordingly.

Please inspect the fitting results by stepping through the different segments using the indicated **Region** arrow buttons. Successful fits are characterized by residuals distributed around the zero line without a systematic trend (lower curve window), and a relatively small standard error of the important model parameters (F primarily). If the error is too high, the results are not reliable, and you are recommended to use a different model with fewer fit parameters. Spillover from the right ventricle (**vRV** parameter) is negligible in non-septal regions. Therefore is only fitted for septal regions, and fixed at zero everywhere else.

A quick summary of the result parameters can be shown by the **View Par**



button in the **Tools** list selection. The summary

| No | Region                 | Model                 | Bloo... | F        | vLV      | vRV      | k2        | mCorr | DOF  | SumSquared  | ChiSquare | AIC        | SC         | MSC       |
|----|------------------------|-----------------------|---------|----------|----------|----------|-----------|-------|------|-------------|-----------|------------|------------|-----------|
| 1  | 17. apex               | Card. NH3 (de G...0.0 |         | 0.922... | 0.396835 | 0.0      | 0.162325  | 0.077 | 15.0 | 1542.579265 | 10.71634  | 47.1243... | 48.0811... | 1.9515... |
| 2  | 14. apical septal      | Card. NH3 (de G...0.0 |         | 0.955... | 0.287005 | 0.114625 | 0.151914  | 0.077 | 14.0 | 596.302918  | 4.144882  | 32.1470... | 32.6315... | 2.58027   |
| 3  | 13. apical anterior    | Card. NH3 (de G...0.0 |         | 0.839... | 0.393579 | 0.0      | 0.151863  | 0.077 | 15.0 | 685.289199  | 5.349615  | 34.61894   | 35.57577   | 2.67319   |
| 4  | 16. apical lateral     | Card. NH3 (de G...0.0 |         | 0.710... | 0.520682 | 0.0      | 0.2559... | 0.077 | 15.0 | 810.805099  | 6.612665  | 38.43426   | 39.39109   | 2.81506   |
| 5  | 15. apical inferior    | Card. NH3 (de G...0.0 |         | 0.726... | 0.34812  | 0.0      | 0.119108  | 0.077 | 15.0 | 562.603764  | 4.979087  | 33.3269... | 34.2837... | 2.68722   |
| 6  | 9. mid inferoseptal    | Card. NH3 (de G...0.0 |         | 0.999... | 0.193669 | 0.116672 | 0.121222  | 0.077 | 14.0 | 791.975902  | 4.468937  | 33.5019... | 33.9865... | 2.24195   |
| 7  | 8. mid anteroseptal    | Card. NH3 (de G...0.0 |         | 1.08505  | 0.280669 | 0.112748 | 0.175925  | 0.077 | 14.0 | 609.336619  | 3.645226  | 29.8347... | 30.3193... | 2.60101   |
| 8  | 7. mid anterior        | Card. NH3 (de G...0.0 |         | 0.883... | 0.326467 | 0.0      | 0.159691  | 0.077 | 15.0 | 1154.566207 | 8.190065  | 42.28509   | 43.24192   | 2.12663   |
| 9  | 12. mid anterolateral  | Card. NH3 (de G...0.0 |         | 0.820... | 0.330656 | 0.0      | 0.060554  | 0.077 | 15.0 | 954.459903  | 6.282711  | 37.5129... | 38.4697... | 2.31796   |
| 10 | 11. mid inferolateral  | Card. NH3 (de G...0.0 |         | 0.857... | 0.196735 | 0.0      | 0.165463  | 0.077 | 15.0 | 1026.267292 | 7.125742  | 39.7793... | 40.7361... | 2.15195   |
| 11 | 10. mid inferior       | Card. NH3 (de G...0.0 |         | 0.947... | 0.191003 | 0.0      | 0.196487  | 0.077 | 15.0 | 974.214937  | 6.082651  | 36.9304... | 37.8872... | 2.33763   |
| 12 | 3. basal inferoseptal  | Card. NH3 (de G...0.0 |         | 0.8776   | 0.13489  | 0.082967 | 0.121221  | 0.077 | 14.0 | 603.084246  | 3.942047  | 31.2438... | 31.7284... | 2.43596   |
| 13 | 2. basal anteroseptal  | Card. NH3 (de G...0.0 |         | 0.893... | 0.329855 | 0.045836 | 0.075054  | 0.077 | 14.0 | 972.813271  | 6.433549  | 40.0607... | 40.5453... | 2.18497   |
| 14 | 1. basal anterior      | Card. NH3 (de G...0.0 |         | 0.978... | 0.337886 | 0.0      | 0.135192  | 0.077 | 15.0 | 1434.200046 | 8.368034  | 42.67204   | 43.62887   | 2.03221   |
| 15 | 6. basal anterolateral | Card. NH3 (de G...0.0 |         | 0.861... | 0.229629 | 0.0      | 0.11696   | 0.077 | 15.0 | 397.254682  | 2.597123  | 21.6117... | 22.5686... | 3.28101   |
| 16 | 5. basal inferolateral | Card. NH3 (de G...0.0 |         | 0.843... | 0.362837 | 0.0      | 0.124658  | 0.077 | 15.0 | 970.258375  | 7.15478   | 39.8525... | 40.8093... | 2.36353   |
| 17 | 4. basal inferior      | Card. NH3 (de G...0.0 |         | 0.961... | 0.316921 | 0.0      | 0.147719  | 0.077 | 15.0 | 841.205371  | 5.067218  | 33.6427... | 34.5995... | 2.48106   |
| 18 | TOTAL MYOCARD          | Card. NH3 (de G...0.0 |         | 0.870... | 0.326519 | 0.0      | 0.122142  | 0.077 | 15.0 | 583.280232  | 3.888748  | 28.8780... | 29.8348... | 2.70206   |

| No | Region | Model   | Blood delay | F        | vLV        | vRV        | k2        | mCorr        | DOF        | SumSquared         | ChiSquare       | AIC        | SC        |
|----|--------|---------|-------------|----------|------------|------------|-----------|--------------|------------|--------------------|-----------------|------------|-----------|
| 1  |        | average |             | 0.890... | 0.30577... | 0.02626... | 0.1281... | 0.077        | 14.7222... | 861.69429044603... | 5.8360789291... | 35.7476... | 36.573... |
| 2  |        | median  |             | 0.880... | 0.32649... | 0.0        | 0.1299... | 0.077        | 15.0       | 826.00523533915... | 5.7161330101... | 35.7746... | 36.731... |
| 3  |        | stdv    |             | 0.089... | 0.08946... | 0.04473... | 0.0448... | 1.3877787... | 0.44790... | 295.54883713566... | 1.9628935556... | 5.84706... | 5.9042... |

contains the parameters of all segments, their average, median and standard deviation as well as criteria for the goodness-of-fit across the segments. For a thorough explanation of the kinetic modeling tool and the calculated information please refer to the *PMOD Kinetic Modeling Tool User's Guide*.

### Saving the Modeling Information

Although it is not mandatory, we recommend saving the full kinetic modeling information (TACs, models and parameters) in a .km file which can always be further analyzed with the PKIN tool. This data can be saved using the **Save KM File** button in the **Tools** list.

### Returning to the Cardiac Tool

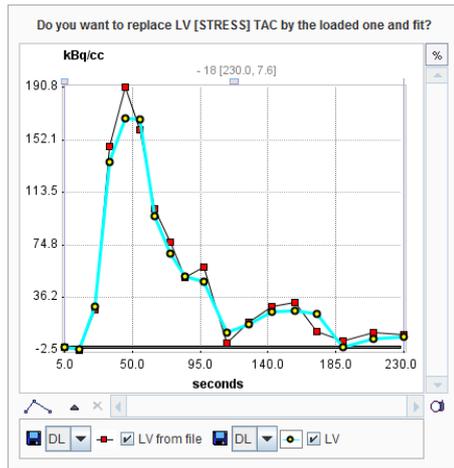
Finally, confirm the PKIN dialog with **Ok** in order to accept the modeling results. The PKIN dialog is closed and the result parameters are returned to the PCARDP tool. Note that for models with parametric mapping these calculations are also done before the results are shown and the user interface is enabled again.

### External Input Curve

In some situations there might be a corrected or externally sampled input curve available. In this case the LV button

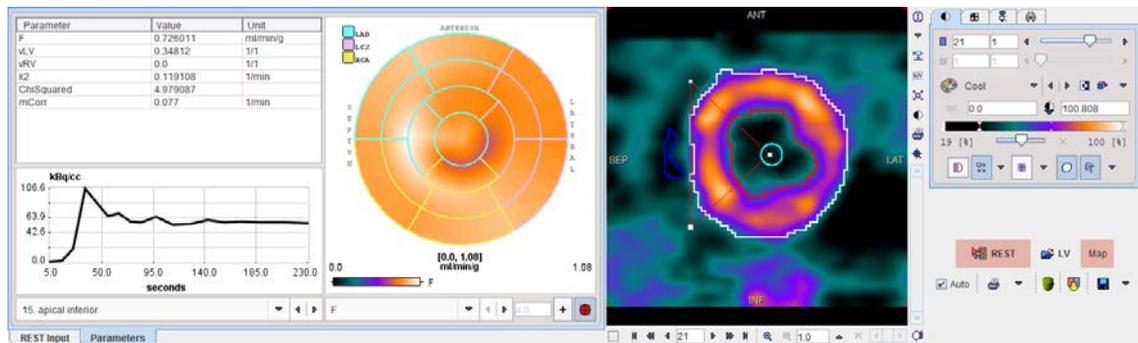


can be used for replacing the TAC derived from the LV VOI. After selecting a curve file, a dialog window is shown for confirmation. After acceptance, the LV curve is replaced and the configured model fitted.



## Results Analysis and Evaluation

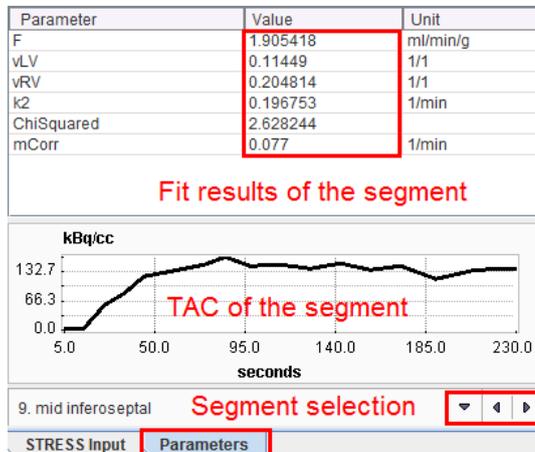
After fitting of the kinetic model has completed, the information on the **Kinetic Modeling** page is updated to allow for results inspection and documentation. The section below illustrates the situation when the polar plot interpolation is enabled.



## Examining the Results

### Parameters per Segment

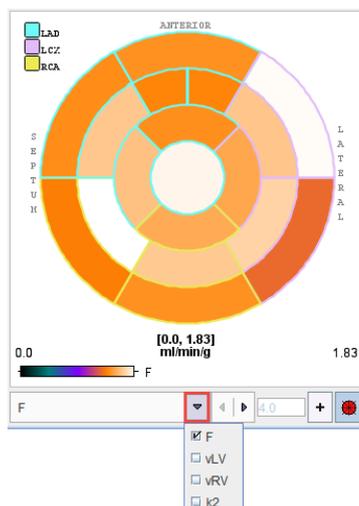
The **Parameters** tab on the **Kinetic Modeling** page shows the modeling results obtained with the individual segmental TACs. After a segment has been selected, the result parameters are shown in the upper table, and the corresponding TAC in the lower curve area.



### Polar Plots

The parameters resulting in the different segments can conveniently be visualized as polar plots. The example below shows the polar plot of the parameter flow (**F**), without interpolation and with the display controls enabled. By default, segments definition is overlaid. These can be easily switched off selecting the toggle button in the lower right corner of the polar plot. The **+** button serves for defining a standard maximal value, which can be entered in the number field left to it.

The list selection at the bottom switch between the model parameters. When the cursor is moved about the polar plot the segmental parameter value is shown in the upper right. Note that the segment structure is clearly visible if no interpolation has been configured for the polar plot.



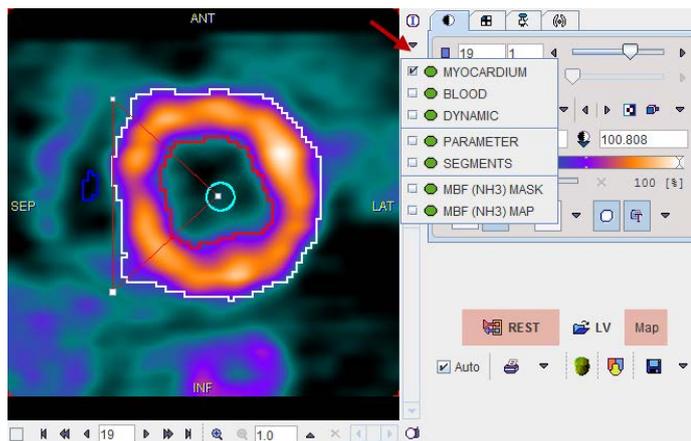
The polar plot display control can be easily switch on/off right clicking on the polar plot area and selecting the **Hide/Show Controls** option.



The **Properties** list entry allows changing the font size and the aliasing.

### Resampled Data and Parameter Images

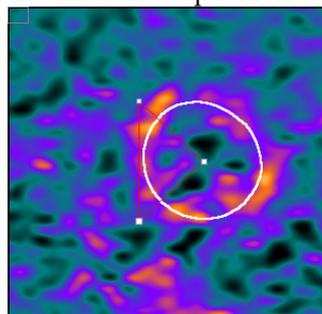
The image display on the right side of **Kinetic Modeling** page initially shows the MYOCARDIUM data. Note, however, that you can switch between more studies by the list selection as illustrated below. Green bullets represent data already available, while red bullets mark data which still needs to be calculated (in the example modeling has not yet been performed).



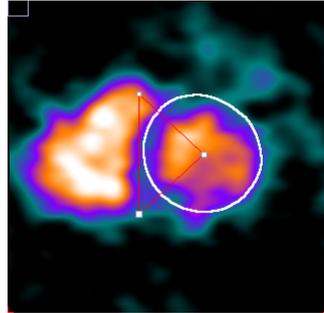
All this data has been resampled based on the **Myocard** VOI, so that the 22 slices cover the area from the apex to the base, plus some additional bounding box.

**MYOCARDIUM** The data calculated in the pre-processing step as a representation of myocardium (already illustrated above).

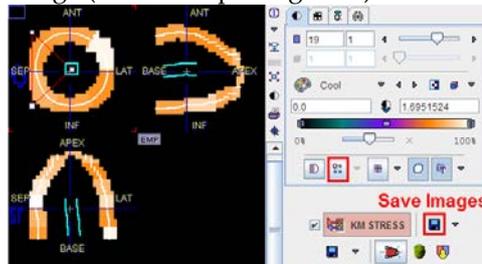
**DYNAMIC** Resampled dynamic image data. Use the volume slider to step through the different acquisition times.



**BLOOD** The data calculated in the pre-processing step as a representation of blood.

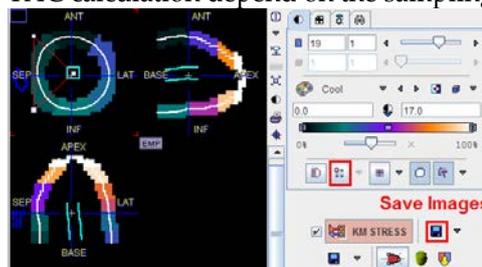


**PARAMETER** The calculated active parameter (eg. flow **F**) turned into a volumetric image (one value per segment).



The interpolation has been disabled in the illustration above to clearly demonstrate the segmental parameter values. Note that the result images can be saved, for instance for fusion with a matched anatomical data set.

**SEGMENTS** Illustration of the segments. Note: The representation is based on the myocardium contour and is only indicative. The actual samples for TAC calculation depend on the sampling scheme.



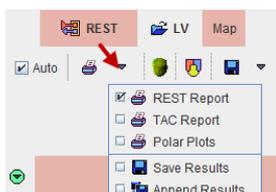

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**Note:** If you click into the polar plot, the image to the right is adjusted so that the corresponding slice is shown. With an orthogonal image layout, the cross is positioned at the sampling location corresponding to the polar plot point.

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## Documentation

Several reports are available and can be generated using the report selection.



### Individual Stress and Rest Reports

The illustration below shows a **STRESS Report** example. Note the results of the different segments, which are summarized by volume-weighted averaging to the vascular territories **LAD, RCA, LCX**, and to a **GLOBAL** average. **TOTAL** represents the kinetic modeling result which was obtained by fitting the TAC composed of volume-weighted contributions from all segments. It can be used as a double-check that the segmental results are reasonable.

Report: 2011\_01\_03 (17:23:34) Study: 2016.02.07 L of 3 STRESS

Results of Cardiolateral PET Analysis:  
 Kinetic: **3R3** **nonlinear / 1R3**  
 Model: Card. **3R3** (4x Cards) **3R3**

| Parameter | Value  | Unit  | Min    | Max    | Min    | Max    | Min    | Max     | Min    | Max    |
|-----------|--------|-------|--------|--------|--------|--------|--------|---------|--------|--------|
| LAD       | 1.4875 |       | 0.1154 | 0.0925 | 28.436 | 0.0    | 0.0925 | 0.1323  | 14.242 | 6.062  |
| 1         | 1.4203 | 2.395 | 0.0925 | 28.436 | 0.0    | 0.0    | 0.1323 | 14.242  | 6.062  | 6.062  |
| 2         | 1.2819 | 0.92  | 0.2271 | 21.324 | 0.0250 | 16.27  | 0.01   | 1.0.076 | 6.062  | 6.062  |
| 7         | 1.4051 | 2.352 | 0.027  | 6.715  | 0.0    | 0.0    | 0.1727 | 1.027   | 4.022  | 4.022  |
| 8         | 1.751  | 0.775 | 0.037  | 77.320 | 0.1727 | 2.053  | 0.1727 | 18.34   | 4.034  | 4.034  |
| 13        | 1.9805 | 5.262 | 0.0547 | 60.52  | 0.0    | 0.0    | 0.2367 | 2.652   | 3.264  | 3.264  |
| 14        | 1.281  | 1.308 | 0.07   | 101.32 | 0.0547 | 7.825  | 0.237  | 18.081  | 2.7    | 2.7    |
| 17        | 1.2539 | 4.333 | 0.1428 | 29.821 | 0.0    | 0.0    | 0.197  | 10.92   | 4.575  | 4.575  |
| RCA       | 1.7558 |       | 0.2459 | 0.073  | 0.073  | 0.073  | 0.073  | 22.577  | 22.577 | 22.577 |
| 3         | 1.375  | 5.532 | 0.236  | 23.076 | 0.0347 | 22.655 | 0.034  | 728.746 | 5.045  | 5.045  |
| 4         | 1.785  | 3.483 | 0.2539 | 12.14  | 0.0    | 0.0    | 0.058  | 2.815   | 6.24   | 6.24   |
| 9         | 1.5054 | 4.683 | 0.1145 | 62.052 | 0.2340 | 2.053  | 0.1360 | 10.504  | 4.033  | 4.033  |
| 10        | 1.735  | 4.855 | 0.972  | 13.44  | 0.0    | 0.0    | 0.053  | 54.14   | 3.083  | 3.083  |
| 15        | 1.4321 | 4.959 | 0.323  | 6.827  | 0.0    | 0.0    | 0.127  | 28.07   | 2.952  | 2.952  |
| LCX       | 1.282  |       | 0.237  | 0.0    | 0.0    | 0.0    | 0.1808 | 21.852  | 21.852 | 21.852 |
| 5         | 1.2457 | 5.5   | 0.1365 | 22.336 | 0.0    | 0.0    | 0.1528 | 27.247  | 5.381  | 5.381  |
| 7         | 1.7071 | 5.33  | 0.233  | 15.14  | 0.0    | 0.0    | 0.173  | 20.091  | 5.33   | 5.33   |
| 11        | 1.2375 | 6.213 | 0.2368 | 18.336 | 0.0    | 0.0    | 0.121  | 56.013  | 4.213  | 4.213  |
| 12        | 1.6021 | 3.707 | 0.1259 | 20.075 | 0.0    | 0.0    | 0.1329 | 2.045   | 3.893  | 3.893  |
| 16        | 1.4351 | 4.855 | 0.978  | 20.83  | 0.0    | 0.0    | 0.134  | 22.587  | 2.887  | 2.887  |
| GLOBAL    | 1.294  |       | 0.1342 | 0.0303 | 0.0303 | 0.0303 | 0.1342 | 76.642  | 76.642 | 76.642 |
| TOTAL     | 1.2    | 1.05  | 0.2544 | 6.81   | 0.0    | 0.0    | 0.1251 | 10.36   | 16.872 | 16.872 |

-) - not fitted or not in kinetic volume maps

The kinetic parameters(s)

| Parameter | Value | Unit  |
|-----------|-------|-------|
| 1/lambda  | 0.371 | 1/min |

Comment

1. basal anterior 2. basal anterior medial 3. basal anterior lateral 4. basal anterior medial 5. basal anterior lateral 6. basal anterior lateral 7. basal anterior 8. basal anterior medial 9. basal anterior lateral 10. basal anterior 11. basal anterior medial 12. basal anterior lateral 13. basal anterior 14. basal anterior medial 15. basal anterior lateral 16. basal anterior 17. basal anterior

Annotations

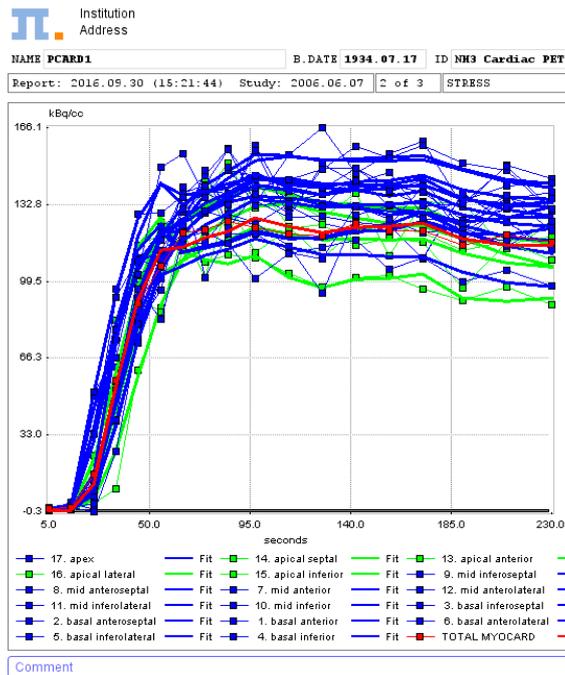
T 11 75% Overlay

Zoom Pages

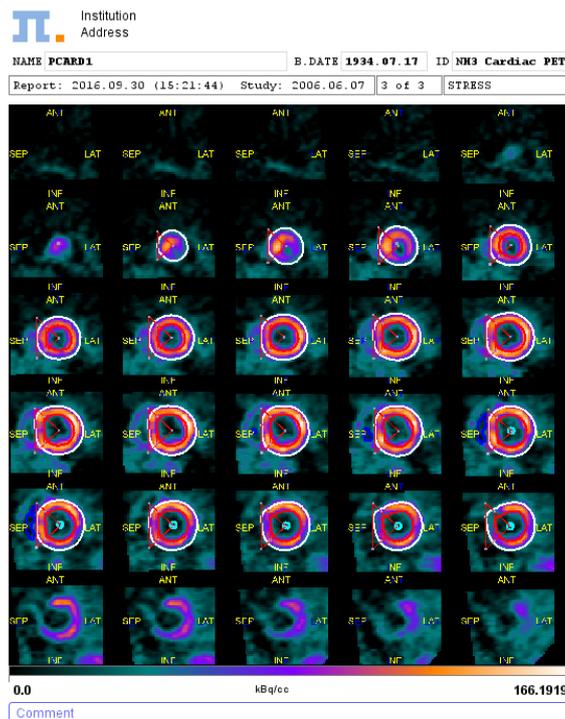
Print (Page 1) Save As 1188 x 1684 pixels Cancel

Note the buttons **Print** for printing a hardcopy of the report, and **Save as** for saving the report in a graphic format (JPEG, TIFF) or in DICOM. The latter button can be switched to generate a capture with lower resolution.

The second page of the main report shows the segmental TACs

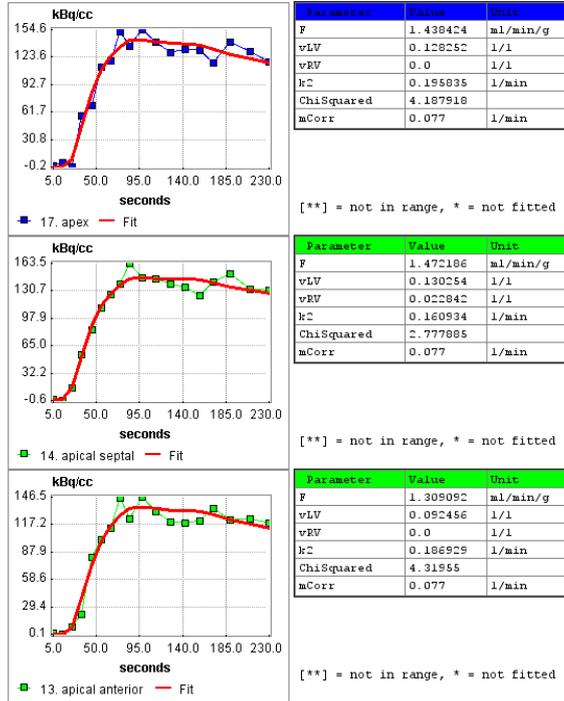


The third page allows to print images from the dynamic study in SA orientation. The report layout is fixed to 6x5 images such that 30 slices images are always visible.



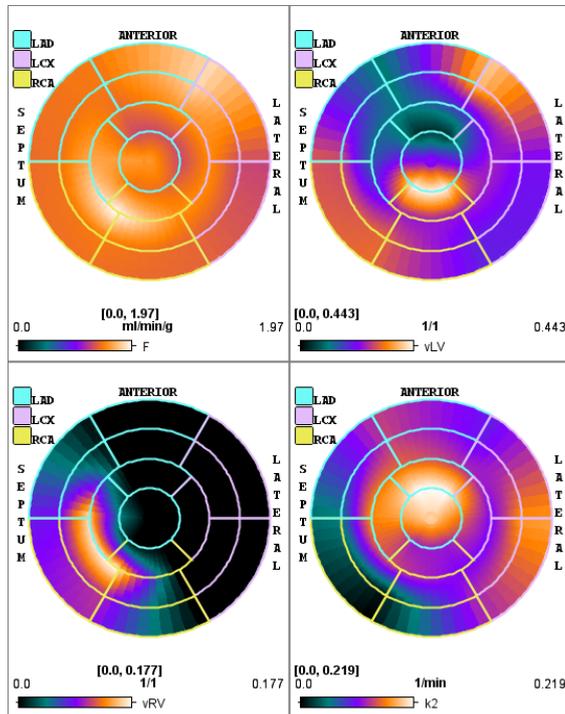
## TAC Report

The **TAC Report** shows the segmental TACs together with the fitted model curve and the model result parameters. Note the different pages which are needed to document all segments.



## Polar Plot Report

The **Polar Plots** report allows to summarize the result parameters as polar plots. Note in the example below how the right ventricle spillover **vRV** parameter is only fitted in the septal segments.



## Save Numeric Results

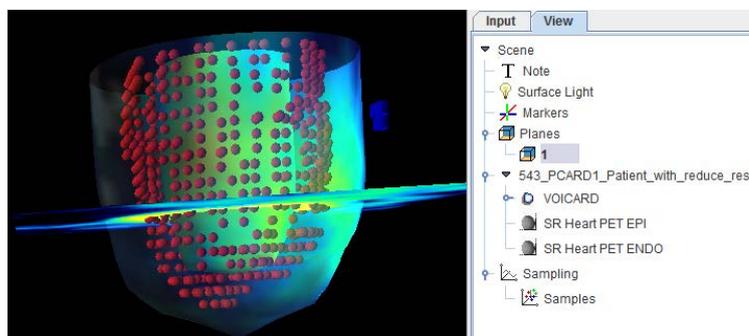
The numeric results contained in the main report can be saved using the entry **Save Results**. This generates a simple ASCII text file which can be opened in many editors as well as in MS Excel, for further processing. Use the entry **Append Results** to append the results to an existing file.

## Advanced Data Exploration (Options)

Although PCARDP results in a quantitative summary of cardiac function, the user may sometimes want to investigate and visualize the results in more detail. If he has licensed the image fusion option (PFUS) and/or the 3D rendering option (P3D), he has versatile tools available which can be readily employed as outlined below.

## Visualization of the Samples found by Polar Sampling (3D Option required)

The pixels found during the sampling process can be visualized together with the short axis images using the  button. The option **Heart 3D + Sampling points** calls the 3D tool which renders the shape of the myocardium model together with the sampling points. The example below shows the sampling points as red spheres, the myocardium ENDO and EPI models as surfaces with the texture of the MYOCARDIUM image, and a short axis slice of the anatomical images with transparency.



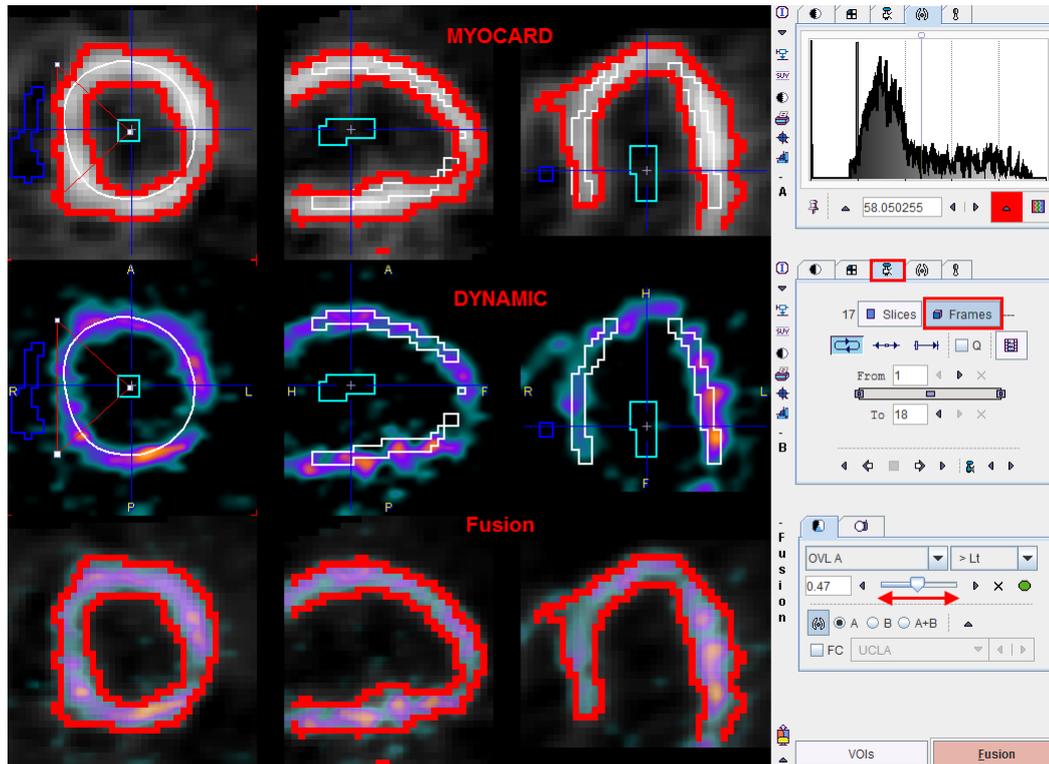
Note that if a sampling scheme with averaging has been selected, the neighbor points are *not* shown.

To learn more about the many possibilities exploring the data in P3D please refer to the *PMOD 3D Rendering User Guide*.

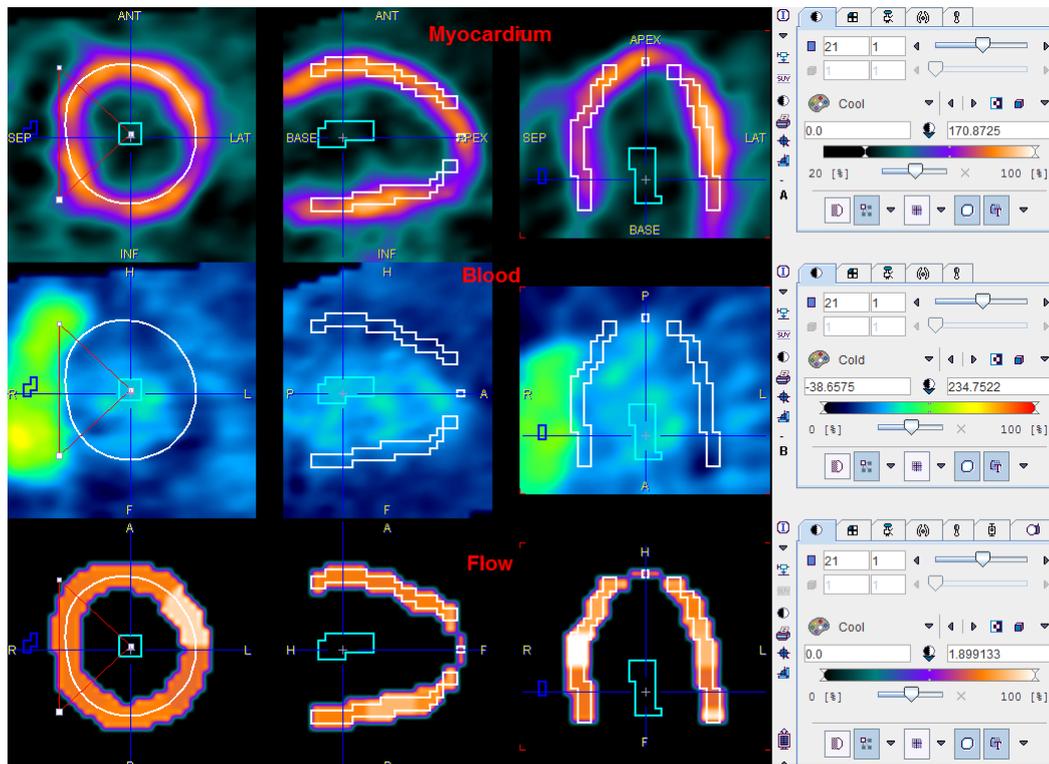
## Fusion Display of all Data Sets

During processing, PCARDP calculates different types of data in the area of the heart. All of this data together with the VOIs can directly be loaded into the image fusion tool by the  button. This tool has numerous flexible visualization options which are illustrated by the two examples below. Please refer to the User's Guide of the PMOD fusion tool to learn about the full capabilities.

The illustration below shows how the dynamic images can be fused with the myocardium information. By playing a movie of the dynamic images over the acquisition duration the appearance and washout of the tracer can be observed and patient motion be detected.



Instead of fusing two images, the tool can also be switched to display three images in parallel, as illustrated below.



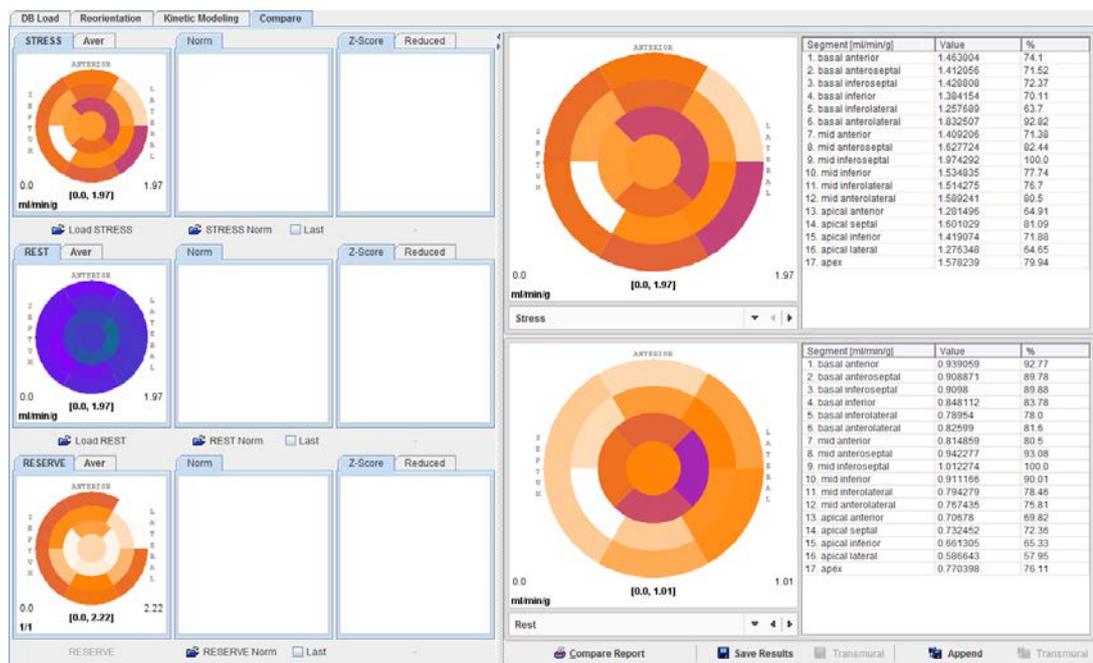
## Rest/Stress Comparison

The third page **Compare** supports two types of comparisons.

- ▶▶ If the patient had both rest and stress perfusion studies, the segmental perfusion reserve can be calculated as configured, usually by dividing stress perfusion by rest perfusion.
- ▶▶ If the patient was studied in a standard condition and a normal database is available, the deviation of the patient results from the standard pattern can be calculated.

In both cases, the results are presented as polar plots and as tables.

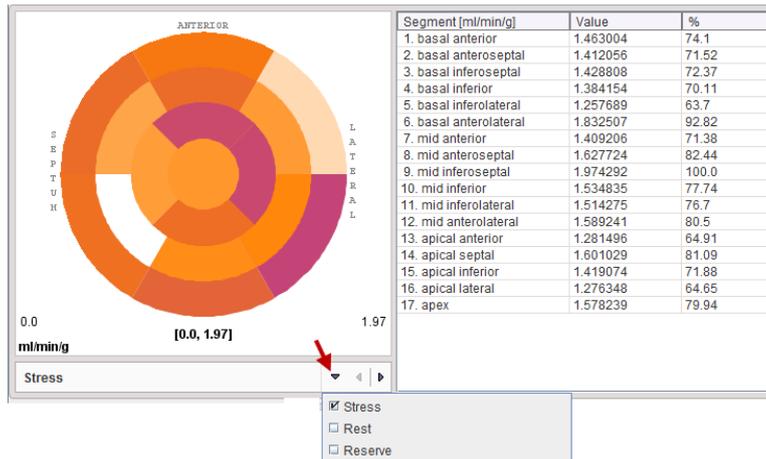
Please activate the **Compare** button on the **Kinetic Modeling** page to start the result comparison and continue on the **Compare** page.



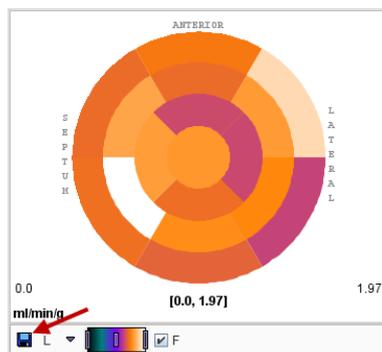
## Stress/Rest Comparison

The current stress and rest results are shown as the upper two polar plots in the first column, and below them the reserve polar plot. If a database is available and has been selected, the second column contains the normal stress, rest and reserve polar plots. The third column is prepared for the polar plots showing the deviation between the patient results and the normal database as z-score values.

The right side of the page contains two enlarged polar plots with their numeric values shown in a table next to them. Initially, they show the stress and rest information, but the user can switch them, for instance to show the perfusion reserve as illustrated below.



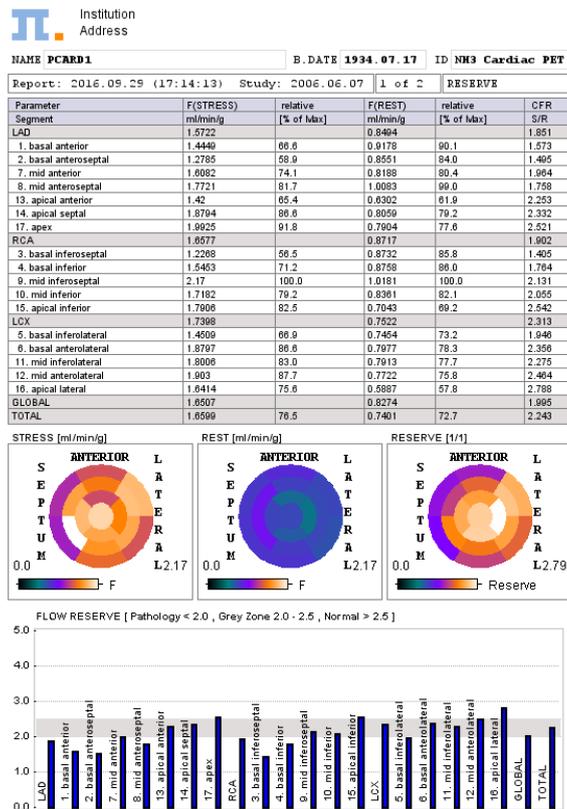
Using right-click into the plot area the controls can be shown.



The saving icon indicated above allows saving the polar plot information for later inclusion into a cardiac normal database.

## Rest/Stress Summary Report

The **Reserve Report** button compiles the Stress/Rest/Reserve information into a report summary page. The upper part contains a tabular summary of the absolute and relative flows (% of segmental maximum) as well as the coronary perfusion reserve (CFR) in the different segments. The same information is then presented as polar plots, and finally as a bar plot to provide a intuitive overview of the situation.

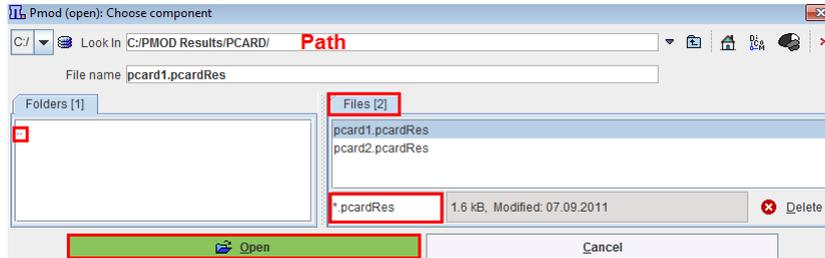


As usual with PMOD reports it can be annotated, saved in different formats, and printed.

## Saving and Inspecting Numeric Results

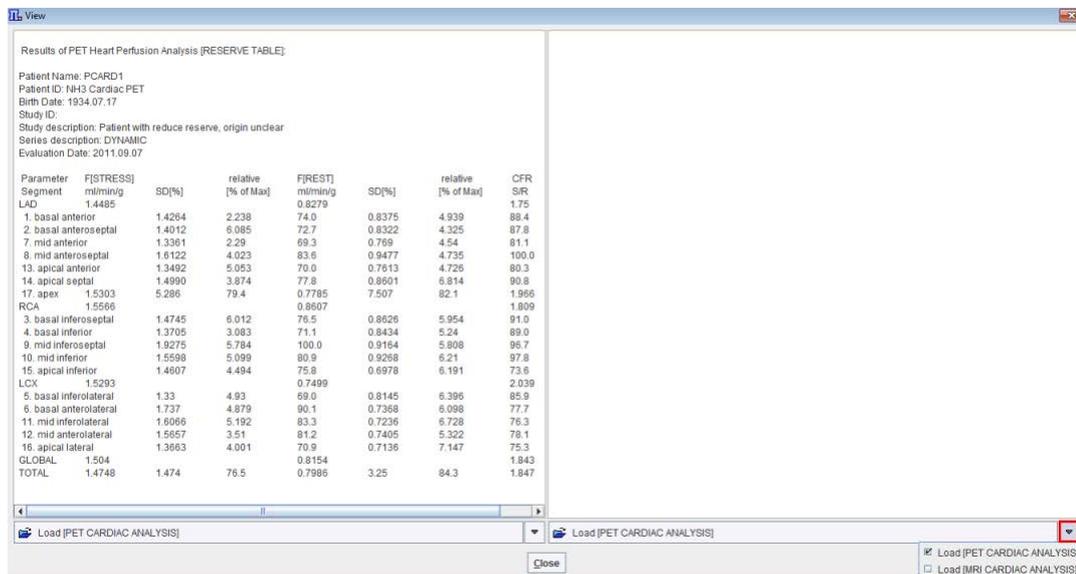
The numeric information of the table can also be saved or appended to a text file using the **Save Results** and the **Append Results** buttons, respectively. The saved file receives a **.pcardRes** suffix and can be visualized in Excel or a text editor (e.g Notepad).

Two different numeric results can be opened and compared within PCARDP module. This can be easily achieved activating the **View Results**  **View Results** option from the task bar to the right. Initially, a window appears allowing to select either a file from the database or a disk file. The  **Load from File System** button opens a dialog window.



In the upper part the current path is indicated. The program automatically points to the directory of the last successful loading operation. It has elements for changing the directory: the navigation buttons in the **Folder** section (.. indicating one level up). All files suitable for loading (having the right suffix, \*.**pcardRes**) in the search directory are listed in the **Files** section. The **Open** button starts loading the selected file, **Cancel** quits the operation, and **Delete** erases the file from the disk.

Finally, a comparison window displays in the left section the initial loading results:



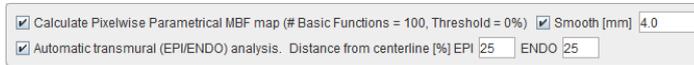
In the right section of the panel the bottom **Load** button allows loading results obtained either from MRI or PET cardiac analysis for a side-by-side comparison. The **Close** button exits the comparison window.

### Database Comparison

We are sorry the description of the database functionality (which is available) is not yet completed. Please contact us if you have data available for creating a normal database.

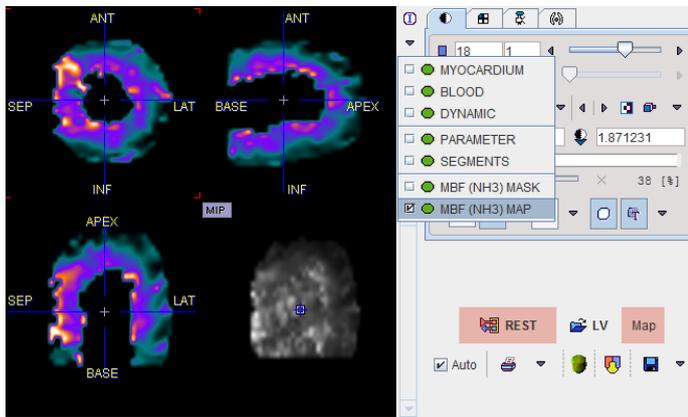
## Special Results for Ammonia

For ammonia, a *basis-function approach* (on page 100) has been implemented for calculating perfusion in each pixel of a myocardium mask. Based on the resulting map the perfusion across the heart wall can be analyzed in a transmural analysis. This functionality has to be enabled in the *configuration panel* (on page 11).



## Parametric MBF Maps for Ammonia

The analysis of a  $\text{NH}_3$  study results in a parametric MBF map if this option has been enabled in the modeling configuration. It is calculated in the background after the kinetic modeling, and can also be started with the **Map** button. The map can be shown with the selection illustrated below, and saved using the saving button below **Map**.

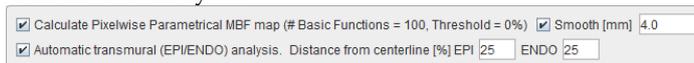


Note that the **MBF (NH3) MASK** is derived from the model of the left ventricle by extension to the inner and the outer.

## Transmural Perfusion Analysis

Sciagrà et al. have used the parametric MBF maps to study transmural abnormalities in patients with hypertrophic cardiomyopathy [1]. The analysis method has been implemented in PCARDP. It has the following *configuration* (on page 11) requirements:

- 1) *Selection* (on page 11) of **NH3** as the tracer and activation of parametric mapping and transmural analysis.



*Selection* (on page 13) of an **EPI/ENDO** segmentation type.

*Selection* (on page 13) of a **Model crossing** polar sampling method.

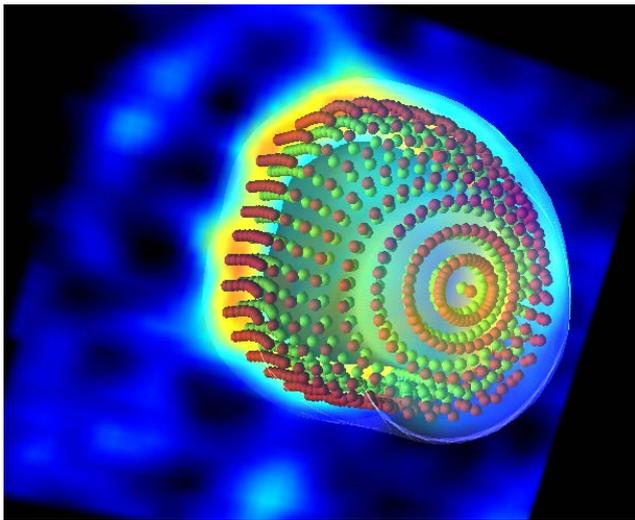
With these settings, the program performs parametric MBF mapping followed by a transmural analysis whenever kinetic modeling is started.

## Sampling of Transmural Perfusion

For each segment, two separate perfusion averages are calculated representing endocardial (ENDO) and epicardial tissue (EPI). The sampling points in the MBF map are offset from the centerline between the contours by percentages defined in the **Distance from centerline** configuration. 50% translates into the middle between the centerline and the boundary. The transmural sampling points can be inspected on the **Kinetic Modeling** page with the 3D rendering button

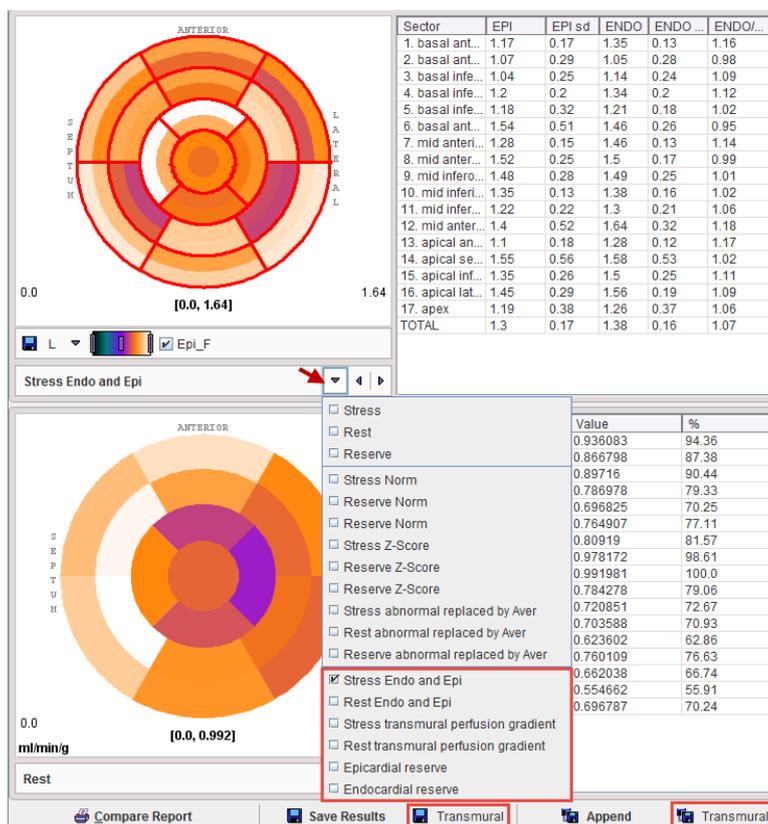


The capture below shows the results obtained with a 25% **Distance from centerline**.



## Results

With transmural analysis enabled, additional results can be selected on the **Compare** page.



### Stress Endo and Epi

Stress results. For each segment and layer the average and standard deviation of the MBF values at the sampling points are listed, as well as the ENDO/EPI gradient. The polar plot shows both perfusion values per segment.

### Rest Endo and Epi

Same results as above for Rest.

### Stress transmural perfusion gradient

Similar as **Stress Endo and Epi**, except that the polar plot shows the gradient.

### Rest transmural perfusion gradient

Similar as **Rest Endo and Epi**, except that the polar plot shows the gradient.

### Epicardial reserve

Ratio Stress/Rest of the segmental perfusion in the epicardial layer.

### Endocardial reserve

Ratio Stress/Rest of the segmental perfusion in the endocardial layer.

The numerical results can be saved with the two **Transmural** save buttons.

## Reference

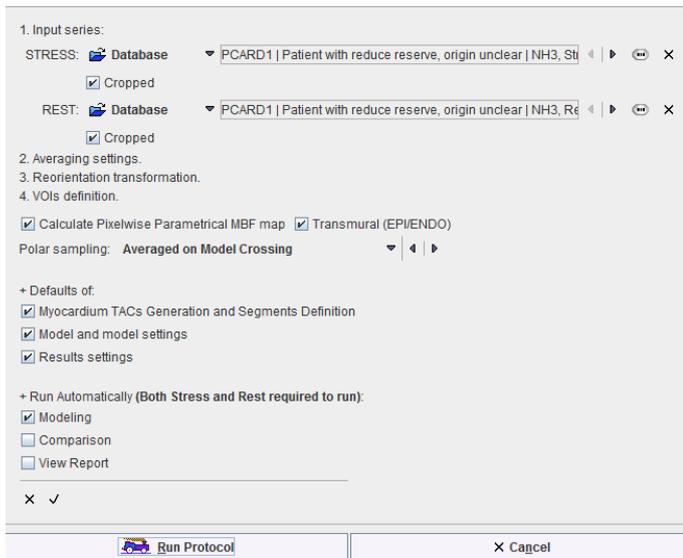
1. Sciagrà R, Passeri A, Cipollini F, Castagnoli H, Olivotto I, Burger C, Cecchi F, Pupi A. Validation of pixel-wise parametric mapping of myocardial blood flow with <sup>13</sup>NH<sub>3</sub> PET in

patients with hypertrophic cardiomyopathy. *European Journal of Nuclear Medicine and Molecular Imaging*. 2015;42(10):1581-1588.

## Protocol Files

The quantification of a cardiac rest/stress study is a complex task which may involve manual adjustments. To ensure the exact reproduction of a PCARDP analysis the entire set of definitions can be saved using the **Save Protocol** button which can be found in the lower status line.

Protocols can later be retrieved using the **Load Protocol** button. After protocol selection a dialog window appears offering some choices. If all options are checked, the analysis will be exactly reproduced. If you would like to test the analysis with a different kinetic model, change the model configuration beforehand with the  button and remove the check of the **Model and model Settings** box. Activate **Run Protocol** to start processing from scratch.



1. Input series:

STRESS:  Database ▼ PCARD1 | Patient with reduce reserve, origin unclear | NH3, Sti ◀ ▶ ⌂ ✕

Cropped

REST:  Database ▼ PCARD1 | Patient with reduce reserve, origin unclear | NH3, R6 ◀ ▶ ⌂ ✕

Cropped

2. Averaging settings.

3. Reorientation transformation.

4. VOIs definition.

Calculate Pixelwise Parametrical MBF map  Transmural (EPI/ENDO)

Polar sampling: Averaged on Model Crossing ▼ ◀ ▶

+ Defaults of:

Myocardium TACs Generation and Segments Definition

Model and model settings

Results settings

+ Run Automatically (Both Stress and Rest required to run):

Modeling

Comparison

View Report

✕ ✓

 Run Protocol  Cancel

## Pre-Processing Steps with Factor Analysis (Water only)

The factor analysis methodology for use in the quantification of dynamic  $H_2^{15}O$ -PET studies is based on the work of F. Hermansen and co-workers from the Hammersmith Hospital, London, UK [3,4,5,27]. Note that for this analysis PET transmission images with exactly the same geometry as the emission images can be used.

### Principle of the Factor Analysis (FA)

The principle of the cardiac  $H_2^{15}O$ -PET factor analysis is model-based and consists of the following steps:

- 1) An estimate of the blood  $H_2^{15}O$  activity concentration is derived from a lung VOI.

The expected uptake and washout in myocardium is calculated based on a 1-tissue compartment model, the blood activity as the input curve, and an average myocardial perfusion value.

The two types of time courses (blood, myocardium) are fed into a factor analysis procedure which calculates two weights per time point, the myocardial  $m_i$  factors and the blood factors  $b_i$ .

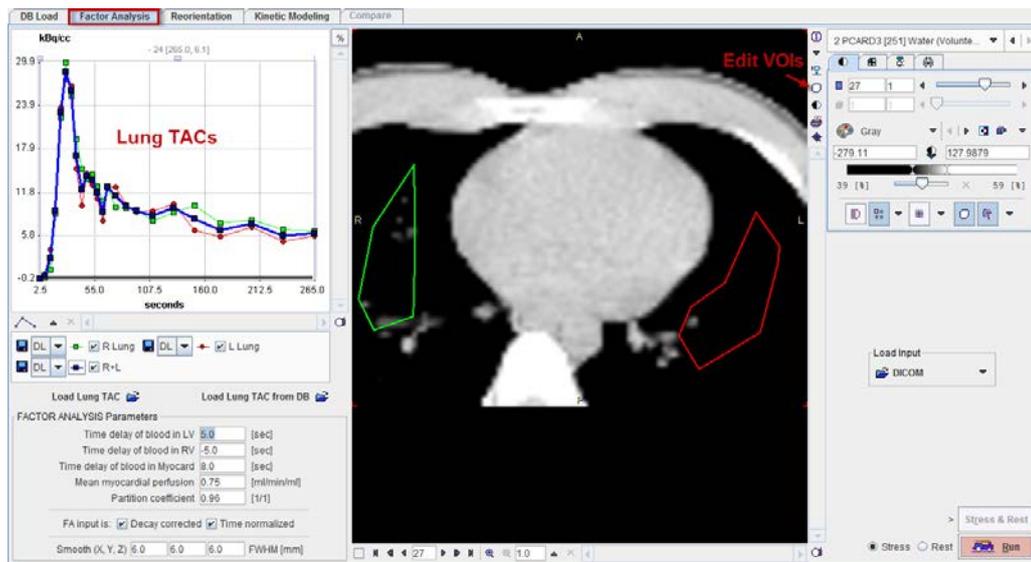
A myocardium factor image can then be obtained by summing the frames weighted by the  $m_i$  factors, and a blood factor image by summing the frames weighted by the  $b_i$  factors.

## Factor Analysis Configuration

To use the factor analysis with cardiac  $H_2^{15}O$ -PET studies it must be *configured* (on page 11) by setting the radio button **Preprocessing** accordingly in the tracer configuration page as illustrated below.

The screenshot shows a software interface for tracer configuration. At the top, there are tabs for different tracers: H2O, NH3, Rb, Acetate, and FDG. The 'H2O' tab is selected and highlighted with a red box. Below the tabs, there is a 'Preprocessing' section with two radio buttons: 'Factor Analysis' (which is selected and highlighted with a red box) and 'Time average (subtraction)'. There is also a checkbox for 'Run VOI Tool automatically after Transmission study was loaded'. Below that, there is a 'Model' dropdown menu set to 'Card. H2O (Tissue fraction) [PKcardiacDoubleSpilloverModel]' and a '?' button. At the bottom, there is an 'Active parameter name' field with 'F' entered, and a range selection option 'In range -> from 0.0 to 8.0'. The footer of the interface reads 'Blood & Myocardium estimation: Factor Analysis'.

When the configuration is closed, an additional page **Factor Analysis** shows up in PCARDP. the illustration below shows that situation after the lung VOI preparation.

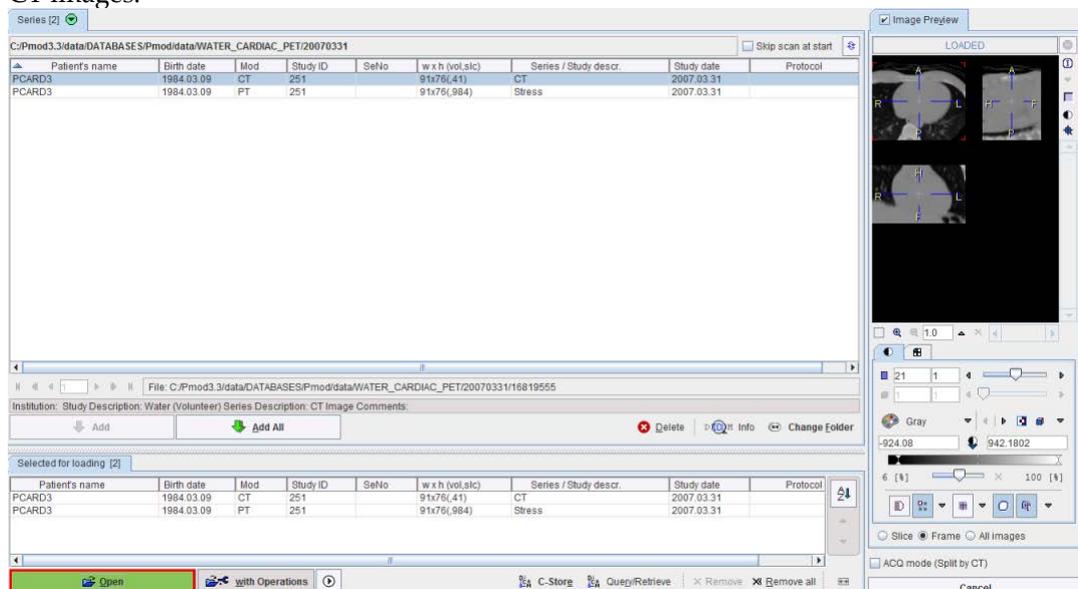


## Derivation of the Lung TAC

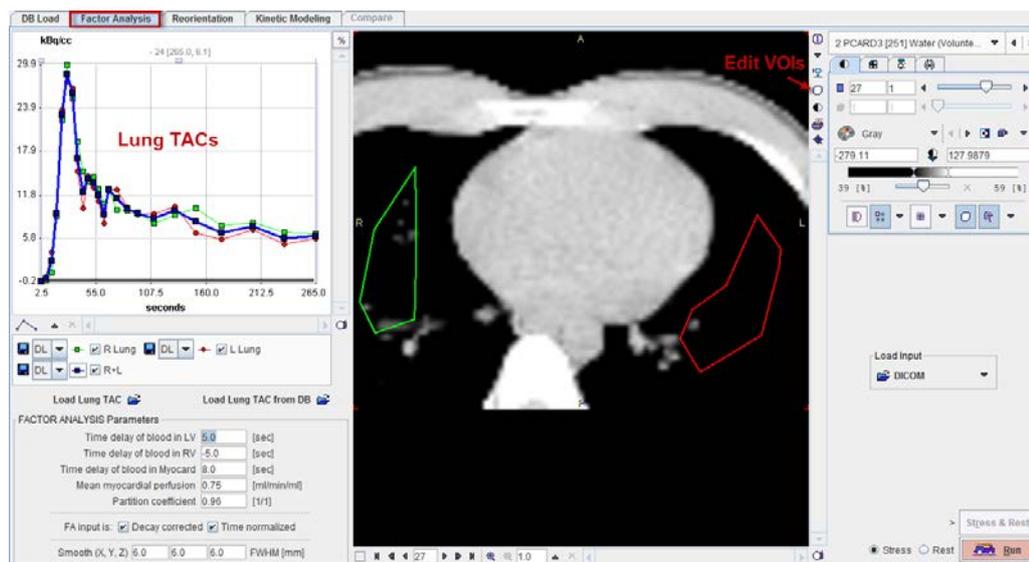
The TAC of the lungs provides a reasonable approximation of the shape of the blood curve. It is obtained in a lung VOI which has traditionally been outlined in matched transmission images because of poor anatomical information in the early water images. With images acquired using current scanners the lung VOIs may directly be outlined in the PET images.

Please perform the following steps for an analysis using CT images.

- ▶ Using the **Load Input** button load *both* the dynamic emission images and the matching CT images.



- ▶ After the images have been loaded, select the **VOI** button. In the appearing VOI construction dialog make sure to switch to the transmission images and draw regions in the left and right lung.



Close the VOI dialog with the **Ok** button.

- ▶ As a result, the emission TACs in the left and right lungs are calculated, averaged and displayed in the curve area (see illustration above).

#### Notes:

1. It is important that the acquisition times of the dynamic images are correct.
2. If the acquisition has been performed using a hybrid PET/CT scanner it should be possible to use the CT images for defining the Lung VOIs, because PMOD relates the VOI to the scan landmark which is normally identical in both scans.

If the CT images are not required for the location of the lungs, VOI outlining can be directly performed in the water images. In this case it is even possible to load Stress and Rest images, outline the VOIs, and activate the **Stress & Rest** button.

If the lung TAC is already available as a file the loading of the transmission data and the VOI outlining is not necessary. In this case it is sufficient to load the dynamic  $H_2^{15}O$ -PET images, then load the lung TAC with one of the buttons **Load Lung TAC** or **Load Lung TAC from DB**, Then the FA can immediately be started.

## Factor Analysis

From the lung TAC three synthetic TACs are calculated which will be used in the factor analysis:

- ▶ the TAC of blood in the left ventricle (LV): approximated by the lung TAC shifted to a later time (positive delay),
- ▶ the TAC of blood in the right ventricle (RV): approximated by the lung TAC shifted to an earlier time (negative delay),
- ▶ the TAC in myocardium: calculated from the LV TAC as the input curve (shifted by a specified delay) with a single-tissue compartment model, a **Mean myocardial perfusion** value, and the **Partition coefficient** of water.

Note that these three TACs are only used internally and are not shown in the user interface.

The parameters for generating the TACs can be entered in the **FACTOR ANALYSIS Parameters** area:

In this area there are two additional configuration boxes:

**FA input is decay corrected** Check the box if the dynamic data used in the FA is decay corrected. If it is not checked, a decay correction to the scan starting time will be performed using the half-time of  $^{15}\text{O}$  (the kinetic model in the factor analysis assumes decay-corrected data).

**FA input is time normalized** Check the box if the dynamic images have units of counts/sec or kBq/cc. Otherwise it is assumed that the images contain counts and a normalization is performed by dividing the pixel values by the acquisition durations.

The **Run** button



starts the factor analysis.

- 1) The factors are calculated, one set for myocardium, and another set for the blood volume.

These factors are used in a weighted averaging of the dynamic frames to generate the factor images of the myocardium and the factor images of the blood pool.

To make the images look smoother a **Gaussian Smoothing** filter is applied.

The smoothed factor images together with the dynamic images are transferred to the **Reorientation** page. To direct them into the right image container, please set the **Stress/Rest** radio button accordingly.

---

**Note:** If rest and stress studies are to be analyzed in parallel, the factor analysis must be performed sequentially, directing the results once to **Rest**, and once to **Stress**.

---

From then on processing continues with short axis reorientation, VOI definition and kinetic modeling as described *above* (on page 23) for the other tracers.

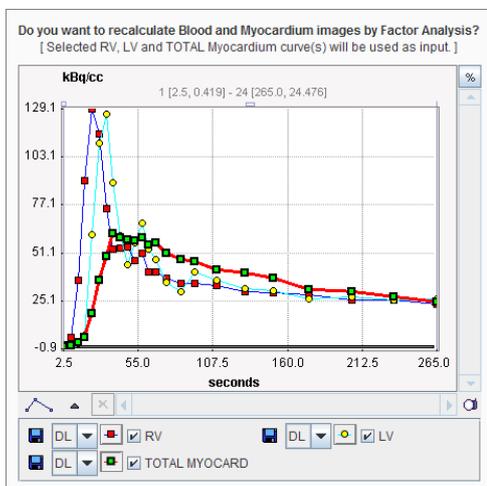
## Iteration of Factor Analysis

Initially, the FA employs approximations of the activity in the LV, the RV and the Myocardium derived from the lung activity. However, after a FA has been performed and

the TACs have been calculated, they represent a more accurate information and can be used in a new FA iteration. Therefore, on the **Kinetic Modeling** page, a new button **FA** appears as illustrated below.



When it is activated, a dialog window appears which shows the TACs to be used.



If the user confirms with **Yes**, the FA is repeated with this information. Note that the resulting factor images are in the original orientation and need to be transformed to the short axis orientation again.

## Normal Database Creation

The concept of the normal database assumes that the perfusion and the metabolism of the myocardium in a healthy left ventricle shows a consistent pattern. It furthermore assumes that the segmentation model is a suitable standardization of the anatomy across persons. Under these premises, the results obtained with healthy hearts can be pooled for a statistical analysis to establish the average and the normal variation in each segment. This information represents the *normal database* for a certain type of cardiac scans. Results found in a patient scan can then be compared against this database resulting in an absolute deviation from the normal value per segment which can also be expressed as a fraction of the standard deviation (z-score).

The principle steps for building a normal database are:

- ▶▶ Recruitment of a sufficient number of healthy normal volunteers. Note that it would be desirable to form age and gender matched control groups.
- ▶▶ Performing the acquisition observing a strict protocol. The tracer should be applied in a consistent way, and the same stress condition used. The same type of attenuation correction should be applied, and the image reconstruction performed with the same algorithm and parameters. It is recommended use a reconstruction zoom and offset so that the reconstructed field-of-view is focused on the heart.
- ▶▶ Carefully analysing the data using PCARDP following a standard procedure. Note that the same kinetic and segmentation models should be used to pool the data. Kinetic models with fewer parameters are to be preferred to minimize the problem of fitting instabilities.
- ▶▶ The resulting rest, stress and reserve polar maps are the basis of the normal database. PCARDP includes a **Norm Edit** tool which allows to create new databases, and add normal polar plots to them. Finally, the tool calculates the average and the standard deviation of the normal values in each segment. These will be used in the evaluation of patient data.

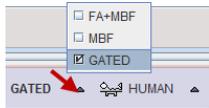
We are sorry the description of the database functionality (which is available) is not yet completed. Please contact us if you have the data for creating a normal database.

# Gated Data Processing

The GATED analysis workflow is applicable to ECG-gated PET and SPECT data. Gated acquisitions use ECG-triggering to divide the signal into different phases of the heartbeat, which are reconstructed as images. The resulting images capture the heart in different phases of contraction, forming the basis for the analysis of heart function.

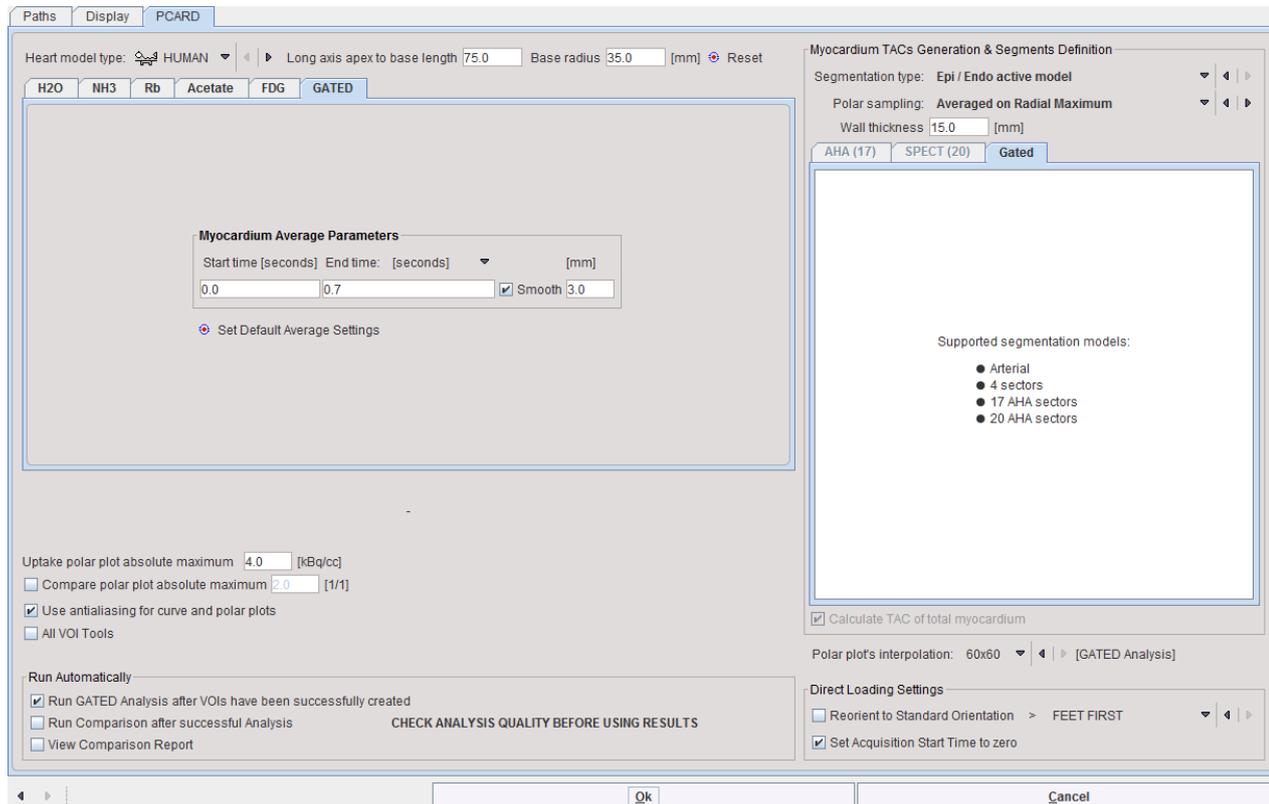
## Processing Configuration

The configuration window is opened with the  button next to the **Cardio PET** menu or if the processing type is changed in the lower status line.



## Analysis Selection

Please select the **Heart model type** corresponding to species studied. In order to optimize the automatic outlining, the long axis length and the left ventricle radius at base level can be adjusted by entering corresponding numbers.



Similar to the MBF Analysis, a **MYOCARDIUM** image is generated by averaging the gate images between the **Start** and **End** times specified, and subsequently applying an optional **Smooth** parameter. In the example above all gates between 0 and 0.7 seconds (gate start times) will be averaged, and then smoothed with a 3D Gaussian filter of 3mm full-width at half maximum.

As indicated in the **Gated** tab, four heart segmentation models are supported for averaging the results: **Arterial** (flow territories), **4 sectors**, **17 and 20 AHA sectors**.

## Optional Settings

- ▶▶ **Uptake polar plot absolute maximum:** Allows establishing a fixed color table maximum for the uptake polar plots display.
- ▶▶ **Compare polar plot absolute maximum:** Allows defining a fixed color table maximum for the comparison polar plots display.
- ▶▶ **Use antialiasing for curve and polar plots:** Controls whether lines and points are drawn with antialiasing or not. With the checkbox enabled graphics look smoother.
- ▶▶ **All VOI Tools:** Allows accessing all VOI tools when manual adjustment need to be performed after automatic VOI outlining.

## Flow of Processing

The section **Run Automatically** contains three boxes. If they are checked, a processing will be started as soon the data for it is available:

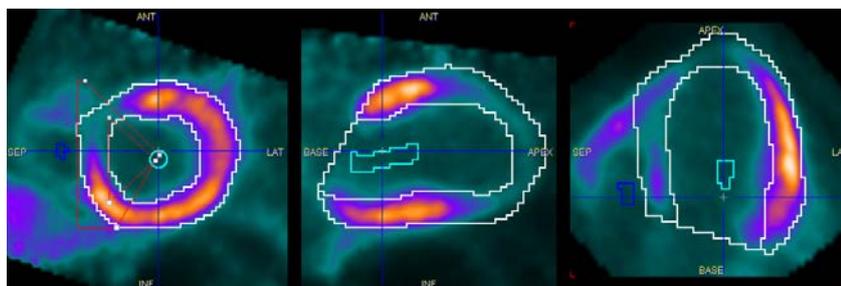
- ▶▶ **Run GATED...** If this box is checked, TACs are calculated and the gated analysis performed as soon as a complete set of VOIs has been defined.
- ▶▶ **Run Comparison ..** : If this box is checked, the gated analysis results are automatically transferred to the comparison page. Note that it is advised to inspect the results before relying on the generated report.
- ▶▶ **View Comparison Report:** If this box is checked, the report page is shown each time data is transferred to the comparison page.

## Contouring and Segmentation

There are two options available for the myocardium detection procedures:

### 1) Epi/Endo outline described *previously*

**Epi/Endo active model:** this segmentation technique is based on the *active model* [https://en.wikipedia.org/wiki/Active\\_contour\\_model](https://en.wikipedia.org/wiki/Active_contour_model) technique in 3D (active surface). Initially, a heart model is fitted to the averaged data. It is used for initializing the active surfaces in each gate, which are then fitted to the data. The procedure is performed for the Epi and Endo surfaces.



The uptake is sampled in the resulting heart models by polar sampling as described *previously*.

## Data Processing Steps

Processing a gated study consists of the following steps:

- 1) Loading of the gated image series. If data at rest and stress are available, they can be loaded in a single operation.

Generation of an average myocardium image by averaging a range of gate images as described in *Generating Myocardium Image by Averaging* (on page 69) section.

Transforming the data sets into standard short axis orientation, as described in *Standard Reorientation of the Heart* (on page 89). An automatic procedure is available. If it fails, the orientation must be manually adjusted by the user.

Definition of the endo- and epicardial outlines in the different gate images. There is an automatic procedure which starts from the average, propagates the outlining result to the individual gates, and the adjusts them individually. If the automatic procedure fails, the outlines have to be adjusted manually by the user.

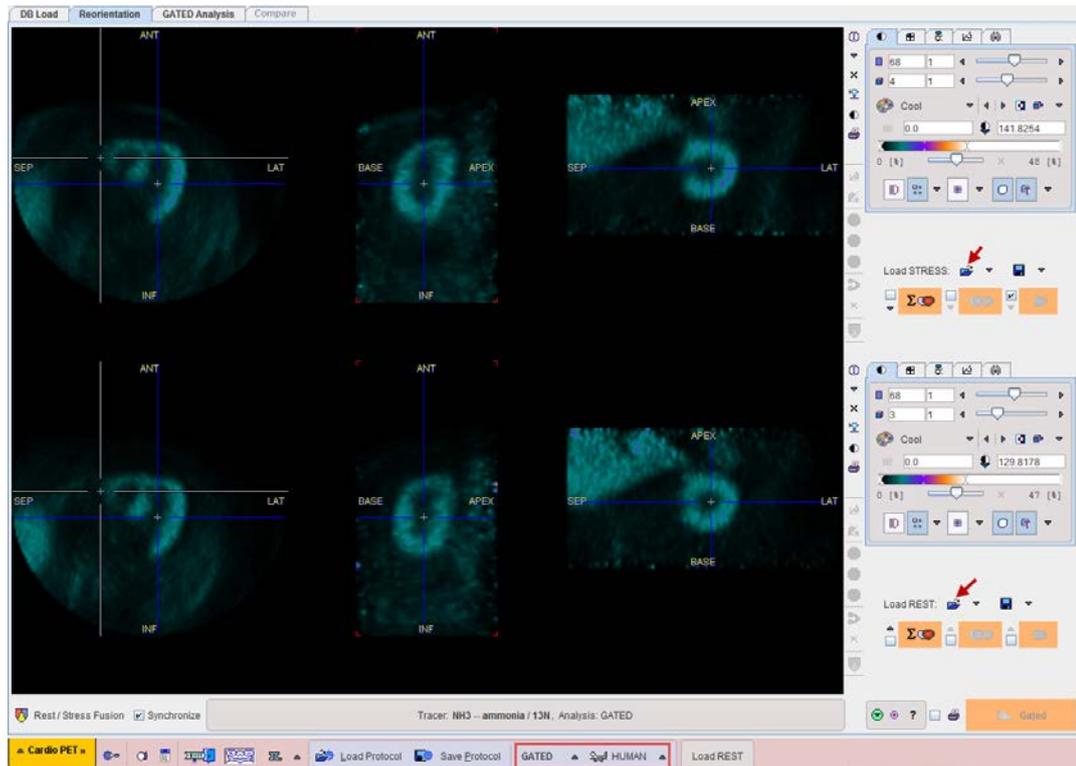
Based on the contours, calculation of various parameters of left ventricle function: end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), peak filling rate (PFR), time to peak filling rate (TPFR), filling rate during the first third of the filling time (1/3 filling time) and first third filling fraction (1/3 filling fraction).

The results of the gated analysis are summarized by tables and plots, and can be documented in reports.

## Data Loading

The layout of PCARDP is designed for processing the stress study in the upper half of the window, and the rest study in the lower half. Otherwise the results will be labeled incorrectly and the comparison will be wrong. If only one study is processed, it should be loaded into that part which is more appropriate for labeling. Note that if two studies are selected for loading in the **DB Load** page or using the loading button in the taskbar to the right, *the first one will be considered as stress, and the second one as rest*. When loading DICOM data, PCARDP will analyze the encoded information and show warnings if rest and stress series seem interchanged.

The **Reorientation** layout is illustrated below. The individual data sets can be loaded using the buttons in the **STRESS** and **REST** area.

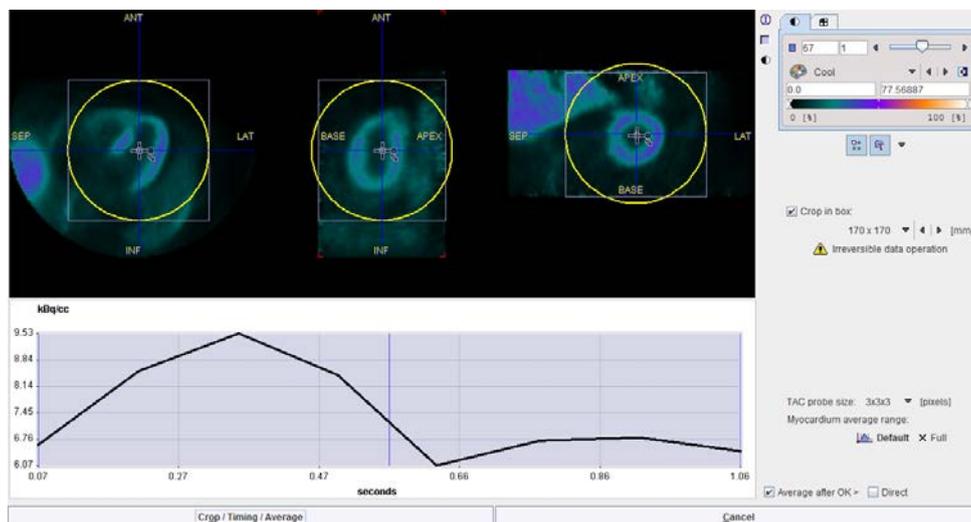


Note the configured settings in the status line, in the example above **GATED** and **HUMAN**.

Activate the  button to proceed with the cropping/averaging process for calculating the myocardium image.

## Generating Myocardium Image by Averaging

The **Crop Heart** dialog window serves for creating an approximation of the LV myocardium, which will be used for initializing the contouring.



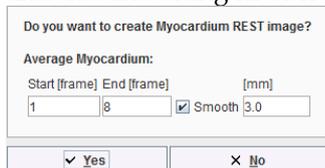
The shaded area represents the time range for the gate averaging. It can be adjusted by dragging the vertical edges. **Default** resets the range, and **Full** includes all gates. The resulting average image is shown in the image window at the top.

Enable the **Crop in box** in order to define a cropping volume. A yellow sphere is shown in the overlay. Its size can be changed with the list selection, and its center defined by dragging the handles. It should be placed such that the whole heart is enclosed, with enough margin for the short axis reorientation. The cropped image can be masked outside the sphere by checking the **Mask** box.

With each click into the image an average time-activity curve (TAC) at that location is calculated and shown in the curve panel. The sampling is performed by averaging the pixels with the configurable **TAC probe size**.

The action button to continue is located in the lower left. It changes the naming according to the enabled options. With all options enabled (recommended) the button is labeled **Crop/Timing/Average**.

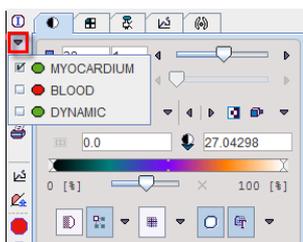
- ▶▶ Cropping is an irreversible operation. Therefore an explicit confirmation is requested before it is executed. Note that cropping is only supported once. Thereafter, only changing of the time-averaging definition will be possible.
- ▶▶ Before time-averaging is performed, a confirmation window is shown with the frame and the smoothing filter from the default configuration, so that they can be edited.



Upon confirmation, the averaging, cropping and masking is performed as prescribed.

## Arrangement of the Result Images

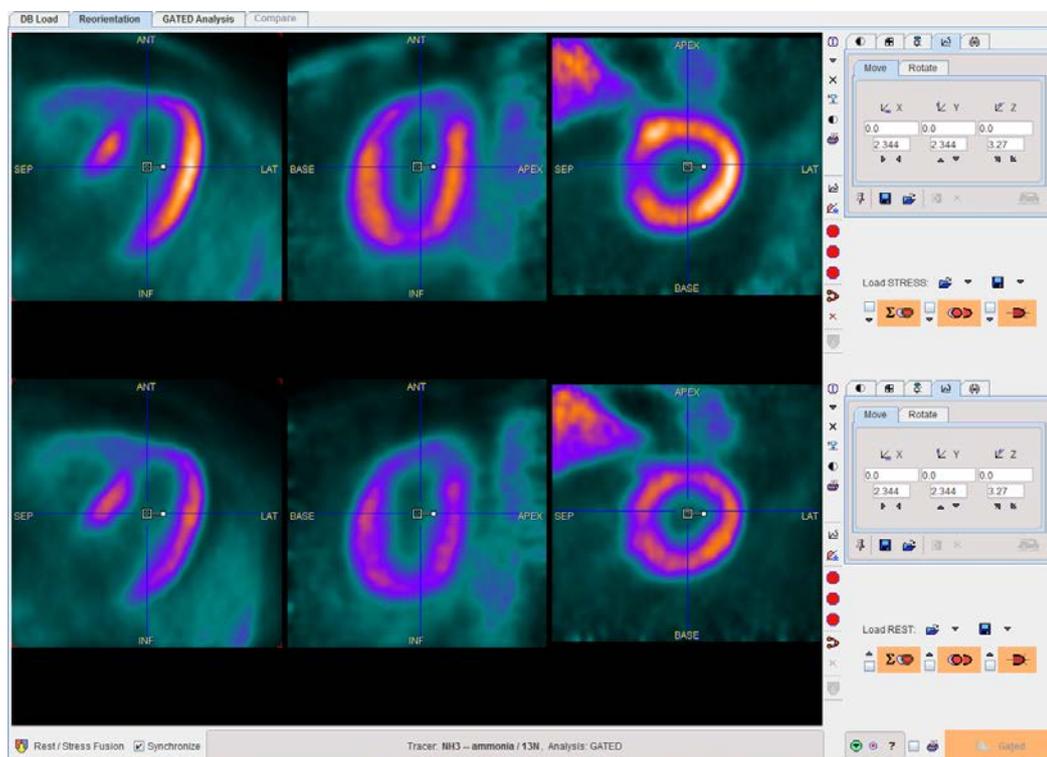
Whenever the time-averaging is performed, a new image study called **MYOCARDIUM** is calculated, and the display is switched to **MYOCARDIUM**. The user can switch between the original **DYNAMIC** study and the averaging results by the study selection as illustrated below. Note the red **BLOOD** entry which has no function in the gated analysis.



To transform the image into standard SA orientation activate the dedicated button . If the "automatic" check for the SA reorientation is on, this step is immediately performed after averaging.

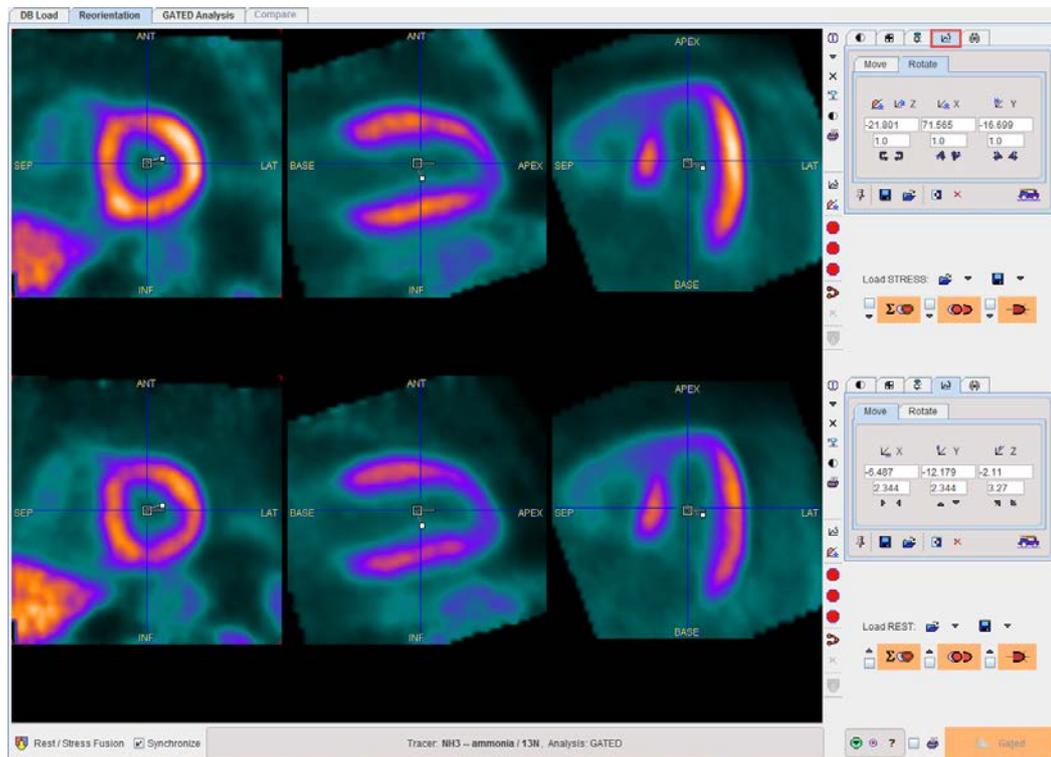
## Transforming Images into Standard Short Axis Orientation

The images are reoriented, and the resulting transformation parameters shown in the reslicing tab. The results of the SA orientation for the STRESS study is illustrated below in the upper row:



If the automatic reorientation returns an inadequate result please fine-tune manually as explained *previously* (on page 23).

Once the right orientation for the STRESS study has been found use the arrow below the **Heart standard orientation** box to copy the short axis transformation to the rest study. After the transformation is copied, the REST images are immediately resliced:

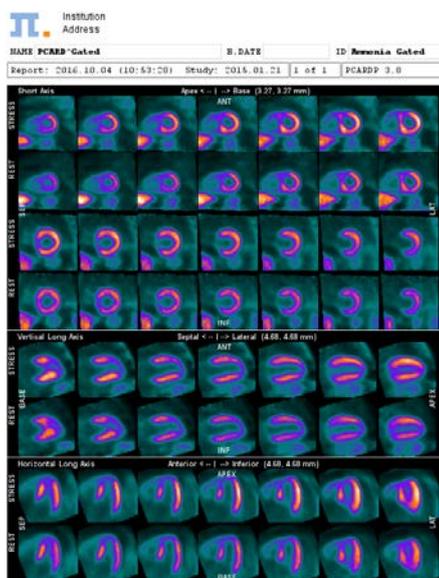


### Standard Cardiological Report Page

When the images are in proper SA orientation, a Stress-Rest comparison report can be generated from the averaged data using the report button located left to the **Gated Analysis** button.



The report layout is organized in three main sections: the upper section shows 14 slices in SA orientation of the Stress study and the corresponding slices of the Rest study; the middle section displays the 7 Stress and Rest slices in vertical long axis orientation; the bottom section shows 7 Stress and the corresponding Rest slices in the horizontal long axes orientation.

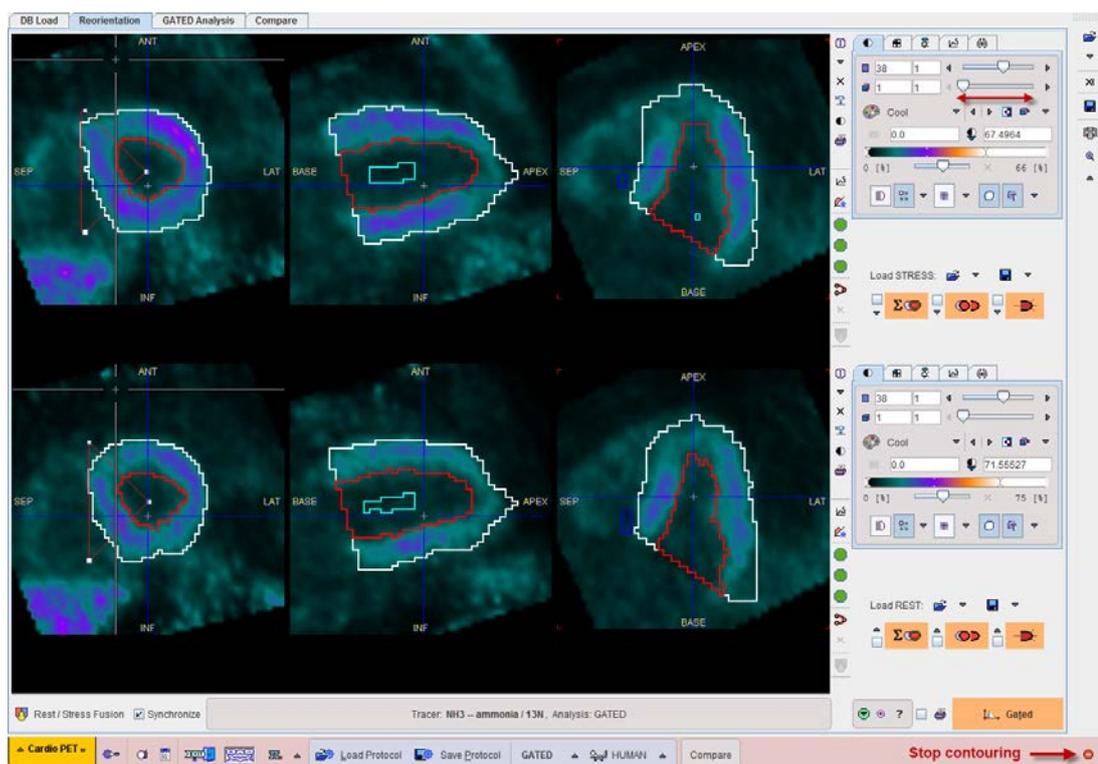


As usual, the report can be annotated, printed or captured in different formats and sizes.

After the images have been brought into standard short axis orientation, continue with the definition of the myocardium contours by activating the  button. Again, if the "automatic" check is on, this step is immediately performed.

## Myocardium Outlining by Volume-of-Interest

An initial contouring is performed on the average **MYOCARDIUM** images by fitting the heart model to the data. It is the initial contour which will be iteratively adjusted to the image at each individual gate. Obviously, if the initial model calculation results in a bad fit, the following adjustments will also fail. In such a case the process can be interrupted with the button indicated below. As explained for the MBF data processing, *markers* (on page 28) can be used to improve the initial fit.



After the Outline VOIs have been defined, the **Gated** button becomes active. When it is selected the following tasks are performed:

- ▶▶ Polar sampling for each gate according to the segmentation model defined in the configuration.
- ▶▶ Calculation of the LV volume/time curve from the endocardial contours.
- ▶▶ Calculation of the various functional metrics values described in the next section.

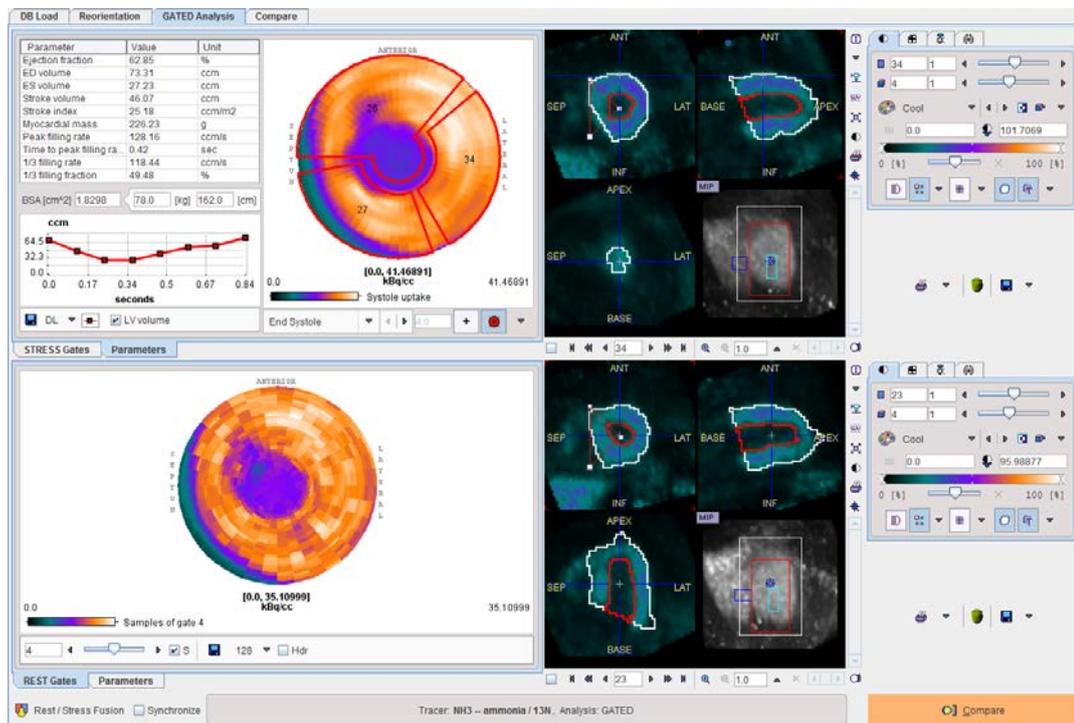
---

**Note:** If complete data is available in the **Rest** and **Stress** rows, the above processing needs to be performed for both of them.

---

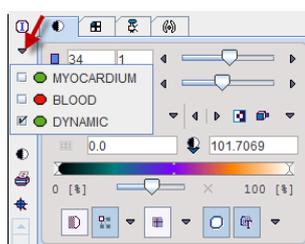
## Gated Analysis Results

The calculation results are displayed on the **GATED Analysis** page as illustrated below:



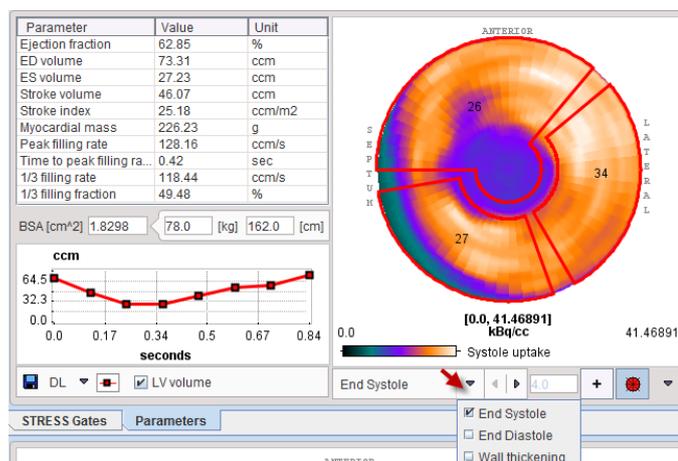
## Resampled Data

The image display on the right side of **GATED Analysis** page initially shows the **DYNAMIC** (Gated) data. Note, however, that you can switch to **MYOCARDIUM** image by the list selection as illustrated below. Green bullets represent data available for the gated analysis, while red bullets mark data which are not available.



## Heart Function Results

The **Parameters** tab shows the results obtained for a processed gated study.



### Parameter Table

The table lists the estimated functional metrics, namely

- Ejection fraction (EF) ▶▶ Fraction of outbound blood pumped from the heart with each heartbeat, calculated as  $(EDV-ESV)/EDV$ .
- End Diastolic Volume, EDV (ED volume) ▶▶ Volume of the left ventricle at diastole.
- End Systolic Volume, ESV (ES volume) ▶▶ Determined as the biggest volume of the endocardial contour in the cardiac cycle.
- ▶▶ Is closely related to venous compliance.
- ▶▶ Volume of the left ventricle at the end of contraction.
- ▶▶ Determined as the smallest ventricle volume of the endocardial contour in the cardiac cycle.
- Stroke Volume (SV) ▶▶ Blood volume pumped from the left ventricle of the heart per beat, calculated as  $EDV-ESV$ .
- Stroke Index (SI) ▶▶ Stroke volume (SV) in relation to the body surface area (BSA), calculated as  $SV/BSA$ .

---

**NOTE:** SI is provided only if the patient height and weight are available, otherwise it is NaN. Note that these fields can be edited.

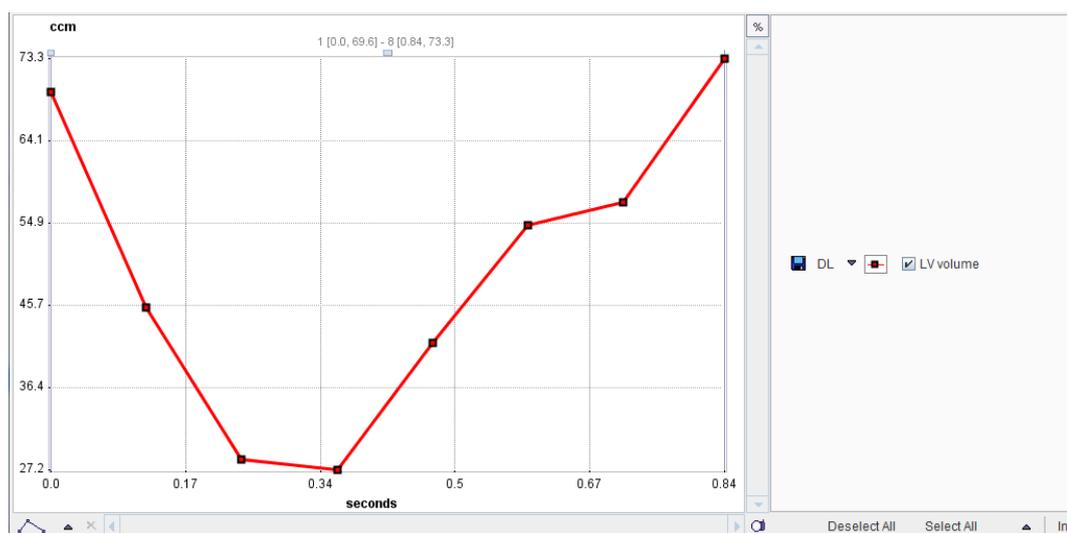
---

- Myocardial Mass (MM) ▶▶ Approximated by multiplying the difference of the epi- and endocardial volumes by the density of the myocardial tissue (1.04 g/cm<sup>3</sup>).
- Peak Filling Rate (PFR) ▶▶ Most rapid change in the ventricular volume, usually occurring in the initial period of fast filling.
- ▶▶ Is defined as the maximal value of the first derivative of the time-volume curve.

- Time to Peak Fill Rate (TPFR) ▶ Interval in milliseconds between the time of minimal ventricular volume (ESV) and the time of the determined peak filling rate (PFR).
- 1/3 filling rate ▶ Filling rate from the time of minimal ventricular volume (ESV) to 1/3 of the total filling time.
- 1/3 filling fraction ▶ Fraction of volume filled until 1/3 filling time.

### LV Time-Volume Curve

In the plot section the volume of left ventricle is shown as a function of time in the heart cycle. To inspect the curve in a larger window, click with the right mouse button into the curve area and select **View in Separate Window** from the context menu. The example below shows a typical time-volume curve.



A time-volume curve is expected to have its minimum (end-systole) at gate3 or 4, and its maximum (end-diastole) at frame 1 or 8 in gated acquisitions with 8 frames. Major deviations from this behavior indicate a gating failure, and the acquisition should be repeated.

### Polar Plots

The polar plots show either the tracer uptake at the **End Systole** or **End Diastole**, or the percent **Wall Thickening**. An overlay showing 3 vascular territories (**Arterial**), 4 **Sectors** or 20 segments (**20 AHA sectors**) can be selected from the pull-down menu to right of the overlay toggle .

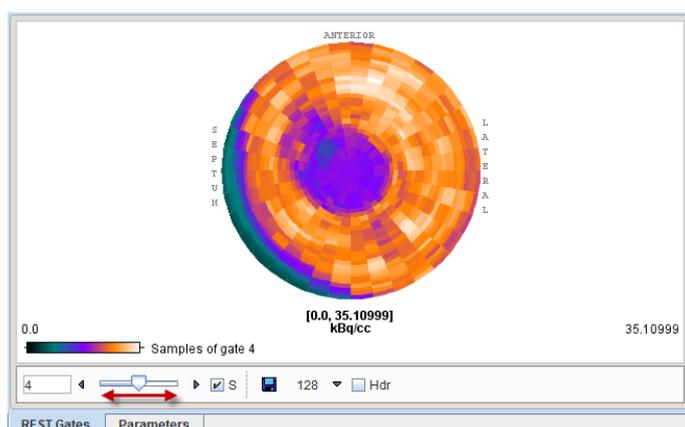


By default, **Arterial** definition is used. The + button allows using an explicitly defined maximum rather than the maximum in the data, which can be specified in the adjacent number field. The numbers in the polar plot overlay represent the average value in the territory or sector. When the cursor is moved about a polar plot the instantaneous value is

shown in the upper right. The polar plot display control can be switched on/off by right clicking into the polar plot area and selecting the **Hide/Show Controls** option. After enabling the controls, the thresholds of the color table can be interactively adjusted. With the **Properties** entry in the context menu, display properties like **Description's font size** can be changed.

## Polar Plots of Uptake

The result of radial sampling is visualized on the **REST Gates** or **Stress Gates** tab of the **GATED Analysis** page as a dynamic polar plot. The gate selection allows scrolling through the gates and monitor the concentration in the sampled tissue voxels. Note that the polar plot is only available with the outlines obtained automatically.



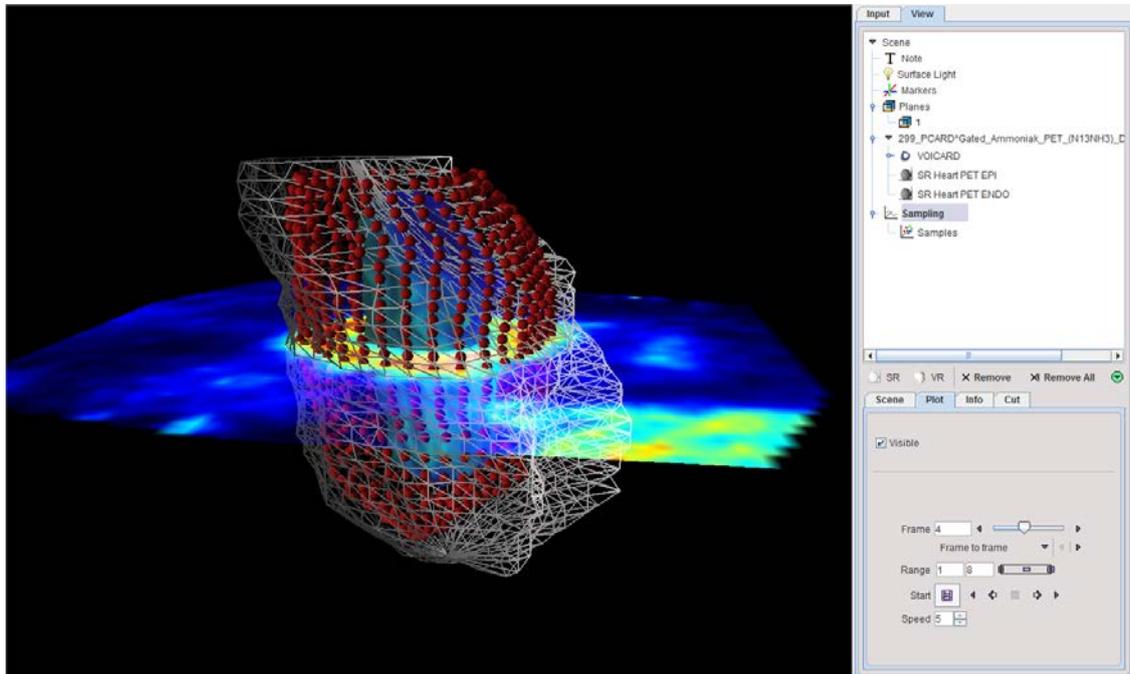
The **S** box enables synchronization between the polar and image display frames. The dynamic polar sampling can be saved activating the saving icon. Optionally, the header can be appended during the saving procedure enabling the **Hdr** checkbox. After saving, the polar plots can be analyzed outside the PCARDP tool, for example in the PMOD-R interface.

## 3D Visualization (3D Option Required)

The geometry of the analysis can be visualized together with the short axis images using the button



The right button calls the 3D tool which renders the shape of the myocardium model together with the sampling points. The example below shows the sampling points for the uptake as red spheres, the ENDO model as a surface, and the EPI model as a wire-frame surface. Additionally, a transparent short axis slice of the PET image is included.

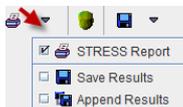


To learn more about the many possibilities exploring the data in P3D please refer to the *PMOD 3D Rendering User Guide*.

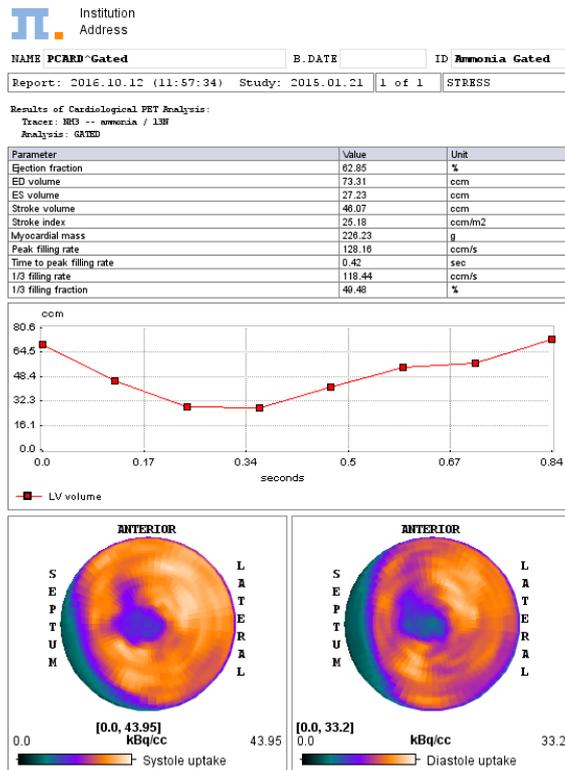
## Documentation

### Report (STRESS, REST separate)

A report can be generated using the selection illustrated below.



The layout is organized in three main sections: the upper section lists the functional parameters; the middle section shows the time-volume curve of the left ventricle; the bottom displays the **Systole** and **Diastole uptake** polar plots.



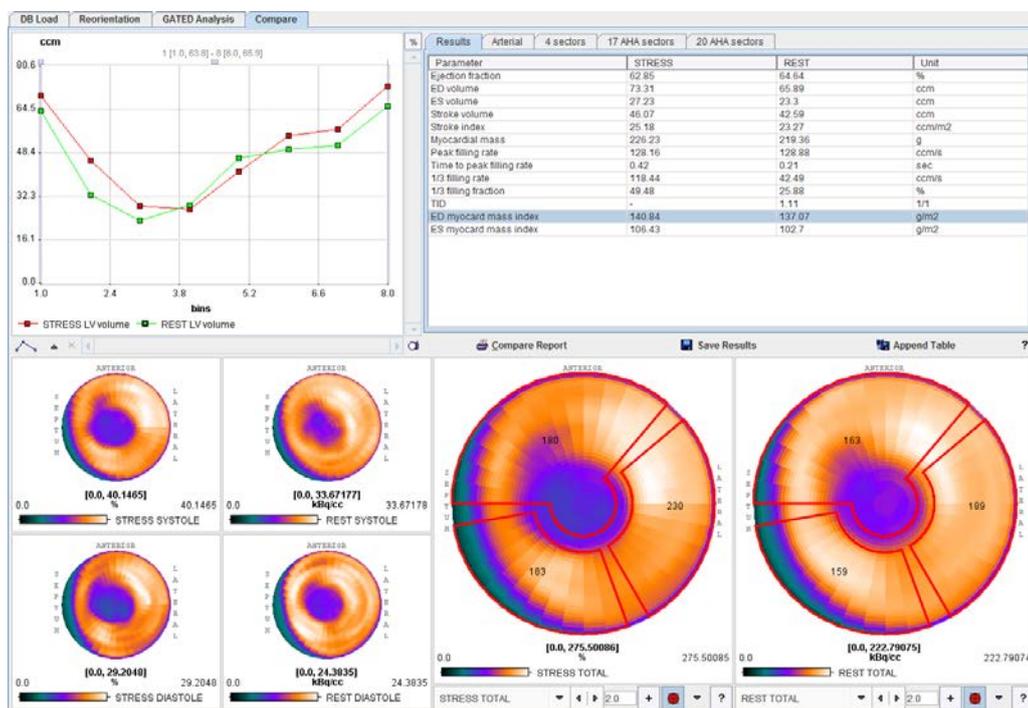
As usual, the report can be annotated, printed or captured in different formats and sizes. Note the buttons **Print** for printing the report, and **Save as** for saving the report in a graphic format (JPEG, TIFF) or in DICOM.

### Save Numeric Results

The numeric results contained in the main report can be saved using the entry **Save Results**. This generates a simple ASCII text file which can be opened in many editors, such as MS Excel, for further processing. Use the entry **Append Results** to append the results to an existing file.

## Rest/Stress Comparison

The **Compare** button on the **GATED Analysis** page starts the result comparison and shows it on the **Compare** page.



The page is organized in four main areas described below.

### Time-Volume Curves Area

The volume curves of the left ventricle at STRESS and REST are shown in the upper left corner as a function of the gate bin.

### Tables Area

The results of the gated analysis are summarized in four tables accessible via the tabs:

#### Results

All functional parameters are listed in this table as described in the **Heart Function Results** (on page 76) section. Additionally, three parameters are available which compare STRESS and REST.

**Transient ischemic dilation index TID:** volume ratio between the STRESS and REST at maximal ventricular volume ( $STRESS\_EDV/REST\_EDV$ ).

**ED myocard mass index:** Myocardial mass at end diastole divided by the body surface area (MM/BSA).

**ES myocard mass index:** Myocardial mass at end systole divided by the body surface area (MM/BSA).

**Arterial** This tab shows the uptake related results averaged in the vascular territories **LAD**, **RCA** and **LCX**.

| Results | Arterial  | 4 sectors |           | 17 AHA sectors |            | 20 AHA sectors |       |       |  |
|---------|-----------|-----------|-----------|----------------|------------|----------------|-------|-------|--|
| Sector  | Stress ED | Rest ED   | Stress ES | Rest ES        | Stress TOT | Rest TOT       | REV   | DIFF  |  |
|         | %         | %         | %         | %              | %          | %              | 1/1   | 1/1   |  |
| LAD     | 18.04     | 17.14     | 27.03     | 24.3           | 179.87     | 162.76         | 13.47 | 13.49 |  |
| RCA     | 20.07     | 17.14     | 26.93     | 22.42          | 183.11     | 158.59         | 13.55 | 82.47 |  |
| LCX     | 23.28     | 19.93     | 34.51     | 28.9           | 230.03     | 188.94         | 5.89  | 12.53 |  |

**4 sectors** This tab shows the uptake related results averaged in the **Anterior**, **Septal**, **Inferior** and **Lateral** sectors as well as an **Apical** average.

**17 AHA sectors** This tab shows the uptake related results averaged in the sectors of the AHA 17 segment model.

**20 AHA sectors** This tab shows the uptake related results averaged in the sectors of the AHA 20 segment model.

### Polar Maps Areas

The lower left shows polar maps of STRESS and REST uptake at systole and diastole. The two larger polar plots can be configured to show any of the following 8 results:

**STRESS  
DIASTOLE** Uptake of the STRESS scan at the end of diastole.

**REST  
DIASTOLE** Uptake of the REST scan at the end of diastole.

**STRESS  
SYSTOLE** Uptake of the STRESS scan at the end of systole.

**REST SYSTOLE** Uptake of the REST scan at the end of systole.

**STRESS TOTAL** Average uptake of the STRESS scan across the polar plots of all gates.

**REST TOTAL** Average uptake of the REST scan across the polar plots of all gates.

**STRESS WALL  
THICKENING** Percentage wall thickening in the STRESS scan.

**REST WALL  
THICKENING** Percentage wall thickening in the REST scan.

**REVERSIBILITY** Difference of the **REST TOTAL** and **STRESS TOTAL** polar plots after normalizing them to 1.

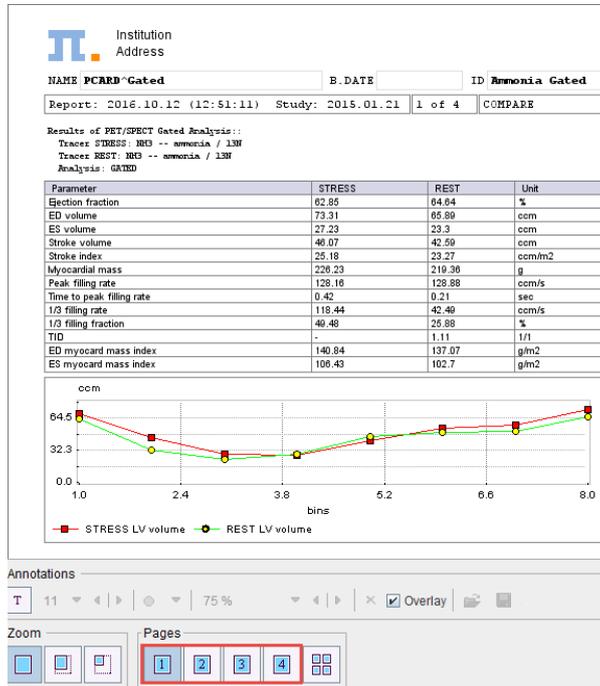
$$REVERSIBILITY = REST\_TOTAL\_norm - STRESS\_TOTAL\_norm.$$

**STRESS  
DIFFERENCE** Negative of **REVERSIBILITY**.

$$STRESS\_DIFFERENCE = STRESS\_TOTAL\_norm - REST\_TOTAL\_norm.$$

## Rest/Stress Summary Report

The **Compare Report** button compiles the Stress/Rest information into a report of four pages, which can be selected in **Pages** area. The first page contains the **Results** tab content in the upper section and the time/volume curves of the STRESS and REST gated studies.

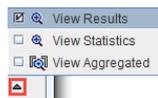


The second page content consist of polar maps of the STRESS and REST uptake at the end of the systole and diastole, the third and fourth contain the tabular information from the various segmentation models.

## Saving and Inspecting Numeric Results

The numeric information of the **Results** tab can also be saved or appended to a text file using the **Save Results** and the **Append Results** buttons, respectively. The saved file receives a **.pcardRes** suffix and can be visualized in Excel or a text editor (e.g Notepad).

Two different numeric results can be opened and compared using View Results from the taskbar.



A dialog windows opens for selecting the first result file, and the data are shown in the left side of the appearing window.

The screenshot shows a software interface with two side-by-side windows, both titled 'Load [PET CARDIAC ANALYSIS]'. The left window displays patient information and a table of parameters. The right window shows a 'Load' button for a second result file.

**Patient Information:**

Results of PET/SPECT Gated Analysis:  
 Patient Name: Patient\_1\Gated\_PET\_1  
 Patient ID: AW1331062624.524.1437124648  
 Birth Date:  
 Sex:  
 Weight: 86.0  
 Size: 1.78  
 Study ID:  
 Study Description:  
 Series Description: DYNAMIC  
 Study Date: 2015.07.16  
 Evaluation Date: 2015.10.23

**File Name:** D:\00-data\Gated\Patient-1\DICOMPA0\ST0\SE1MM140

| Parameter                        | Value  | Unit   |
|----------------------------------|--------|--------|
| Ejection fraction STRESS         | 20.12  | %      |
| Ejection fraction REST           | 19.93  | %      |
| ED volume STRESS                 | 245.26 | ccm    |
| ED volume REST                   | 212.92 | ccm    |
| ES volume STRESS                 | 195.92 | ccm    |
| ES volume REST                   | 172.53 | ccm    |
| Stroke volume STRESS             | 49.34  | ccm    |
| Stroke volume REST               | 40.29  | ccm    |
| Stroke index STRESS              | 24.16  | ccm/m2 |
| Stroke index REST                | 19.73  | ccm/m2 |
| Myocardial mass STRESS           | 451.08 | g      |
| Myocardial mass REST             | 455.04 | g      |
| Peak filling rate STRESS         | 172.56 | ccm/s  |
| Peak filling rate REST           | 193.07 | ccm/s  |
| Time to peak filling rate STRESS | 0.05   | sec    |
| Time to peak filling rate REST   | 0.25   | sec    |
| 1/3 filling rate STRESS          | 168.31 | ccm/s  |
| 1/3 filling rate REST            | 120.93 | ccm/s  |
| 1/3 filling fraction STRESS      | 51.88  | %      |
| 1/3 filling fraction REST        | 46.66  | %      |
| TID STRESS                       | -      | 1/l    |
| TID REST                         | 1.15   | 1/l    |
| ED myocard mass index STRESS     | 229.45 | g/m2   |
| ED myocard mass index REST       | 228.67 | g/m2   |
| ES myocard mass index STRESS     | 212.33 | g/m2   |
| ES myocard mass index REST       | 216.99 | g/m2   |

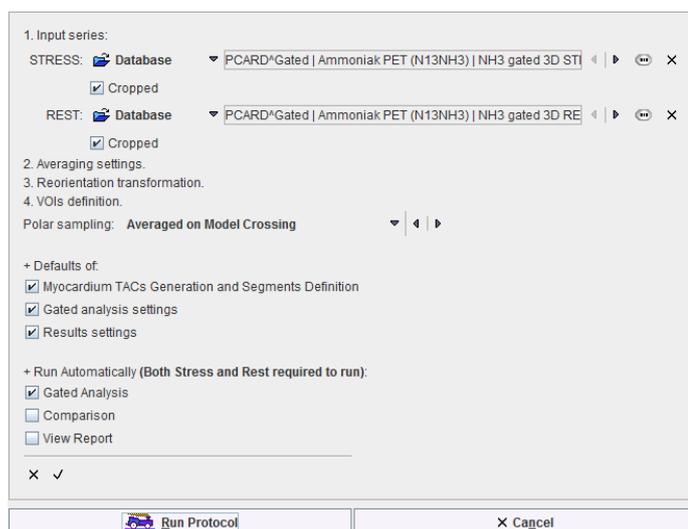
The right window shows a 'Load' button for a second result file, with a 'Close' button below it.

The **Load** button in the upper right allows loading a second result for a side-by-side comparison. The **Close** button exits the comparison window.

## Protocol Files

The quantification of a gated cardiac rest/stress study is a complex task which may involve manual adjustments. To ensure the exact reproduction of a PCARDP analysis the entire set of definitions can be saved using the **Save Protocol** button which can be found in the lower status line.

Protocols can later be retrieved using the **Load Protocol** button. After protocol selection a dialog window appears offering some choices. If all options are checked, the analysis will be exactly reproduced. If a **Defaults of** option is not enabled, the current definition will be used instead of the definition in the protocol file.



Activate **Run Protocol** to start processing from scratch.

## Static Data Processing

The processing of static scans is much simpler than a full functional quantification, because kinetic modeling is not applicable. However, PCARDP can still generate a polar map and a numeric table of the uptake values. Please switch the processing mode to **MBF** before starting and *configure* (on page 13) an appropriate sampling mode.

### Static Scan Processing

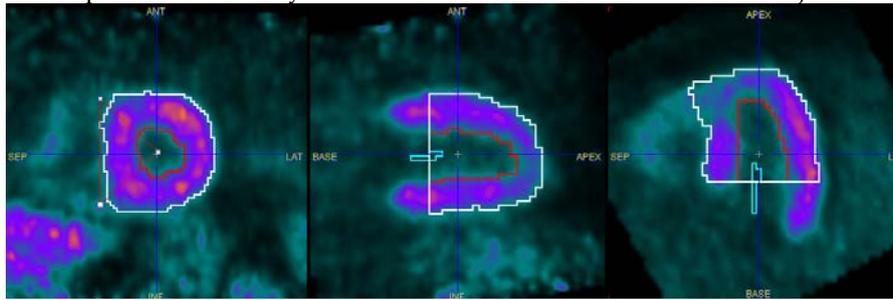
1) Load the image data in either row.

Perform the automatic short axis reorientation, with manual adjustments if needed so the the orthogonal slices confirm a standard position.

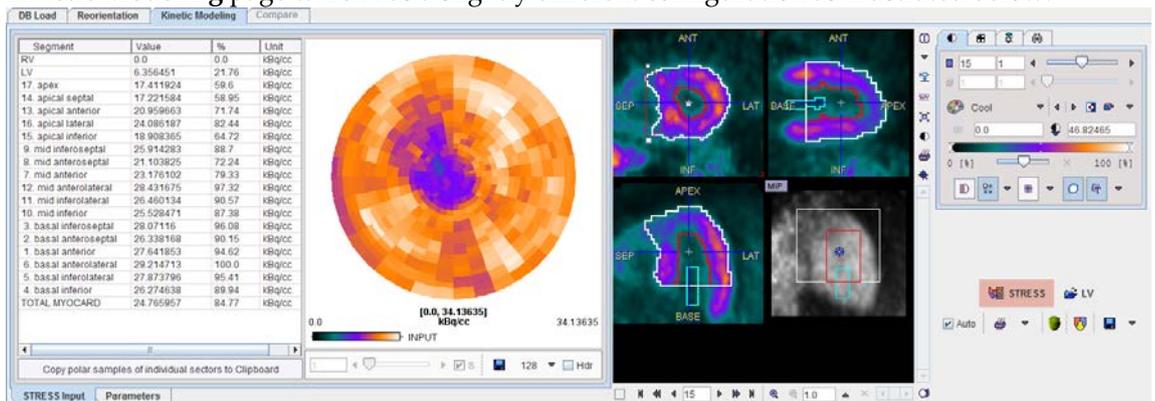
Define the five markers in the apex and at the basal locations using .

Activate the automatic contouring.

Check the position of the Myocardium contours in the VOI tool and adjust them if necessary.



Select the **Statistics** Button to start the segmentation process. The result is shown on the **Kinetic Modeling** page which has a slightly different configuration as illustrated below.



The table to the left contains the average uptake values in the different segments. The polar plot in the middle shows the uptake values obtained by the polar sampling process, and the images to the right illustrate the contour placement. Note that if you click into the polar plot, the image to the right is adjusted so that the corresponding slice is shown. With an orthogonal layout, the cross is positioned at the sampling location corresponding to the polar plot point.

Print the summary report using the **REST** (or **STRESS**) **Report** button, and save the numeric values using the **Save Results** button (switch button from **REST Report** to **Save Results**).

If you need the values of the individual samples in the polar use the button **Copy polar samples of individual sectors to Clipboard**, and then paste into a program such as Excel for further processing.

Page 1 of the **REST** (or **STRESS**) **Report** contains the segmental uptake values. To allow a quick overview a column with the percent uptake relative to the maximum has been added.

 Institution  
 Address

|                               |                            |                         |
|-------------------------------|----------------------------|-------------------------|
| NAME <b>PCRPB - Gated</b>     | S. DATE                    | ID <b>Ammonia Gated</b> |
| Report: 2016.10.10 (14:20:46) | Study: 2016.01.21   1 of 2 | STRESS                  |

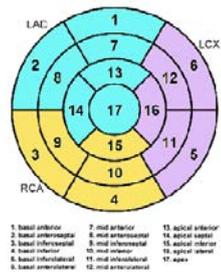
Results of Cardioligand PET Analysis:

Trace:

Mode: **EMTC**

| Segment                | Value     | relative   |
|------------------------|-----------|------------|
|                        | kBq/cc    | [% of Max] |
| RV                     | 8.9       | 0.0        |
| LV                     | 8.309401  | 23.70      |
| 17. apex               | 17.411924 | 59.8       |
| 14. apical septal      | 17.221514 | 58.95      |
| 13. apical anterior    | 20.056683 | 71.74      |
| 18. apical lateral     | 24.088187 | 82.44      |
| 15. apical inferior    | 18.808365 | 64.72      |
| 9. mid inferoseptal    | 25.914293 | 88.7       |
| 8. mid anteroseptal    | 21.193825 | 72.24      |
| 7. mid anterior        | 23.178192 | 78.33      |
| 17. mid anterolateral  | 20.431875 | 67.32      |
| 11. mid inferolateral  | 20.460134 | 66.57      |
| 10. mid inferior       | 20.620471 | 67.38      |
| 3. basal inferoseptal  | 28.07118  | 98.08      |
| 2. basal anteroseptal  | 28.338189 | 98.19      |
| 1. basal anterior      | 27.848353 | 94.82      |
| 6. basal anterolateral | 29.214713 | 100.0      |
| 5. basal inferolateral | 27.873799 | 95.41      |
| 4. basal inferior      | 29.274638 | 99.84      |
| TOTAL MYOCARD          | 24.788987 | 84.77      |

Comment



The polar plot is available using the **Polar Plots** report button.

## Chapter 2

**PCARDP Reference****In This Chapter**

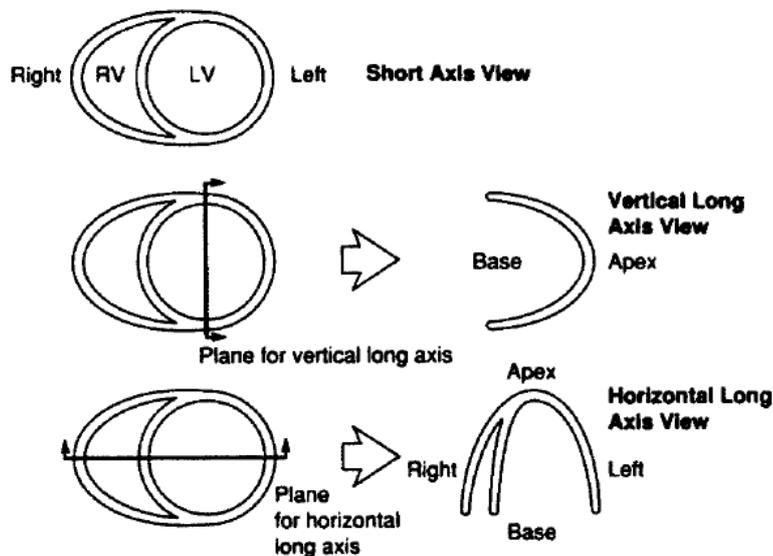
|                                                       |     |
|-------------------------------------------------------|-----|
| Myocardium Segment Models .....                       | 89  |
| Generation of Blood Volume and Myocardium Images..... | 94  |
| Kinetic Models.....                                   | 95  |
| References.....                                       | 110 |

# Myocardium Segment Models

## Standard Reorientation of the Heart

Images resulting from PET or SPECT studies are usually not oriented along the heart axes and therefore do not clearly depict the ventricles, the atria, and the myocardial regions supplied by the major coronary arteries.

It is recommended by the AHA [1] to perform a reorientation of the data so that the long axis of the heart (line apex to the center of the mitral valve) becomes orthogonal to the image planes, and the slice images show *short axis* cuts. This approach maintains the integrity of the cardiac chambers and the distribution of coronary arterial blood flow to the myocardium. From this orientation slice images at 90° angles can also be generated showing the heart as *vertical long axis* and *horizontal long axis* cuts (see illustration below). These correspond to the apical 2-chamber and the apical 4-chamber planes traditionally used in 2D echocardiography.



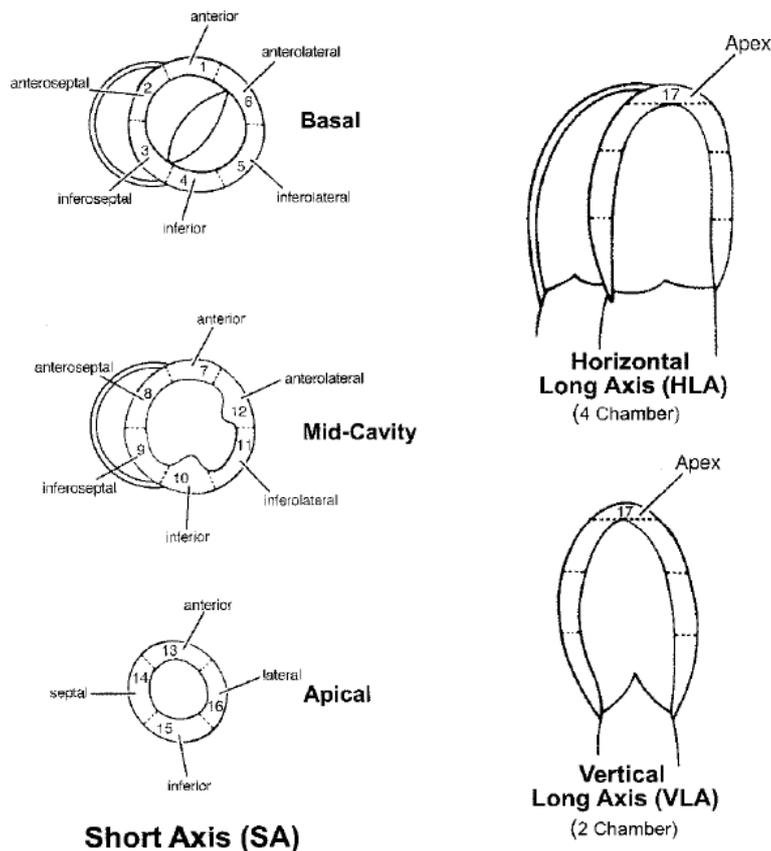
**Figure 1.** Cardiac plane definition and display for tomographic imaging modalities.<sup>4</sup>

## 17-Segment Model (AHA)

### Left Ventricle Segmentation Procedure

The muscle and cavity of the left ventricle can be divided into a variable number of segments. Based on autopsy data the AHA recommends a division into 17 segments for the regional analysis of left ventricular function or myocardial perfusion:

- ▶ The left ventricle is divided into equal thirds perpendicular to the long axis of the heart. This generates three circular sections of the left ventricle named *basal*, *mid-cavity*, and *apical*. Only slices containing myocardium in all 360° are included.
- ▶ The *basal* part is divided into six segments of 60° each. The segment nomenclature along the circumference is: *basal anterior*, *basal anteroseptal*, *basal inferoseptal*, *basal inferior*, *basal inferolateral*, and *basal anterolateral*. The attachment of the right ventricular wall to the left ventricle can be used to identify the septum.
- ▶ Similarly the *mid-cavity* part is divided into six 60° segments called *mid anterior*, *mid anteroseptal*, *mid inferoseptal*, *mid inferior*, *mid inferolateral*, and *mid anterolateral*.
- ▶ Only four segments of 90° each are used for the apex because of the myocardial tapering. The segment names are *apical anterior*, *apical septal*, *apical inferior*, and *apical lateral*.
- ▶ The apical cap represents the true muscle at the extreme tip of the ventricle where there is no longer cavity present. This segment is called the *apex*.

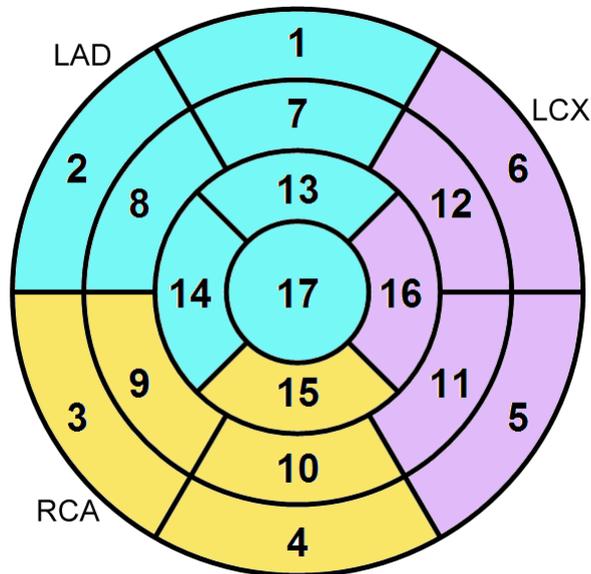


### Polar Plots

If functional values have been obtained in the 17 cardiac segments by some quantification method, they can be arranged as a polar plot with the

- ▶▶ apex in the center,
- ▶▶ the four apical segments as a first ring,
- ▶▶ the six mid-cavity segments as the second ring,
- ▶▶ and the six apical segments as the outermost ring.

Such an arrangement makes it easy to compare the outcome in different conditions (eg. rest/stress) or between patients. The arrangement together with numbers identifying the cardiac segments is illustrated below.



| Basal Segments |                     | Mid-cavity Segments |                   | Apical Segments |                 |
|----------------|---------------------|---------------------|-------------------|-----------------|-----------------|
| 1.             | basal anterior      | 7.                  | mid anterior      | 13.             | apical anterior |
| 2.             | basal anteroseptal  | 8.                  | mid anteroseptal  | 14.             | apical septal   |
| 3.             | basal inferoseptal  | 9.                  | mid inferoseptal  | 15.             | apical inferior |
| 4.             | basal inferior      | 10.                 | mid inferior      | 16.             | apical lateral  |
| 5.             | basal inferolateral | 11.                 | mid inferolateral | 17.             | apex            |
| 6.             | basal anterolateral | 12.                 | mid anterolateral |                 |                 |

The relative contribution of the basal, mid-cavity, and apical segments are 35% (6/17), 35% (6/17), and 30% (5/17), respectively.

### Coronary Artery Territories

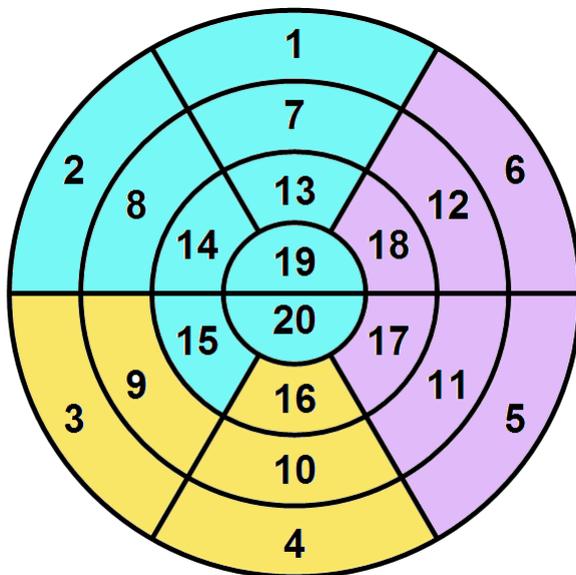
The AHA guidelines emphasize that there is a "tremendous variability in the coronary artery blood supply to myocardial segments". The greatest variability occurs at the apical cap, which can be supplied by any of the three arteries. With the recognition of the anatomic

variability the individual segments may be assigned to specific coronary artery territories as follows.

| Coronary Artery:               | Segments               |
|--------------------------------|------------------------|
| Left Anterior Descending (LAD) | 1, 2, 7, 8, 13, 14, 17 |
| Right Coronary Artery (RCA)    | 3, 4, 9, 10, 15        |
| Left Circumflex (LCX)          | 5, 6, 11, 12, 16       |

## 20-Segment Model (ASNC)

In SPECT nuclear cardiology studies a 20-segment model has also been used [2]. It is similar to the 17-segment model, but the apical part is divided into 8 segments instead of 5 as illustrated by the polar arrangement below.



| Basal Segments         | Mid-cavity Segments   | Apical Segments          |
|------------------------|-----------------------|--------------------------|
| 1. basal anterior      | 7. mid anterior       | 13. apical anterior      |
| 2. basal anteroseptal  | 8. mid anteroseptal   | 14. apical anteroseptal  |
| 3. basal inferoseptal  | 9. mid inferoseptal   | 15. apical inferoseptal  |
| 4. basal inferior      | 10. mid inferior      | 16. apical inferior      |
| 5. basal inferolateral | 11. mid inferolateral | 17. apical inferolateral |
| 6. basal anterolateral | 12. mid anterolateral | 18. apical anterolateral |

19. anteroapical
20. inferoapical

## Generation of Blood Volume and Myocardium Images

The quantification of cardiac PET studies requires that the tracer uptake and clearance in the myocardium is monitored by a dynamic acquisition sequence starting at the time of tracer application. To adequately sample the rapidly changing activity concentrations the acquisitions need to be very short at the beginning, and may last somewhat longer at later times after the bolus has passed the heart for the first time. As a consequence of the short acquisitions, the individual images are noisy and often do not show enough anatomical detail to

- ▶ reorient the images into the standard short axis orientation, and to
- ▶ localize the different heart segments and the blood spaces.

PCARDP provides two mechanisms for generating images with more anatomic information from the dynamic sequence:

- 1) **Average Subtraction Method:** This approach is simple and universal. It is based on the fact that a tracer which is applied as a venous bolus first arrives with a high concentration in the right ventricle, after the passage through the lungs with somewhat decreased activity in the left ventricle, and only afterwards reaches the myocardium, while the concentration in the blood spaces decreases by the continuous clearance. Therefore, an image of the blood volume space can be generated by averaging some of the very early acquisitions. The optimal begin and end times of the averaging depend on how fast the bolus was applied, when the PET scan was started, and must therefore be adjustable for each acquisition. Similarly, tracers tend to accumulate in the myocardium (except for water) over time. Therefore, averaging a range of late frames can potentially provide an anatomical image of the myocardium. To improve the myocardium contrast PCARDP supports the option to subtract from the myocardium images a weighted fraction of the blood volume images. The optimal parameters used for the average subtraction method must be experimentally determined. Once a good setting has been found it should be usable for studies of the same type as long as the tracer application is done in the same way and acquisition protocol is constant.

**Factor Analysis (Water only):** The factor analysis is a more sophisticated approach to derive weighting factors for the different acquisitions. A blood image is obtained by averaging all frames scaled with the respective blood factors, and a myocardium image by averaging all frames scaled with the respective myocardium factors. The factor analysis is model-driven. It requires an approximate input curve, a typical myocardium blood flow value (depending on the condition), and time delays between the occurrence of the activity in the ventricles and the myocardium. Given this information, the expected activity in myocardium can be calculated. Together with the blood activity it is fed into a factor analysis procedure which calculates the factors which provide an optimal contrast between the blood and the myocardium.

## Kinetic Models

Different tracers are applied for cardiac PET studies. For all of them kinetic models have been developed which allow to quantify cardiac function:

- ▶▶ Water ( $H_2^{15}O$ )
- ▶▶ Ammonia ( $^{13}NH_3$ )
- ▶▶ Rubidium ( $^{82}Rb$ )
- ▶▶ Acetate ( $^{11}C$ -acetate)
- ▶▶ FDG ( $^{18}F$ -Deoxyglucose)

These models available for these tracers are described in the following sections.

### Assumptions of the Cardiac Models

- ▶▶ The cardiac models usually apply a geometrical spillover with two correction terms: correction for signal from the left and right ventricle.
- ▶▶ For calculating the myocardial perfusion per g tissue a density of 1.04 g/ml for myocardial tissue is applied.
- ▶▶ Usually the PET signal from the left ventricle or the atrium is used as a measure of the tracer activity in blood. Depending on the tracer, corrections are applied to this blood curve for calculation the concentration of parent tracer with is required as the input curve of the models.

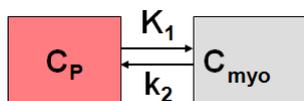
Exceptions to these rules are specified in the description of the individual models.

## Cardiac Flow from Ammonia PET

There are three model variants available for the quantification of myocardial blood flow from  $^{13}NH_3$  ammonia bolus PET data, the 1-tissue compartment model and the 2-tissue compartment model with metabolic trapping. The 1-tissue model is preferably used with the first 2-4 minutes of a dynamic measurement, while the 2-tissue model is also adequate for longer durations. This may compensate to some extent the increased vulnerability to identifiability problems due to the higher number of fit parameters in the 2-tissue model.

### Card. NH3 (de Grado)

The **Card. NH3(De Grado)** model has been developed by DeGrado et al. [1] for cardiac PET studies using  $^{13}NH_3$  ammonia bolus injection. It is based on a 1-tissue compartment model with plasma activity  $C_p(t)$  and total uptake in myocardium  $C_{myo}(t)$ .



## Operational Model Curve

The plasma activity is calculated from the total activity in the left ventricular cavity  $C_{lv}(t)$  by a linear metabolite correction with factor  $mCorr$

$$C_p(t) = (1 - mCorr * t) C_{lv}(t)$$

A value of  $mCorr=0.077$  [1/min] has been found in humans [1]. The resulting differential equation for myocardial uptake is

$$\frac{dC_{myo}(t)}{dt} = K_1 C_p(t) - k_2 C_{myo}(t)$$

where  $K_1$  equals myocardial blood flow  $F$ . The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV}) C_{myo}(t) + V_{RV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where

$V_{LV}$  = spill-over fraction of the blood activity in the left ventricle  $C_{LV}(t)$ ,

$V_{RV}$  = spill-over fraction of the blood activity in the right ventricle  $C_{RV}(t)$ .

DeGrado et al. recommend to only use the first 4 minutes of data after injection of the tracer to reduce the effects of metabolite buildup and washout.

## Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶▶ The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.
- ▶▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- ▶▶ The spill-over fraction from the right ventricle  $V_{RV}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.
- ▶▶ The **valid** flag for all data samples after 4 minutes is set to false, and they are consequently not considered in the fit.

## Parameter Fitting

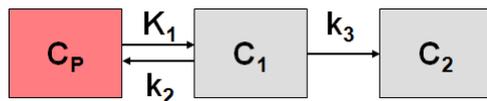
The model includes the 4 fitable parameters **F**, **vRV**, **vLV** and **k2**. Please inspect the **%SE** standard error to get information about the reliability of the parameter estimates.

## Reference

1. DeGrado TR, Hanson MW, Turkington TG, Delong DM, Brezinski DA, Vallee JP, Hedlund LW, Zhang J, Cobb F, Sullivan MJ et al: Estimation of myocardial blood flow for longitudinal studies with  $^{13}\text{N}$ -labeled ammonia and positron emission tomography. *J Nucl Cardiol* 1996, 3(6 Pt 1):494-507.

## Card. NH<sub>3</sub> (UCLA, 2 Parameters)

This model implements a 2-tissue compartment model with only two fitted tissue rate constants. It was developed by Choi et al. for cardiac PET studies using  $^{13}\text{NH}_3$  ammonia bolus injection and was called the *Modified Two-Parameter Model*, [1] eq (5).



## Operational Model Curve

The system of compartmental differential equations for this compartment structure is given by

$$\begin{aligned} \frac{dC_1(t)}{dt} &= K_1 C_P(t) - (k_2 + k_3) C_1(t) \\ \frac{dC_2(t)}{dt} &= k_3 C_1(t) \end{aligned}$$

with  $K_1$  corresponding to myocardial blood flow  $F$ . The  $k_3$  rate constant corresponding to glutamine formation was converted into a  $K_1$ -dependent value by the relation

$$k_3 = K_1 (1.65 e^{1.25/K_1} - 1)$$

Similarly, the  $k_2$  rate constant of ammonia washout was converted into a  $K_1$ -dependent value by

$$k_2 = K_1 / V_{ND}$$

with the  $V_{ND}$  representing the distribution volume of ammonia in the  $C_1$  compartment which was assumed to be constant ( $V_{ND}=0.8$ ).

In contrast to Choi's method, the model incorporates not only a spillover from the left ventricle, but for septal regions also from the right ventricle. The operational equation is then given by

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})(C_1(t) + C_2(t)) + V_{LV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where

$V_{LV}$  = spill-over fraction of the blood activity in the left ventricle  $C_{LV}(t)$ ,

$V_{RV}$  = spill-over fraction of the blood activity in the right ventricle  $C_{RV}(t)$ .

Because the model does not include a metabolite correction, only the samples within 2 minutes after injection should be used for the fit [1].

### Implementation Notes:

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶▶ The left ventricle curve must be loaded as the **Plasma activity** curve.
- ▶▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- ▶▶ The spill-over fraction from the right ventricle  $V_{RV}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.
- ▶▶ The **valid** flag for all data samples after 2 minutes is set to false, and they are consequently not considered in the fit.

### Parameter Fitting

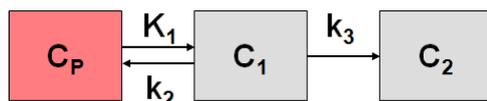
The model includes the three fitable parameters **F**, **vLV**, **vRV**. Please inspect the %SE standard error to get information about the reliability of their estimates. The input parameters **Vnd** (0.8), **EF scale** (1.65) and **EF Exp** (1.25) are related to the conversion of  $k_2$  and  $k_3$  as described above and can be adjusted if needed.

### Reference

1. Choi Y, Huang SC, Hawkins RA, Kim JY, Kim BT, Hoh CK, Chen K, Phelps ME, Schelbert HR: Quantification of myocardial blood flow using  $^{13}\text{N}$ -ammonia and PET: comparison of tracer models. J Nucl Med 1999, 40(6):1045-1055. *PDF*  
<http://jnm.snmjournals.org/content/40/6/1045.full.pdf>

### Card. NH3 (2 Compartments)

The **Card NH3 (2-Tissue)** model developed by Hutchins et al. [1] is an implementation of the irreversible 2-tissue-compartment model for cardiac PET studies using  $^{13}\text{N}$  ammonia bolus injection. The compartment model has the following structure



where  $C_1$  is free tracer in tissue, and  $C_2$  is metabolically trapped tracer in the form of  $^{13}\text{N}$  glutamine. Because ammonia is considered in this model as freely diffusible across the capillary wall, the unidirectional uptake parameter  $K_1$  equals the myocardial perfusion.

## Operational Model Curve

The system of differential equations is

$$\begin{aligned}\frac{dC_1(t)}{dt} &= K_1 C_p(t) - (k_2 + k_3) C_1(t) \\ \frac{dC_2(t)}{dt} &= k_3 C_1(t)\end{aligned}$$

To allow the fitting of data over an extended period, the model includes the exponential metabolite correction described by van den Hoff et al. [2]

$$C_p(t) = \begin{cases} C_{LV}(t) & t \leq t_0 \\ e^{-\ln 2(t-t_0)/T_{1/2}} C_{LV}(t) & t > t_0 \end{cases}$$

with a delay  $t_0=0.48$  min and half-time  $T_{1/2}=6.69$  min.  $C_{LV}(t)$  is the total tracer concentration measured in the left ventricular cavity, including metabolites.

Additionally, the model incorporates a cardiac dual spillover correction by the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})(C_1(t) + C_2(t)) + V_{LV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where

- $V_{LV}$  = spill-over fraction of the blood activity in the left ventricle  $C_{LV}(t)$ ,
- $V_{RV}$  = spill-over fraction of the blood activity in the right ventricle  $C_{RV}(t)$ .

## Implementation Notes:

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶ The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.
- ▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustments are performed within the model:

- ▶ The spill-over fraction from the right ventricle  $V_{RV}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.
- ▶ The **valid** flag for all data samples after 2 minutes is set to false, and they are consequently not considered in the fit.

## Parameter Fitting

The model includes the five fitable parameters **F**, **vLV**, **vRV**, **k2**, **k3**. Please inspect the %SE standard error to get information about the reliability of their estimates. The input parameters **MC T0** (0.48) and **MC T12** (6.69) are related to the metabolite correction as described above and can be adjusted if needed.

### Alternate Model Card NH3 (2-Tissue, $K_1/k_2$ )

Due to the increased number of fit parameters it has been found, that the **Card NH3 (2-Tissue)** may suffer from identifiability problems. Therefore, the variant **Card NH3 (2-Tissue,  $K_1/k_2$ )** has been developed using the parameter  $K_1/k_2$  (distribution volume of the first compartment) as a fit parameter instead of  $k_2$ . In this configuration physiological restrictions can be imposed on  $K_1/k_2$ , or  $K_1/k_2$  can be used as a common parameter in a coupled fit.

### References

1. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE: Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. J Am Coll Cardiol 1990, 15(5):1032-1042.
2. van den Hoff J, Burchert W, Borner AR, Fricke H, Kuhnel G, Meyer GJ, Otto D, Weckesser E, Wolpers HG, Knapp WH: [1-(11)C]Acetate as a quantitative perfusion tracer in myocardial PET. J Nucl Med 2001, 42(8):1174-1182. *PDF*  
<http://jnm.snmjournals.org/content/42/8/1174.full.pdf>

### MBF Mapping for NH3

The model for calculating the MBF parametric maps was derived from the parametric mapping method developed by Harms et al [48] for water scans. The operational equation for cardiac PET includes two geometric spillover fractions ( $V_{lv}$ ,  $V_{rv}$ ) from left ventricular and right ventricular blood ( $C_{lv}$ ,  $C_{rv}$ ):

$$C_{Model}(t) = (1 - V_{LV} - V_{RV})C_{myo}(t) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

The tracer concentration in myocardium  $C_{myo}(t)$  is modeled by a one-tissue compartment model and can be obtained by the convolution of the metabolite-corrected input curve with a decaying exponential, multiplied by  $K_1$ :

$$C_{myo}(t) = K_1(1 - mCorr \cdot t)C_{LV}(t) \otimes e^{-k_2 t}$$

For the ammonia tracer  $K_1$  corresponds to myocardial blood flow (MBF), and  $k_2$  to the tissue washout. The linear metabolite correction with slope  $-mCorr$  which is applied in this equation was derived by de Grado et al [30] and is only valid for scan durations up to 4 minutes.

The solution of the operational equation uses basis functions of the form

$$B_i(t) = (1 - mCorr \cdot t)C_{LV}(t) \otimes e^{-k_2 t}$$

With the basis functions, the operational equation can be reformulated as a multi-linear equation

$$C_{Model}(t) = \theta_1 B_i(t) + V_{LV}C_{LV}(t) + V_{RV}C_{RV}(t)$$

with

$$\theta_1 = K_1(1 - V_{LV} - V_{RV})$$

The data analysis methodology then consists of the following two steps:

- 1) As a preprocessing step the basis functions are calculated for a set of  $k_2$  values which span the physiologic relevant range.

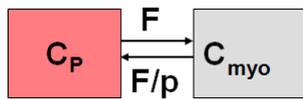
In each pixel the TAC is fitted by solving the operational equation for all basis functions and selecting the solution which best fits the measurement. From the resulting parameters  $\theta_1$ ,  $V_{LV}$  and  $V_{RV}$  the MBF ( $=K_1$ ) can readily be calculated.

If the blood contribution in a pixel is too high ( $V_{LV} + V_{RV} > 0.75$ ), the MBF result is discarded.

## Cardiac Flow from Water PET

### Cardiac Flow from Water PET

The **Card. H<sub>2</sub>O (Tissue fraction)** model has been developed by Hermanssen et al. [1] for cardiac PET studies using H<sub>2</sub><sup>15</sup>O water bolus injection. The distribution of the freely diffusible inert tracer H<sub>2</sub><sup>15</sup>O in myocardium can be described by a 1-tissue compartment model with myocardial blood flow  $F$  and the partition coefficient of water  $p$ , which is defined as (ml water/ml tissue)/(ml water/ml blood).



### Operational Model Curve

The differential equation for the tracer concentration in myocardium is

$$\frac{dC_{myo}(t)}{dt} = FC_p(t) - \frac{F}{p}C_{myo}(t)$$

In practice, the left ventricular time-activity curve is used as the input curve  $C_p(t)$ .

The model curve incorporates two spill-over terms from blood in the left and the right ventricular cavities which are relatively displaced in time. So the operational equation which is fitted to the measured data is

$$C_{Model}(t) = TF C_{myo}(t) + V_{LV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where  $TF$  = tissue fraction,  $V_{LV}$  = spill-over fraction from the left ventricle,  $V_{RV}$  = spill-over fraction from the right ventricle.

### Implementation

As opposed to most models in PKIN a tissue fraction is used for calculating the model curve rather than a strict geometrical correction for compliance with the original model. When

using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶ The left ventricle curve must be loaded as the **Plasma activity** curve.
- ▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- ▶ The spill-over fraction from the right ventricle  $V_{rv}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

### Parameter Fitting

The model encompasses the 5 fitable parameters **F**, **TF**, **vLV**, **vRV** and **p**. However, in practice it is impossible to estimate so many parameters from a time-activity curve with reasonable identifiability. The partition coefficient is therefore fixed per default at a value of 0.96 [1], and the spillover fraction from right ventricular blood vRV is only fitted for septal tissue TACs.

### Reference

1. Hermansen F, Rosen SD, Fath-Ordoubadi F, Kooner JS, Clark JC, Camici PG, Lammertsma AA: Measurement of myocardial blood flow with oxygen-15 labelled water: comparison of different administration protocols. Eur J Nucl Med 1998, 25(7):751-759. *PDF*  
<http://jnm.snmjournals.org/content/39/10/1696.full.pdf>

### Card. H2O (Geometrical corr.)

This model is the same as the one above developed by Hermansen et al. [27], except that it uses a geometrical spillover correction. The operational equation which is fitted to the measured data is

$$C_{PET}(t) = (1 - V_{lv} - V_{rv}) C_{myo}(t) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

where  $V_{lv}$  = spill-over fraction from the left ventricle,  $V_{rv}$  = spill-over fraction from the right ventricle. In practice, the left ventricular time-activity curve is also used as the input curve  $C_p(t)$ .

### Implementation Notes

The right ventricle curve is only used for spillover correction of septal TACs. It must be loaded as the **Total blood** curve. The left ventricle curve serves both as the input curve as well as for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.

The right ventricle spill-over fraction  $V_{rv}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name of the region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with single spill-over from the left ventricle. The reason of this behavior is the usage of this model in the PCARDP tool.

## Cardiac Flow from Rubidium-82 PET

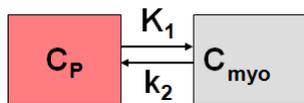
Two kinetic models are available for the quantification of myocardial perfusion from  $^{82}\text{Rb}$  bolus PET data.

1) A 1-tissue compartment model with geometrical spillover correction and correction for flow-dependent extraction.

A 2-tissue compartment model with recovery and spillover correction.

### Card. Rb-82 (1 Compartment)

The **Card. Rb82(1 Compartment)** model has been developed by Lortie et al. [1] for cardiac PET studies using  $^{82}\text{Rb}$  bolus injection. It is based on a 1-tissue compartment model with plasma activity  $C_p(t)$  and total uptake in myocardium  $C_{\text{myo}}(t)$ .



### Operational Model Curve

The differential equation is given by

$$\frac{dC_{\text{myo}}(t)}{dt} = K_1 C_p(t) - k_2 C_{\text{myo}}(t)$$

The model uses the activity in the left ventricular cavity  $C_{\text{lv}}(t)$  is used as the input curve ( $C_p(t) = C_{\text{lv}}(t)$ ). Rb is known to have a flow-dependent extraction fraction, so that  $K_1$ , which is the product of flow  $F$  times extraction fraction  $E$ , is described by the expression

$$K_1 = F E = F (1 - A e^{-B/F})$$

This expression is inserted for  $K_1$  into the differential equation, so that  $F$  becomes a fit parameter, and  $K_1$  is derived from it. The values of the extraction parameters reported by Lortie et al. [1] are

$$A = 0.77$$

$$B = 0.63 \text{ [ml/min/g]}$$

They can be entered as input parameters into the model for changing the form of the extraction function. The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{\text{Model}}(t) = (1 - V_{\text{LV}} - V_{\text{RV}}) C_{\text{myo}}(t) + V_{\text{RV}} C_{\text{LV}}(t) + V_{\text{RV}} C_{\text{RV}}(t)$$

where

$V_{\text{LV}}$  = spill-over fraction of the blood activity in the left ventricular cavity  $C_{\text{LV}}(t)$ ,

$V_{\text{RV}}$  = spill-over fraction of the blood activity in the right ventricular cavity  $C_{\text{RV}}(t)$

## Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶▶ The left ventricle curve must be loaded as the **Plasma activity** curve.
- ▶▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- ▶▶ The spill-over fraction from the right ventricle  $V_{RV}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

## Parameter Fitting

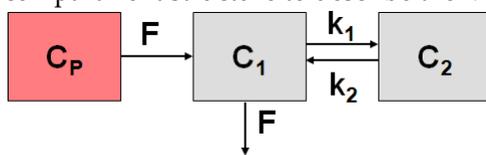
The model includes the 4 fitable parameters **F**, **vRV**, **vLV** and **k2**. Please inspect the %SE standard error to get information about the reliability of the parameter estimates. The scale factor A (**EF scale**) and the exponent B (**EF exp**) of the extraction function can be entered as input parameters.

## Reference

1. Lortie M, Beanlands RS, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA: Quantification of myocardial blood flow with 82Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging 2007, 34(11):1765-1774.

## Card. Rb-82 (2 Compartments)

The **Card. Rb-82 (2 Compartments)** model has been implemented according to the method described and evaluated by Herrero et al [1]. The model is based on the following compartment structure to describe the kinetics of rubidium in the myocardium:



where  $C_1(t)$  represents the fast exchangeable compartment (vascular and interstitial spaces), and  $C_2(t)$  the slow exchangeable compartment (intracellular space), myocardium flow  $F$ , and rate constants  $k_1$  and  $k_2$ .

## Operational Model Curve

The differential equations for the activity concentrations in the different compartments are given by

$$\begin{aligned} \frac{dC_1(t)}{dt} &= F(C_p(t) - C_1(t)) - k_1 C_1(t) + k_2 C_2(t) \\ \frac{dC_2(t)}{dt} &= k_1 C_1(t) - k_2 C_2(t) \end{aligned}$$

The model uses the activity in the left ventricular cavity  $C_{LV}(t)$  is used as the input curve ( $C_p(t)=C_{LV}(t)$ ). The operational equation which is fitted to the measured data is

$$C_{Model} = F_{MM} (C_1(t) + C_2(t)) + F_{BM} C_{LV}(t)$$

where  $F_{MM}$  denotes the tissue recovery coefficient and  $F_{BM}$  the blood to myocardium spillover fraction.

## Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the left ventricle curve must be loaded as the **Plasma activity** curve. The right ventricle curve is not used.

## Parameter Fitting

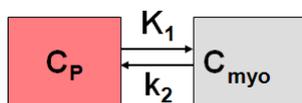
The model encompasses 5 fitable parameters. However, in practice it is impossible to estimate so many parameters from a time-activity curve with reasonable identifiability. Therefore, at least the the recovery coefficient **FMM** is usually fixed. The default from Herrero et al [1] is 0.65, but it depends on the image resolution and should be determined experimentally.

## Reference

1. Herrero P, Markham J, Shelton ME, Bergmann SR: Implementation and evaluation of a two-compartment model for quantification of myocardial perfusion with rubidium-82 and positron emission tomography. *Circulation research* 1992, 70(3):496-507. DOI <http://dx.doi.org/10.1161/01.RES.70.3.496>

## Cardiac Flow from Acetate PET

Van den Hoff et al. [1] have investigated and validated  $^{11}\text{C}$ -acetate as a flow tracer. This methodology is implemented as the **Card Acetate (1 Compartment)** model. It employs a single tissue compartment model



with tracer exchange between arterial plasma  $C_p(t)$  and myocardial tissue  $C_{myo}(t)$ .

## Operational Model Curve

The differential equation  $C_{myo}(t)$  is given by

$$\frac{dC_{myo}(t)}{dt} = K_1 C_p(t) - k_2 C_{myo}(t) = EF C_p(t) - k_2 C_{myo}(t)$$

$K_1$  is the product of flow  $F$  and extraction  $E$

$$K_1 = E \cdot F$$

For acetate, the extraction is flow dependent [1]

$$E(F) = 1 - 0.64e^{-1.2/F}$$

Furthermore a metabolite correction is necessary to derive the plasma activity from whole blood measured in the left cavity [1]

$$C_p = 0.91e^{-\ln 2(t/T_{1/2})} C_{LV}(t)$$

with  $T_{1/2}=5.3$  min. Including these relations into the differential equation yields

$$\frac{dC_{myo}(t)}{dt} = F(1 - 0.64e^{-1.2/F})0.91e^{-\ln 2(t/T_{1/2})} C_{LV}(t) - k_2 C_{myo}(t)$$

which is non-linear in  $F$ . The model curve incorporates a cardiac dual spillover correction, resulting in the operational equation

$$C_{Model}(t) = (1 - V_{LV} - V_{RV}) C_{myo}(t) + V_{RV} C_{LV}(t) + V_{RV} C_{RV}(t)$$

where

$V_{LV}$  = spill-over fraction of the blood activity in the left ventricular cavity  $C_{LV}(t)$ ,

$V_{RV}$  = spill-over fraction of the blood activity in the right ventricular cavity  $C_{RV}(t)$

## Implementation

When using the model from the PCARD module, the data are transferred appropriately. When using it in PKIN the blood data have to be loaded as follows:

- ▶▶ The left ventricle curve must be loaded as the **Plasma activity** curve. No metabolite correction needs to be enabled on the **Blood** panel of PKIN because it is included in the tissue model.
- ▶▶ The right ventricle curve must be loaded as the **Whole blood** curve.

The following automatic adjustment is performed within the model:

- ▶▶ The spill-over fraction from the right ventricle  $V_{RV}$  is automatically fixed to zero if the string "Sep" is *not* contained in the name a region. The assumption is that such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only.

## Parameter Fitting

The model includes the 4 fitable parameters  $F$ ,  $k_2$ ,  $vLV$ ,  $vRV$ . Please inspect the %SE standard error to get information about the reliability of the parameter estimates. The parameters for the correction of the flow-dependent extraction (**EF scale**, **EF exp**) and the metabolites (**MC scale**, **MC T12**) are initialized with the published values [1], but can be edited if needed. The **K1** parameter of the 1-tissue compartment model equivalent to the EF product is provided as a macro parameter.

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## Cardiac Metabolic Rate of Glucose from FDG PET

### Patlak Plot

The Patlak plot has been developed for systems with irreversible trapping [17]. Most often it is applied for the analysis of FDG, which can be modeled as a 2-tissue compartment model with  $k_4=0$ . The Patlak plot belongs to a group of *graphical analysis* techniques, whereby the measured TAC undergoes a transformation and is plotted against some sort of "normalized time".

The Patlak plot is given by the expression

$$\frac{C_T(t)}{C_P(t)} = K \frac{\int_0^t C_P(\tau) d\tau}{C_P(t)} + V$$

This means that the measured PET activity is divided by plasma activity, and plotted at a "normalized time" (integral of input curve from injection divided by instantaneous plasma activity). For systems with irreversible compartments this plot will result in a straight line after sufficient equilibration time. The slope and the intercept must be interpreted according to the underlying compartment model. For the FDG model mentioned, the slope equals  $K_1 k_3 / (k_2 + k_3)$  and represents the influx, while the intercept  $V$  equals  $V_0 + vB$  with the distribution volume  $V_0$  of the reversible compartment  $C_1$  and the fractional blood volume  $vB$ .

### Implementation Notes

The **Patlak Plot** model calculates and displays the transformed measurements as described by the formula above. It allows to fit a regression line within a range defined by the parameters **Start Lin.** and **End Lin.** The results are the regression slope and the intercept. There is also an error criterion **Max Err.** to fit **Start Lin.** For instance, if **Max Err.** is set to 10% and the fit box of **Start Lin.** is checked, the model searches the earliest sample so that the deviation between the regression and all measurements is less than 10%. Samples earlier than the **Start Lin.** time are disregarded for regression and thus painted in gray.

For FDG data, the Lumped constant (LC) and the plasma glucose level (PG) of the patient should be entered. The metabolic rate of glucose MRGlu is then obtained from the regression slope by  $MRGlu = \text{slope} * PG / LC$ .

### Abstract [17]:

"A theoretical model of blood-brain exchange is developed and a procedure is derived that can be used for graphing multiple-time tissue uptake data and determining whether a unidirectional transfer process was dominant during part or all of the experimental period. If the graph indicates unidirectionality of uptake, then an influx constant ( $K_i$ ) can be calculated. The model is general, assumes linear transfer kinetics, and consists of a blood-plasma compartment, a reversible tissue region with an arbitrary number of compartments, and one or more irreversible tissue regions. The solution of the equations for this model shows that a graph of the ratio of the total tissue solute concentration at the times of sampling to the plasma concentration at the respective times ( $C_p$ ) versus the ratio of the

arterial plasma concentration-time integral to  $C_p$  should be drawn. If the data are consistent with this model, then this graph will yield a curve that eventually becomes linear, with a slope of  $K_i$  and an ordinate intercept less than or equal to the vascular plus steady-state space of the reversible tissue region."

## 2-Compartment Model



The FDG model is a standard 2-tissue compartment model with two additional input parameters, the lumped constant (LC) and the plasma glucose concentration (PG). In combination with the estimated  $K_i$ ,  $k_2$ , and  $k_3$  parameters they allow to calculate the metabolic rate of glucose.

---

**Note:** In the FDG model  $k_4$  is initially set to 0 assuming metabolic trapping, but can also be fitted.

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