User's Guide

PMOD Cardiac Modeling (PCARD)

Version 3.3

PMOD Technologies

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Contents

PMOD Cardiac Modeling Tool (PCARD)

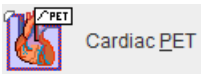
The PCARD tool represents a flexible environment for the quantification of dynamic PET studies of the heart with a broad range of tracers.

PCARD implements the following features:

- 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 TACs to quantify the uptake parameters. Depending on the tracer, the results represent myocardial blood flow (MBF) or a metabolic turnover such as the metabolic rate of glucose (MRGlu).
- Combination of the results to quantify myocardium function in well-defined sectors given by the American Society of Nuclear Cardiology (***ASNC http://www.asnc.org***) and the American Heart Association (***AHA http://www.americanheart.org***).
- Parallel processing of paired stress and rest studies for a side-by-side comparison.
- Generation of a normals database from a set of quantification results obtained from healthy volunteers. Patient data can then be compared against the normal database to quantify deviations in terms of z-score values.

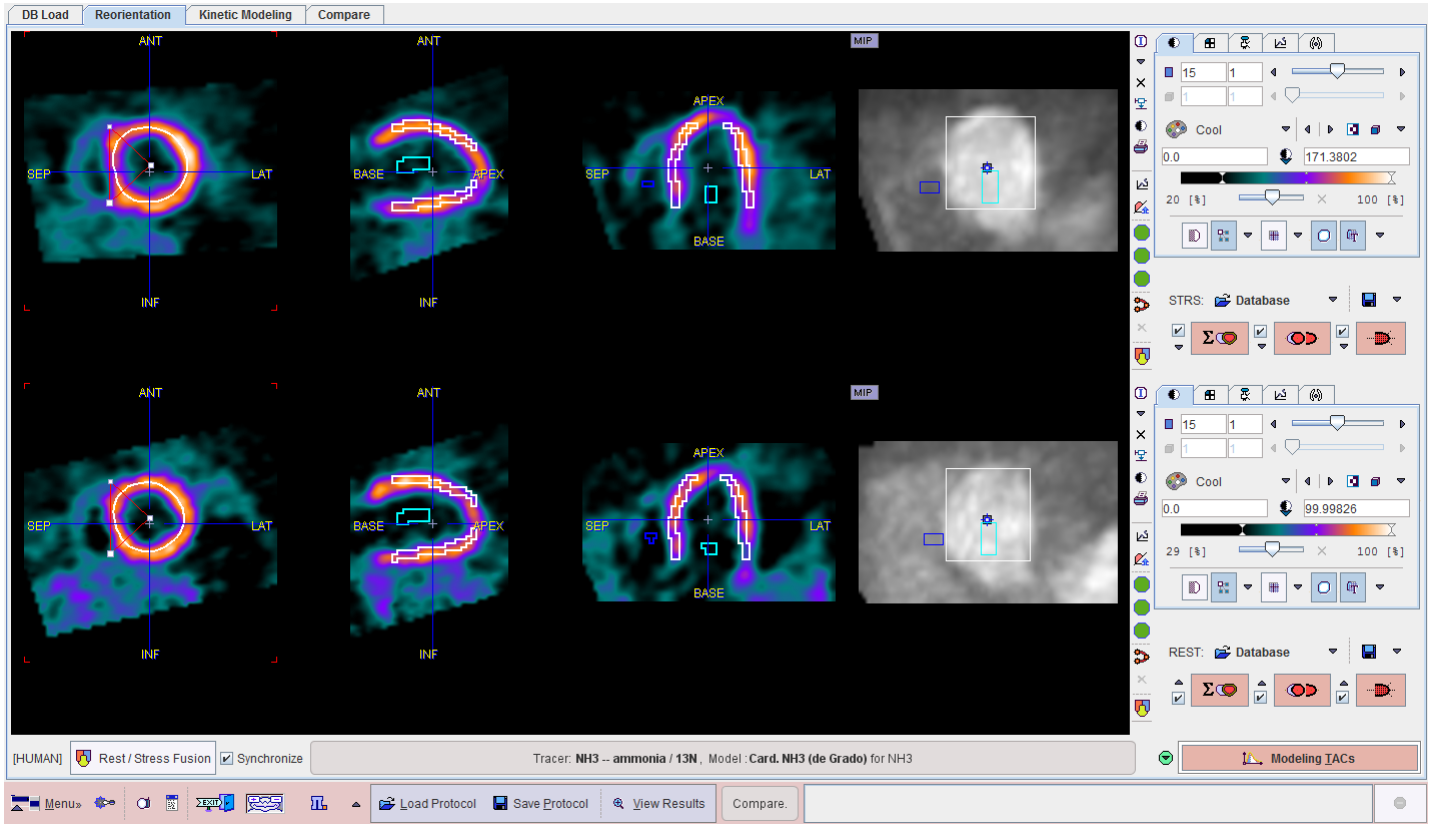
Starting the Cardiac Modeling Tool

The PCARD tool is started with the **Cardiac** button from the PMOD toolbar

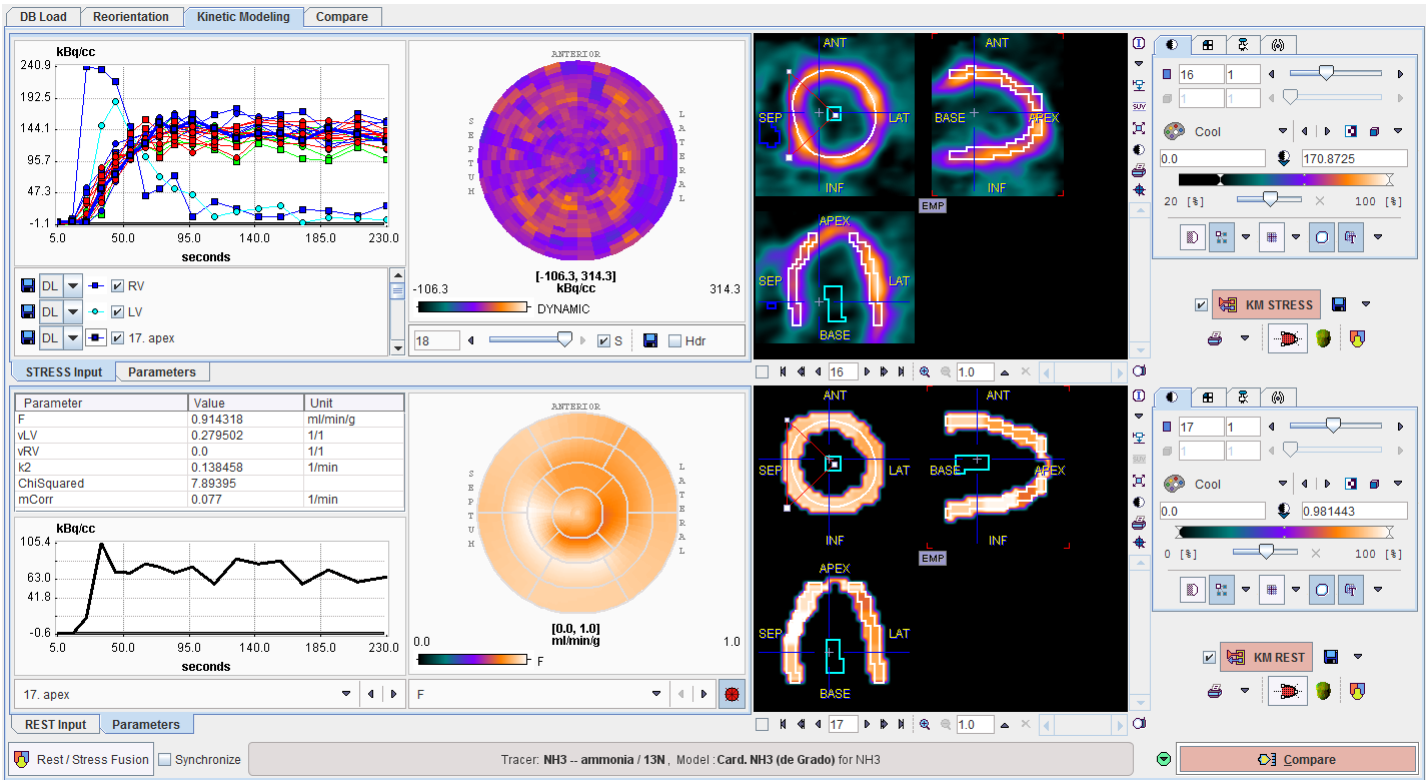


or by directly dragging image files onto the above button.

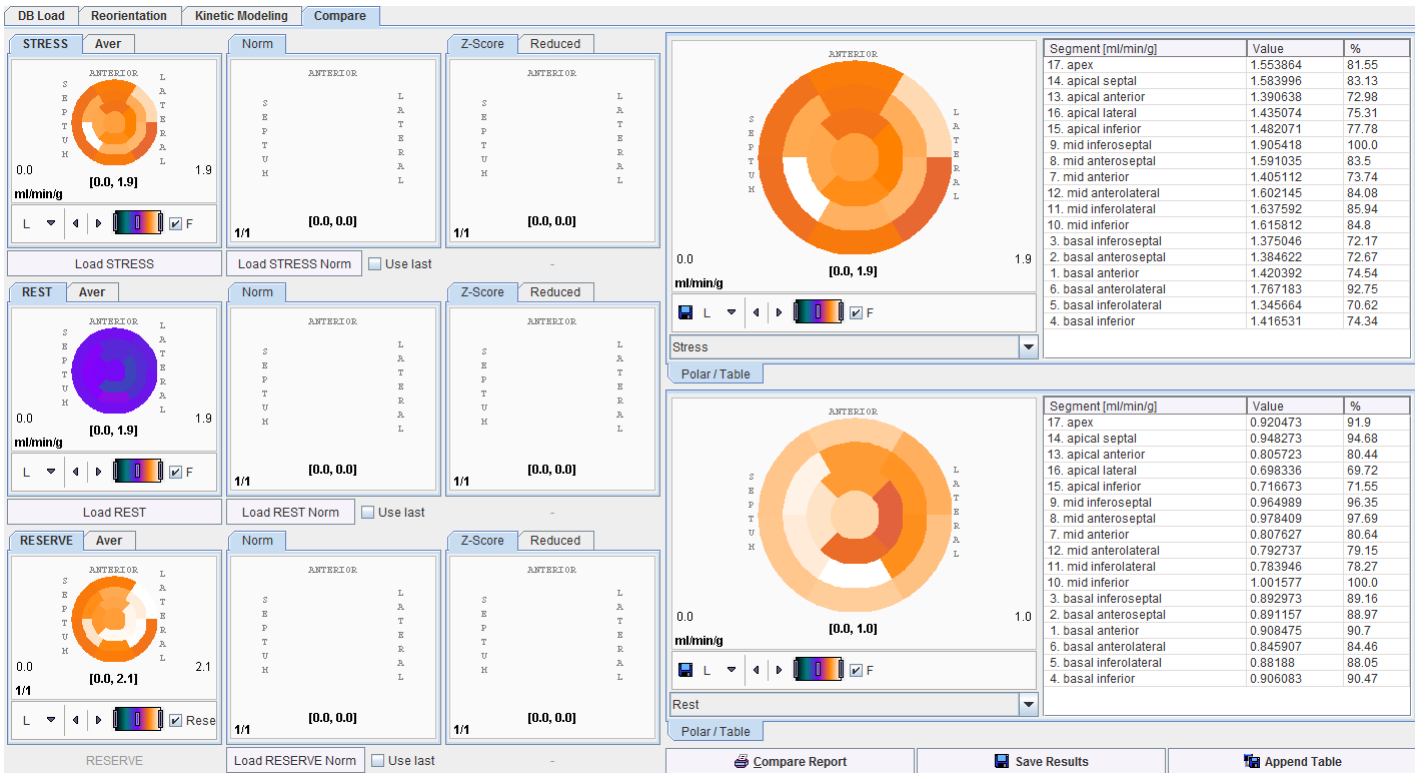
The PCARD Tool has three main pages. The first **Reorientation** page serves for the spatial reorientation of the data to the standard short axis orientation and the definition of the myocardial segments.



The second **Kinetic Modeling** page deals with the kinetic modeling of the segmental TACs and the exploration of the results



The third page **Compare** allows to compare the stress and rest outcome as well as the comparison with a normal database, if one is available.



In the **Reorientation** and **Kinetic Modeling** pages a green circle with a black down arrow button allows closing the configuration of the active page. It is located in the bottom line of the images manipulation panel. Upon activation the color switches to blue allowing to re-open the configuration on the active page.

Note: The hide/show configuration buttons were created for the setups which remain constant after the configuration is properly done and the user do not have to see the configuration parameters. Hiding such controls makes interface simpler and more streightforward while the settings are still very close to the user. These facilities are mainly intended to be used on the new MacOS. However, they are available for Windows as well.

Chapter 1

PCARD Data Processing

Processing a myocardial study with PCARD consists of the following steps:

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

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

3) Generation of anatomical images showing the myocardium and the blood volume as clearly as possible. This is achieved by averaging of appropriate frames as described in the section ***Generation of Blood Volume and Myocardium Images*** (on page 59).

4) 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 54). An automatic procedure is available. If it fails, the orientation must be interactively adjusted by the user.

5) 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 outlined interactively by the user.

6) Calculation of the time-activity curves. The number of myocardial TACs depends on the selected segment model (see ***Myocardium Segment Models*** (on page 54)).

7) 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 60)). The result is a set of model parameters for each TAC.

8) 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.

9) Different types of reports can be generated and printed.

10) 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.

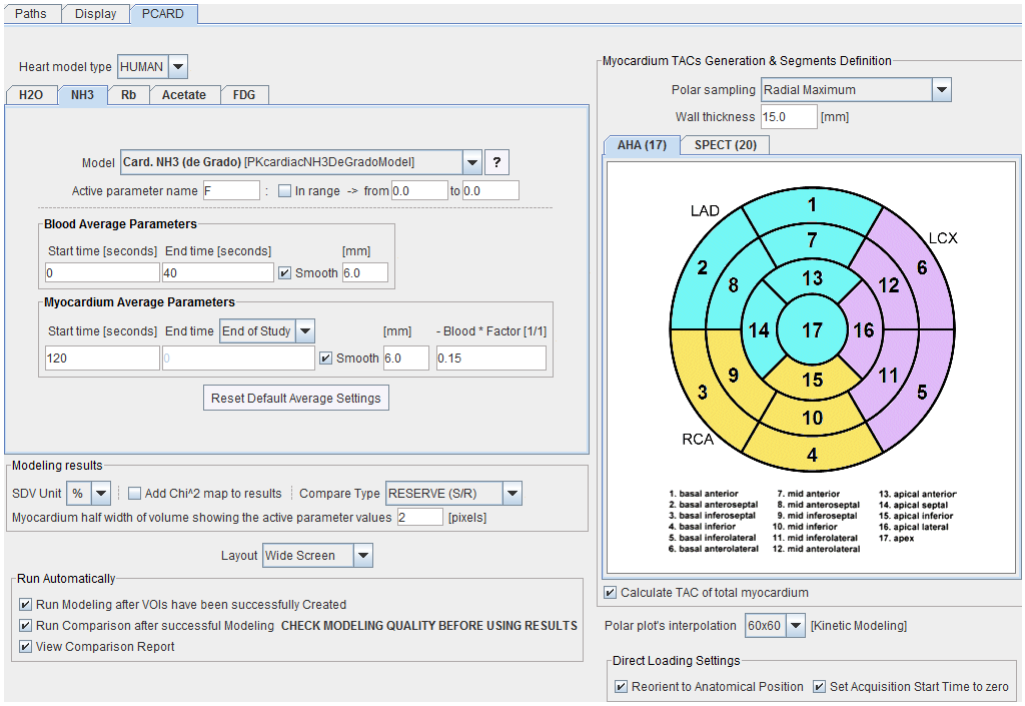
In This Chapter

Processing Configuration

If PCARD is used to process different types of studies it is recommended to check and adjust the PCARD configuration before processing 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 **Menu**.

The following window appears which has the processing settings available on the **PCARD** tab.



The **Heart model type** can be selected from the available selection list: **HUMAN**, **RAT** or **MOUSE** according to the image to be analyzed.

Tracer Selection

Note the tabs labeled with the different PET tracers for which PCARD includes suitable models.

Please select the tab corresponding to the tracer used in the myocardial PET scan, and then adjust the different configurations which are tied to the tracer:

- **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 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.
- **Value of active parameter in range from .. to:** If this option is checked the minimal and maximal value number fields become active and the range can be specified. In case a result parameter is out of the allowed range, it will be excluded from the statistical calculations.

There are two sections for defining 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 59).

- **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 40 seconds (frame start times) will be averaged, and then smoothed with a 3D Gaussian filter of 6mm 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 0.15 of the image generated by the **Blood** configuration will be subtracted.

Note: The **H2O** tracer has an additional choice **Factor analysis** besides the **Average**. Please refer to ***Additional Pre-Processing Steps with Factor Analysis (Water only)*** (on page 47) 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).
- **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 looking 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.
- **Add Chi^2 map to results:** When this box is checked the Chi square value of the kinetic model fit is also returned to **PCARD** and assembled in an additional polar map.
- **Compare Type:** When a patient has been scanned at rest and stress, the results can be compared in two 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 (perfusion) difference is calculated instead. This latter approach avoids the problem of dividing by a small number which may for instance arise in scar tissue.

Layout and Flow of Processing

With the **Layout** selection the user can adjust the layout according the aspect ratio of the computer screen. **Normal Screen** and **Wide Screen** are available. The arrangement on the **Reconstruction** page changes accordingly. The illustrations in this guide were created using **Wide Screen**.

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 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 (normally with the coronary flow reserve) is shown each time data is transferred to the comparison page.

Segmentation Selection

PCARD supports different segmentation models. Currently, the standard ***AHA 17-segment model*** (on page 55) is available, as well as the ***ASNC 20-segment model*** (on page 57) which is often used with SPECT data.

For using a particular segment model the corresponding tab should be selected. During the analysis one time-activity curve per segment is calculated by averaging the signals from all voxels belonging to the segment. It is then fit to a kinetic model, which results in one set of

parameters. The result parameters from all segments are finally displayed as polar plots corresponding the segmentation scheme, and used for generating comprehensive reports.

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

Polar Sampling

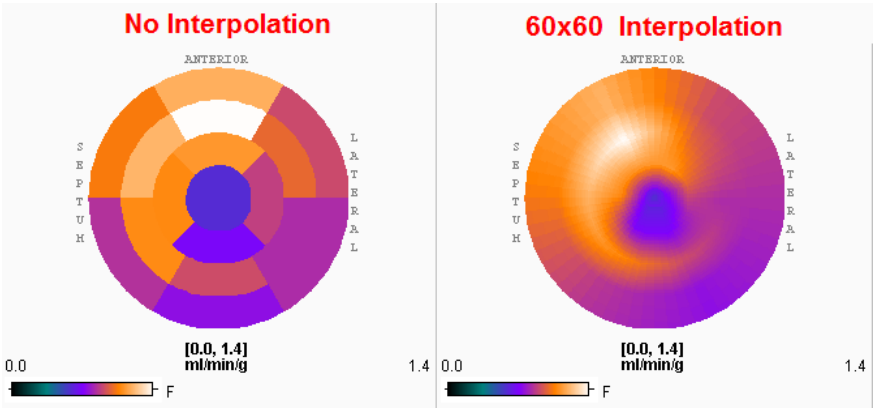
The **Polar Sampling** selection defines how the voxels used in the segment TAC calculation are located. PCARD interpolates the axial range defined by the myocardium model into 20 slices. For each of these slices a radial sampling is performed every 10°. There are three different ways how the myocardium samples are detected:

Radial Maximum	Using the maximum value on the radial profile. The **Wall thickness** determines the range from the model within which the maximum is determined.
Model Crossing	Using the value at the intersection of the radial profile with the myocardial model.
Averaged on Model Crossing	Using a neighborhood of voxels at the intersection of the radial profile with the myocardial model.
Averaged on Radial Maximum	Using a neighborhood of voxels around the determined profile maximum.

Note: the sampling points found by a prescribed sampling scheme can be visualized as circles in the short axis images or as spheres in a 3D rendering (see ***Examining the Results*** (on page 31))

As a means to get a robust global result PCARD allows averaging the 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 or **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.



Saving and Retrieving Configurations

If different types of studies are analyzed with the same PCARD 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 **Menu** and name it suggestively, eg "Ammonia 1-Compartment".

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

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

When PCARD is closed, all configuration settings are stored as the initial PCARD settings. They are loaded again the next time PCARD 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 also 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.

Standard Data Processing Steps

After the configuration has been set appropriately the following processing steps are performed for a full data analysis.

Note: These steps are performed for all studies, except if the factor analysis methodology is applied to water studies. In that case, different pre-processing steps are applied which are described separately in ***Pre-Processing Steps with Factor Analysis (Water only)*** (on page 47).

Data Loading

The layout of card 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 will be comparison 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 fro loading, *the first one will be considered as stress, and the second one as rest*. When loading DICOM data, PCARD will analyze the encoded information and show warnings if the model selection seems inappropriate or rest and stress series interchanged.

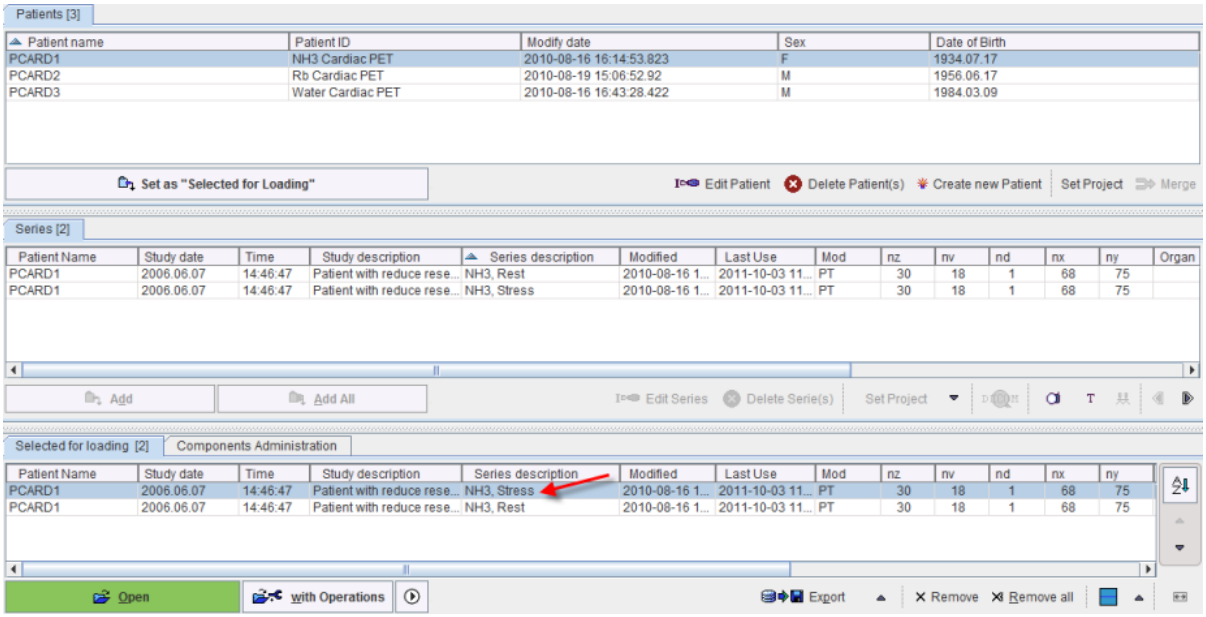
Loading from the Reorientation Page

On the **Reorientation** page data are loaded using the load buttons in the **[STRS]** and **[REST]** area, respectively.

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

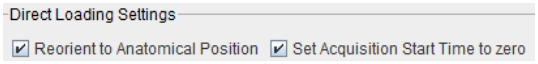
If the database functionality is enabled, the user interface shows an additional tab **DB Load**. On this page, both the rest and the stress studies should be selected for loading, with the stress study on top as illustrated below.



Direct Loading

When selecting image series for loading, activate the **Open** button. If this button is selected, the loading dialog window will not be shown and the images will be loaded immediately.

There are two configuration option: **Reorient to anatomical position** and **Set Acquisition Start Time to zero** for applying another important preprocessing operations:



If the configuration option **Reorient to anatomical position** is enabled, the images are reoriented into the head first supine (HFS) orientation. This adjustment is performed without reslicing, using only rotations by 90 degrees or multiplications of this value. It is applied because a consistent orientation is important for the automatic reorientation routine. If this operation is not adequate, please activate the **with Operation button** and use the **Asistance** button to correctly orient the PET study in anatomical orientation..

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. It is recommended to enable this setting because due to DICOM compatibility issues the whole data may be shifted in time. In such a case, kinetic modeling will most likely fail in applying appropriate metabolite corrections.

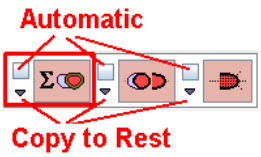
Clearing a Study

When new data is loaded, the previous data and results are cleared. However, it is also possible to explicitly reset the tool. This can be done selectively for STRESS and REST by selecting the **X** button to the right of the image.

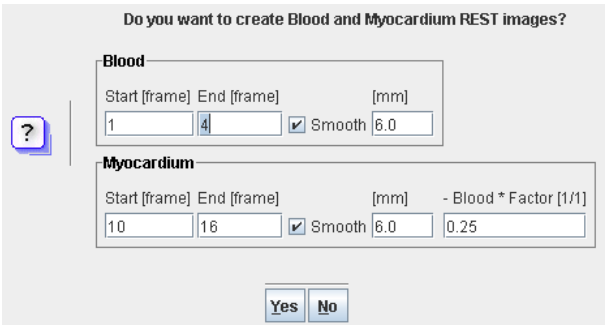
Generating Blood Volume and Myocardium Images by Averaging

The Averaging Dialog

The generation of the anatomical images is controlled by the first group of controls in the processing button area of the rest and stress studies.



The summation button opens a dialog showing the current averaging parameters. Initially, the parameters are derived from the configuration. However, they can be manually edited if needed.



Activating **Yes** starts the averaging calculation from the initial dynamic study. If the images were already rotated to the short axis view before, they are set back to the original orientation.

The box next to the average button is for enabling the automatic mode. If it is checked, the averaging process will be performed as soon as image data is loaded using the current configuration.

Note: The small **arrows** next to the automatic boxes copy a definition from stress to rest, and vice versa. For instance, if the averaging configuration is copied, the same ranges, smoothing and factors will be used for rest and stress.

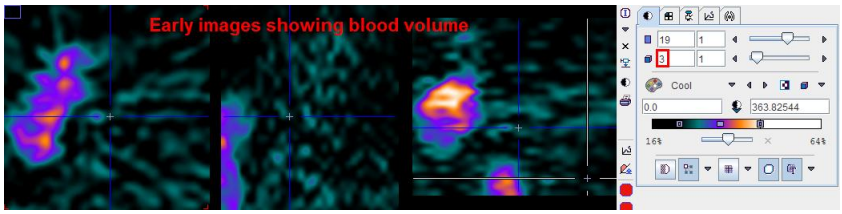
Identifying Appropriate Frame Ranges

Sometimes the tracer uptake may behave differently so that the default ranges do not result in well delineated anatomical images. In such a case the user should interactively try to optimize the averaging process, because poor images will make the data analysis more difficult.

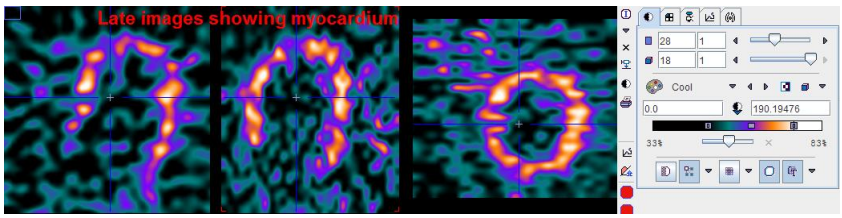
The **Blood** range should start with the first frame which shows a strong signal in the right ventricle, and end before the myocardium begins to be clearly seen. Similarly, the **Myocardium** range should only begin after the signal in the cavities has faded out. It is recommended that the **Myocardium** range ends after some minutes, because the probability

of patient motion increases with the longer frames at the end, particularly if a very long frame is acquired at the end to get images for clinical reviewing.

Note that the averaging range is in frame numbers which makes it easier to customize the definition. The examples below illustrate the situation encountered in an ammonia scan. The frames were stepped to the 3rd acquisition, and the thresholds adjusted so that the localization of the blood becomes roughly notable.

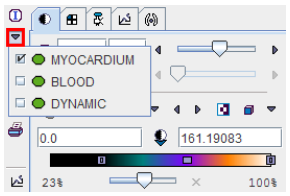


The 18th frame of the same study study shows uptake in the myocardium, but is quite noisy due to a short acquisition duration.

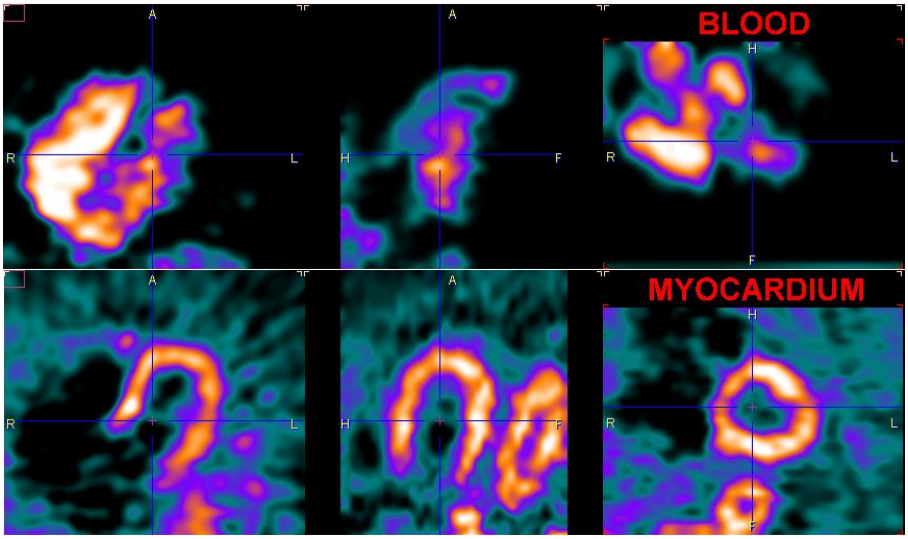


Arrangement of the Result Images

Each time the averaging dialog is closed with the **Yes** button, two new image studies - **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 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 get a well delineated LV blood pool.

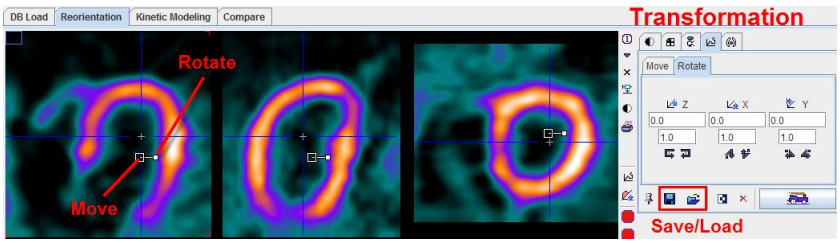


Transforming Images into Standard Short Axis Orientation

The next step is to rotate the images into the standard short axis orientation, see ***Standard Reorientation of the Heart*** (on page 54). An automatic procedure is available, but when it fails a manual interaction is required.

Manual Reslicing

As soon as the averaging process has completed, the display shows the MYOCARDIUM images and is switched into the *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 to rotate 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 exit the reslicing mode in order to avoid unintended manipulations of the orientation. To this end, select any other tab such as the image presentation tab .

Automatic Reslicing

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

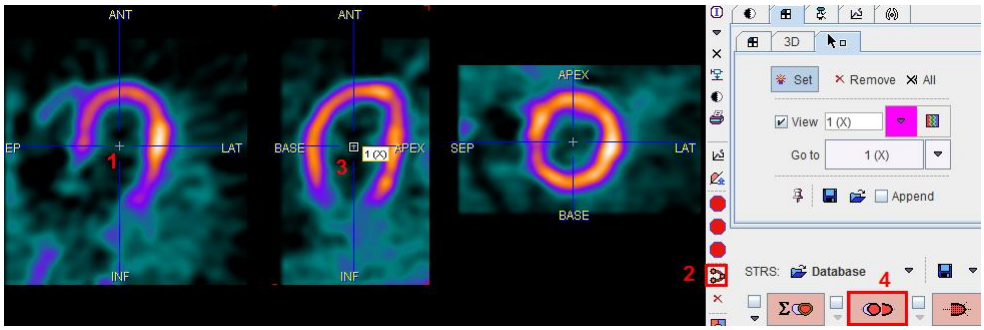
The images are reoriented, and the resulting parameters shown in the reslicing tab.

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 above.

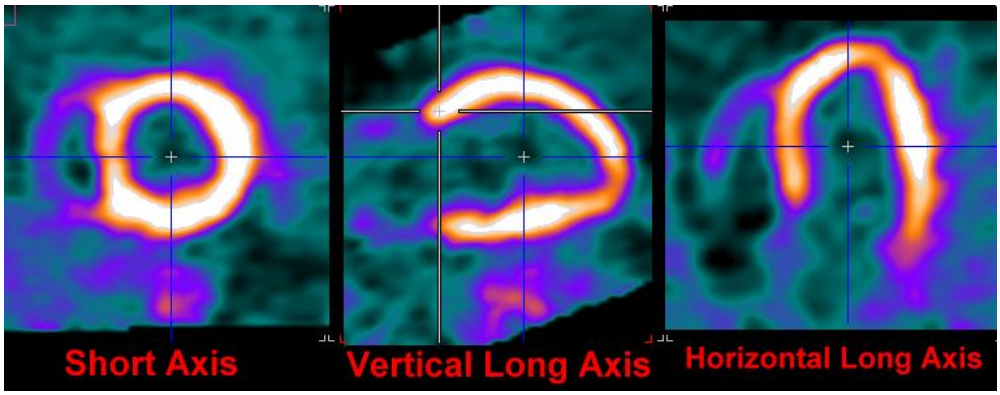
If the automatic reorientation returns an inadequate result, it can be supported by manually defining the left ventricle using a marker. Please proceed as follows:

- 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.

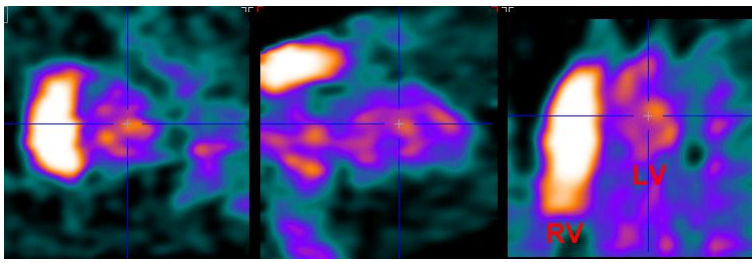


Correct Short Axis Orientation after Reslicing

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 also shown with the same transformation parameters. For the automatic contouring it is also helpful if the heart is centered in the center of the image volume.



Saving Transformations

It is recommended to save the transformations before proceeding to the next step using the button in the lower part of the reslicing pane. By loading this transformation at a later time, the processing can precisely be repeated.

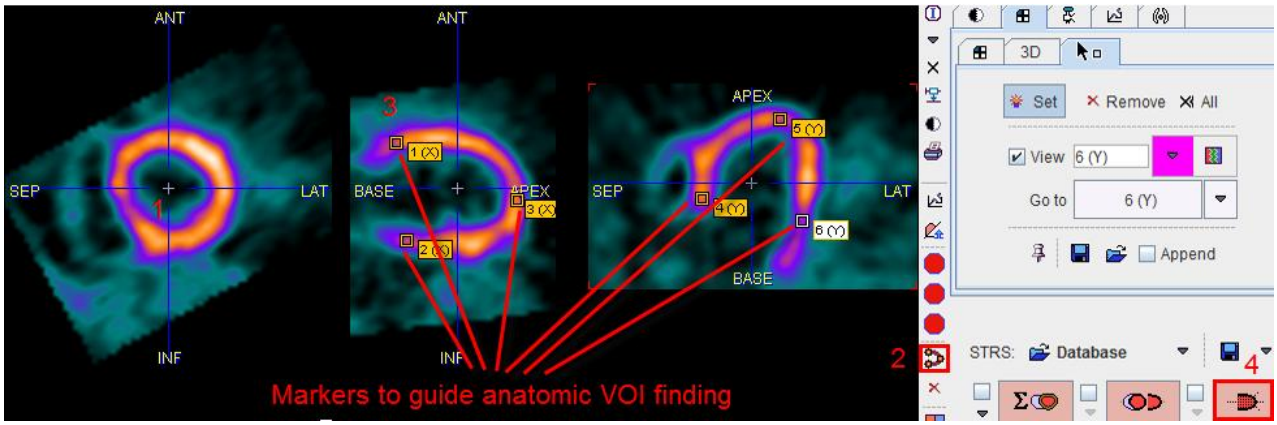
Outlining of the Volumes-of-Interest (VOIs)

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

The next sections describe how the VOIs can be created within PCARD. For general information about VOI creation and manipulation please refer also to the Summary of VOI Capabilities in PMOD section.

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 anatomical landmarks. The markers should be placed at the basal points and the apex of the left ventricle as illustrated below.



Marker Definition Procedure

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

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

3) Click at 5 to 6 points in the long axis views to set markers as indicated in the illustration above. Note that to avoid setting markers when clicking into the image the **Set** toggle button in the **Markers** tab must be switched to inactive.

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

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

Note: The image information above the basal marker points will completely be disregarded in the outlining procedure. The apex point, however, will be adjusted based on the image content. This marker-guided procedure can be applied even after VOIs have been defined.

Automatic VOI Definition

Select the contouring button indicated below

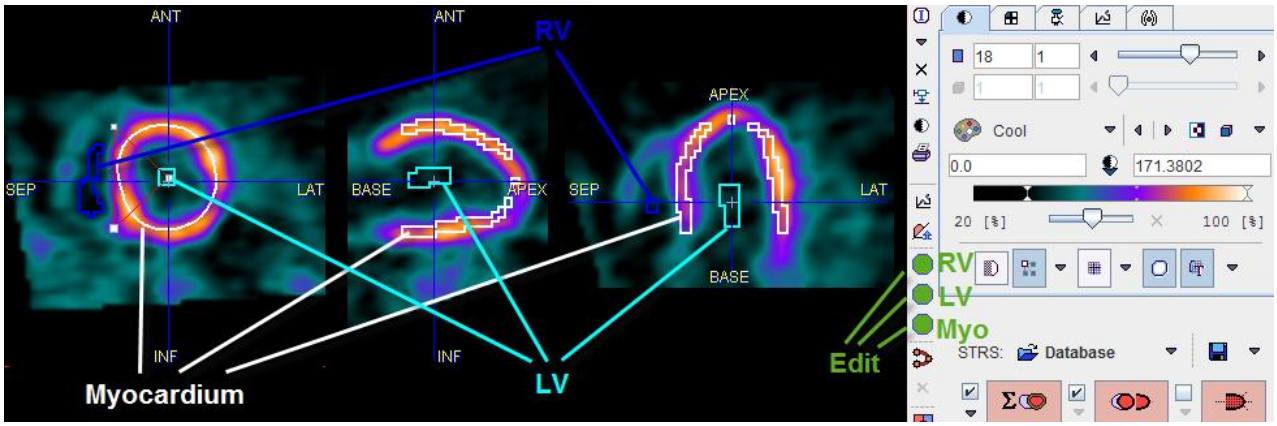
to start the automatic outlining process. The program tries to find a VOI in the right cavity (RV VOI), in the left cavity (LV VOI), and the centerline of the myocardium (Myocard VOI).

The box next to the reorientation button is for enabling the automatic mode. If it is checked, the contouring process is started as soon as anatomical images have been automatically resliced.

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 immediately shown as an overlay in the images. The illustration below explains the different elements in the display.



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.

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

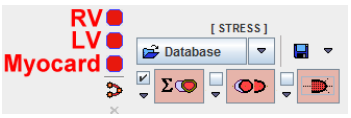
3) As an alternative click anywhere into the images to get new orthogonal slices at that triangulation point.

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.

Manual VOI Definition and Editing of Automatic VOIs

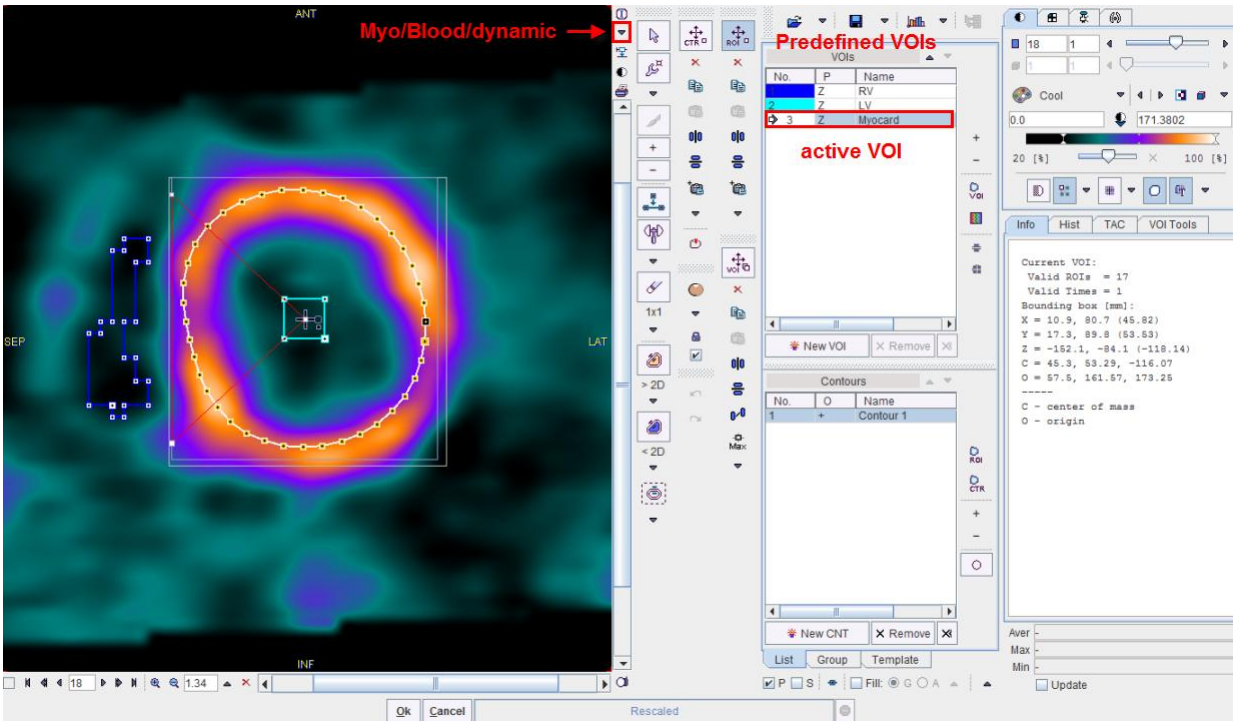
VOIs are created and edited using the standard PMOD VOI tool. It can be started using the three buttons



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 centerline 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 ad the myocardium.

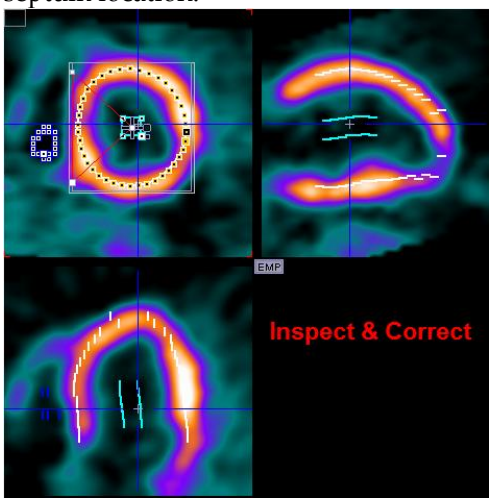
Note also that the three VOIs **RV**, **LV**, and **Myocard** are predefined in the **VOI(s)** list. We recommend using the output from the automatic VOI generation and adjusting the contours rather than outlining fully manually.

Optionally, the VOI contours can be drawn in all planes (P check box enabled) or only in the active plane (P checkbox disabled).

Adjustment of the automatically created Myocard VOI

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

2) 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.

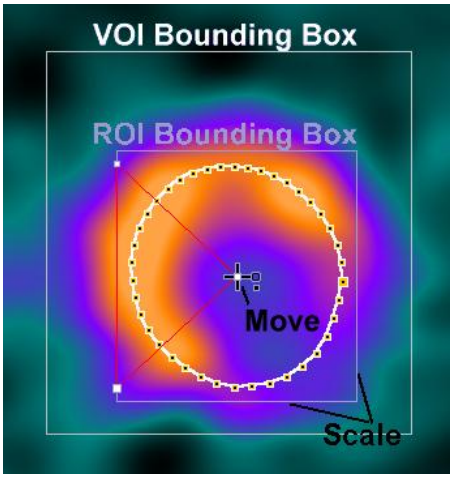


3) To reduce the number of contours at the base click into the short axis images, scroll with the mouse wheel to the slices where the myocardium appears in less than a 360°, and then remove the region-of-interest in that slice by selecting the **ROI Remove** button indicated below.

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

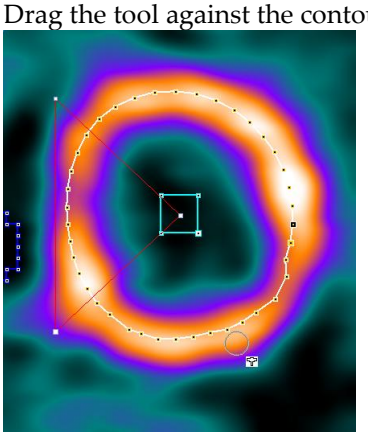
4) To adjust the shape of the contours scroll to a slices where the centerline needs correction. A global adjustment can be attained by scaling and moving the ROI. To this end select the **ROI Action** button

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.

5) In the case of unsuccessful operations use the undo button

to go back to the previous state of VOI definition.

Creating the Myocard VOI Fully Manually

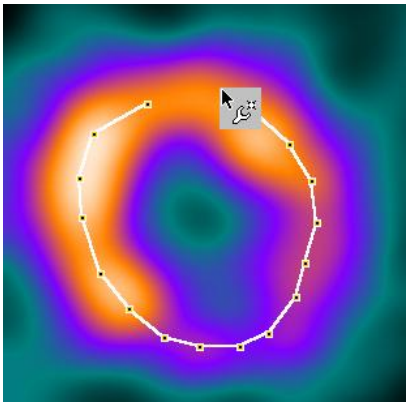
To build the **Myocard** VOI in fully manually:

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

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

3) Select the **ROI Edit** tool

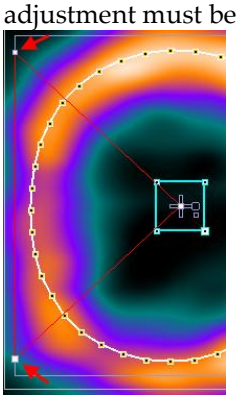
and click along the centerline



closing the contour by clicking at the first point or selecting the **Finish** button. Immediately, the septal 60° angle is shown. Make sure it is correctly

4) 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.

5) Ensure that the septal angle is correctly pointed 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.



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 sectorial 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.

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

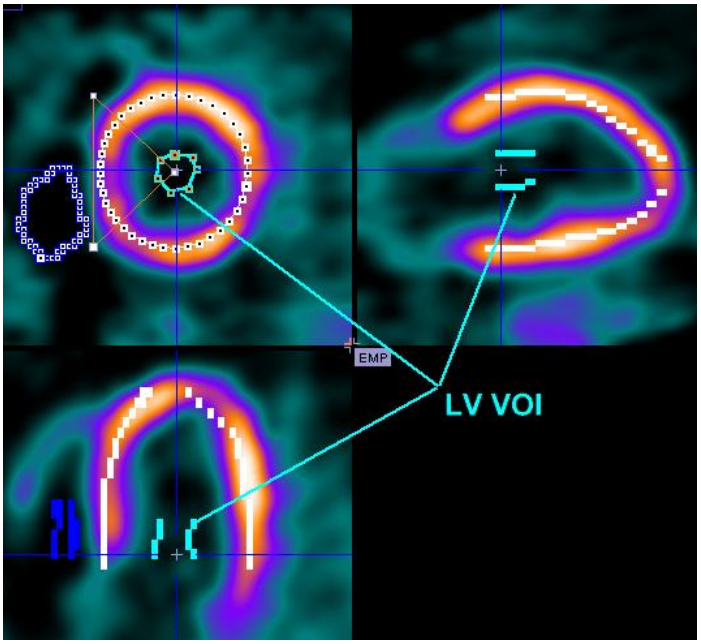
3) Select **LV** in the VOIs list. If the myocardium VOI is still selected, it will be overwritten by the following actions.

4) Select the Iso-contour tool

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

6) 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.

7) Repeat this process in some of the neighbouring slices, until a representative VOI has been defined:



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 a reduction 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.

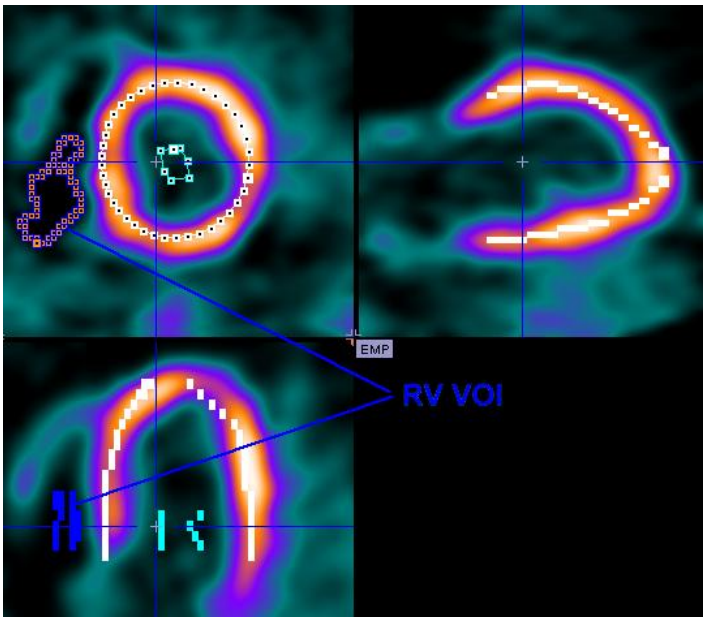
2) Select **RV** in the VOIs list. If the myocardium VOI is still selected, it will be overwritten by the following actions.

3) Select the Iso-contour tool

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

5) 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.

6) Repeat this in some of the neighboring slices, until a representative VOI has been defined:



7) 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 save the current VOI definitions in a file. Be sure to save the completed VOIs because this will allow to repeat and/or optimize the processing at a later time.

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 20 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.

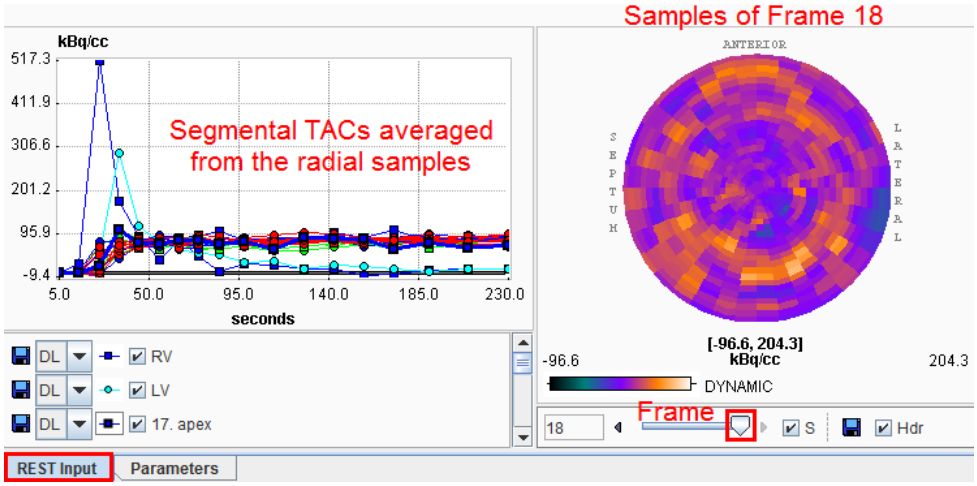
The behavior after completion of the TAC-calculations depends on the configuration of the **KM** buttons on the **Kinetic Modeling** page:

With this *manual* configuration the PCARD tool just switches to the **Kinetic Modeling** page and shows the calculated TACs (recommended).

With this *automatic* configuration the PCARD starts modeling of the calculated TACs with the configured model immediately in the background. The model is fitted to each of the TACs, the results are returned and then shown 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 to scroll 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.

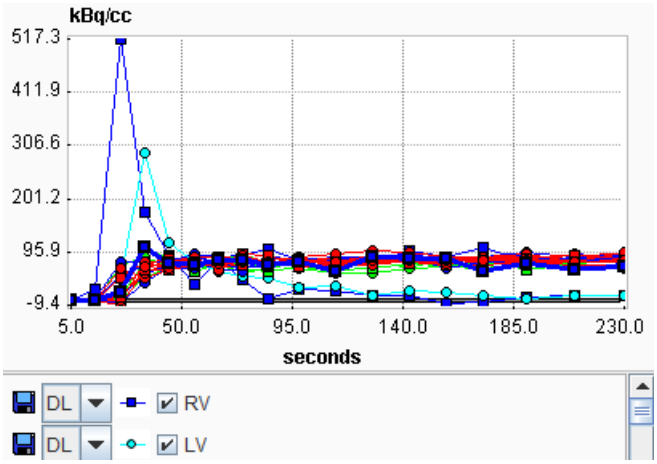


The **S** checkbox allows syncronizing the polar and image display frames. The dynamic polar sampling can be saved activating the **Save** icon. Optionally, the header can be appended during the saving procedure enabling the **Hdr** checkbox. After saving, the polar plots can be analyzed outside PMOD software.

Kinetic Modeling

TAC Inspection

Before kinetic modeling is started 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:

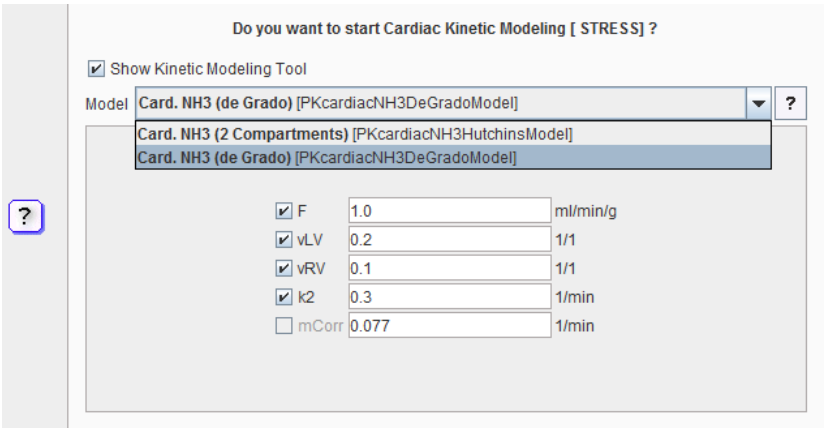
- The RV TAC appears first and typically shows the highest peak of all curves.
- The LV TAC shows a clear peak and then drops below the myocardial activity. Note that the curve shapes depend on the speed of the bolus injection and the heart activity.
- If some of the myocardial TACs have a very similar 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), the 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.

Model Selection

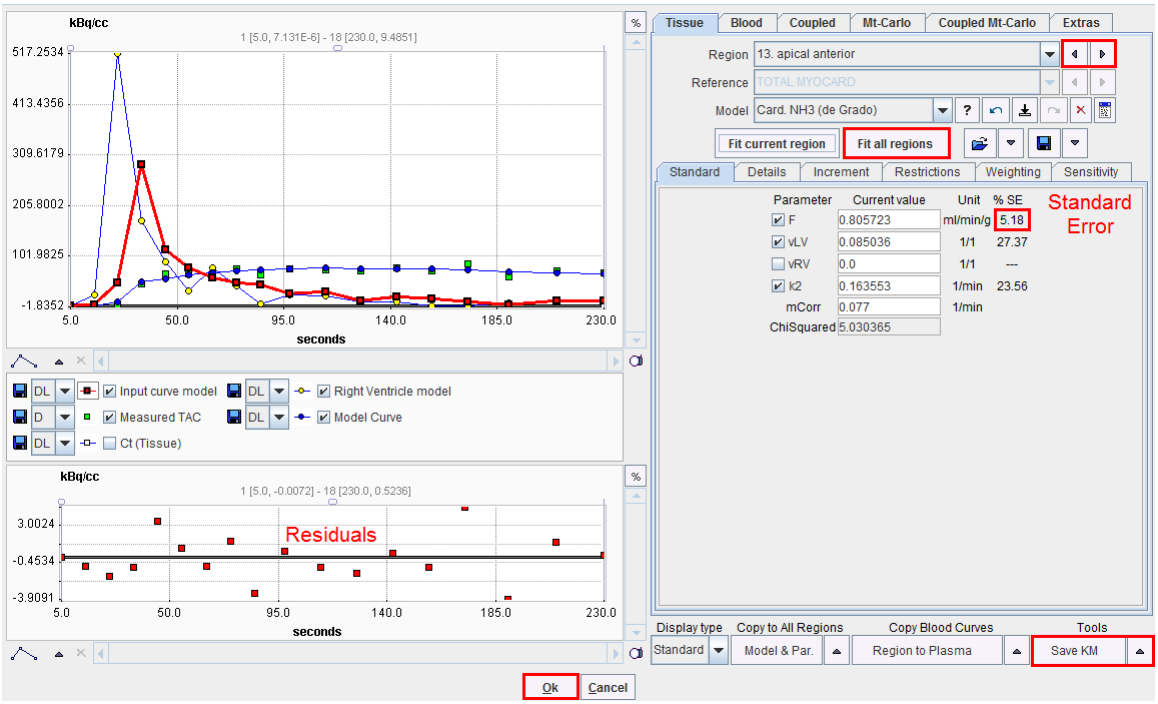
Select the **KM Stress** or the **KM Rest** button to start kinetic modeling of the TACs. A dialog box comes up showing the currently configured model with the starting parameter values, for example



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 models are 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.

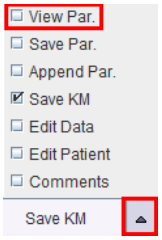
Model Fitting



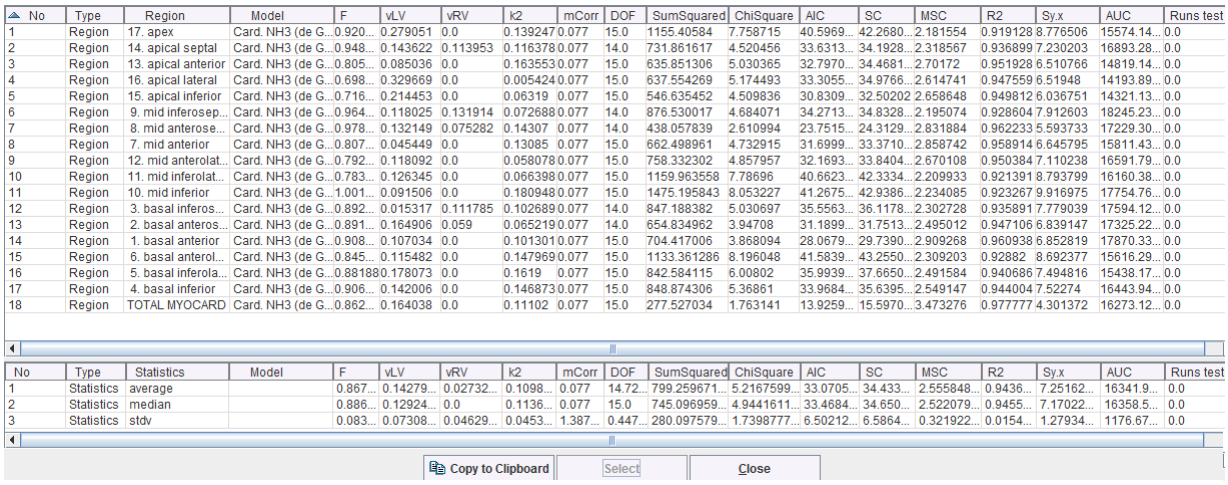
The PKIN dialog window initially shows the first TAC in the curve display as green **Measured** points, and the **Model Curve** with the default model parameters in blue. Use the **Fit all regions** button to fit the model to the TACs of all myocardial segments. The **Parameters** and the **Model Curves** 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. Note that with current PET systems the spillover from the right ventricle is typically low (**vRV** parameter), so it can often not be estimated with high confidence. Therefore, small **vRV** parameters with a high standard error are not critical.

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



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



No	Type	Region	Model	F	vLV	vRV	k2	mCorr	DOF	SumSquared	ChiSquare	AIC	SC	MSC	R2	Sy.x	AUC	Runs test
1	Region	17. apex	Card. NH3 (de G...	0.920...	0.279051	0.0	0.139247	0.077	15.0	1155.40584	7.758715	40.5969...	42.2680...	2.181554	0.919128	8.776506	15574.14...	0.0
2	Region	14. apical septal	Card. NH3 (de G...	0.948...	0.143622	0.113953	0.116378	0.077	14.0	731.861617	4.520456	33.6313...	34.1928...	2.318567	0.936899	7.230203	16893.28...	0.0
3	Region	13. apical anterior	Card. NH3 (de G...	0.805...	0.085036	0.0	0.163553	0.077	15.0	635.851306	5.030365	32.7970...	34.4681...	2.70172	0.951928	6.510766	14819.14...	0.0
4	Region	16. apical lateral	Card. NH3 (de G...	0.698...	0.329669	0.0	0.005424	0.077	15.0	637.554269	5.174493	33.3055...	34.9766...	2.614741	0.947559	6.51948	14193.89...	0.0
5	Region	15. apical inferior	Card. NH3 (de G...	0.716...	0.214453	0.0	0.06319	0.077	15.0	546.635452	4.509836	30.8309...	32.50202	2.658648	0.949812	6.036751	14321.13...	0.0
6	Region	9. mid inferosep...	Card. NH3 (de G...	0.964...	0.118025	0.131914	0.072688	0.077	14.0	876.530017	4.684071	34.2713...	34.8328...	2.195074	0.928604	7.912603	18245.23...	0.0
7	Region	8. mid anterose...	Card. NH3 (de G...	0.978...	0.132149	0.075282	0.14307	0.077	14.0	438.057839	2.610994	23.7515...	24.3129...	2.831884	0.962233	5.593733	17229.30...	0.0
8	Region	7. mid anterior	Card. NH3 (de G...	0.807...	0.045449	0.0	0.13085	0.077	15.0	662.498961	4.732915	31.6999...	33.3710...	2.858742	0.958914	6.645795	15811.43...	0.0
9	Region	12. mid anterolat...	Card. NH3 (de G...	0.792...	0.118092	0.0	0.058078	0.077	15.0	758.332302	4.857957	32.1693...	33.8404...	2.670108	0.950384	7.110238	16591.79...	0.0
10	Region	11. mid inferolat...	Card. NH3 (de G...	0.783...	0.126345	0.0	0.066398	0.077	15.0	1159.963558	7.78696	40.6623...	42.3334...	2.209933	0.921391	8.793799	16160.38...	0.0
11	Region	10. mid inferior	Card. NH3 (de G...	1.001...	0.091506	0.0	0.180948	0.077	15.0	1475.195843	8.053227	41.2675...	42.9386...	2.234085	0.923267	9.916975	17754.76...	0.0
12	Region	3. basal inferos...	Card. NH3 (de G...	0.892...	0.015317	0.111785	0.102689	0.077	14.0	847.188382	5.030697	35.5563...	36.1178...	2.302728	0.935891	7.779039	17594.12...	0.0
13	Region	2. basal anteros...	Card. NH3 (de G...	0.891...	0.164906	0.059	0.065219	0.077	14.0	654.834962	3.94708	31.1899...	31.7513...	2.495012	0.947106	6.839147	17325.22...	0.0
14	Region	1. basal anterior	Card. NH3 (de G...	0.908...	0.107034	0.0	0.101301	0.077	15.0	704.417006	3.868094	28.0679...	29.7390...	2.909268	0.960938	6.852819	17870.33...	0.0
15	Region	6. basal anterol...	Card. NH3 (de G...	0.845...	0.115482	0.0	0.147969	0.077	15.0	1133.361286	8.196048	41.5839...	43.2550...	2.309203	0.92882	8.692377	15616.29...	0.0
16	Region	5. basal inferola...	Card. NH3 (de G...	0.881880	0.178073	0.0	0.1619	0.077	15.0	842.584115	6.00802	35.9939...	37.6650...	2.491584	0.940686	7.494816	15438.17...	0.0
17	Region	4. basal inferior	Card. NH3 (de G...	0.906...	0.142006	0.0	0.146873	0.077	15.0	848.874306	5.36861	33.9684...	35.6395...	2.549147	0.944004	7.52274	16443.94...	0.0
18	Region	TOTAL MYOCARD	Card. NH3 (de G...	0.862...	0.164038	0.0	0.11102	0.077	15.0	277.527034	1.763141	13.9259...	15.5970...	3.473276	0.977777	4.301372	16273.12...	0.0

No	Type	Statistics	Model	F	vLV	vRV	k2	mCorr	DOF	SumSquared	ChiSquare	AIC	SC	MSC	R2	Sy.x	AUC	Runs test
1	Statistics	average		0.867...	0.14279...	0.02732...	0.1098...	0.077	14.72...	799.259671...	5.2167599...	33.0705...	34.433...	2.555848...	0.9436...	7.25162...	16341.9...	0.0
2	Statistics	median		0.886...	0.12924...	0.0	0.1136...	0.077	15.0	745.096959...	4.9441611...	33.4684...	34.650...	2.522079...	0.9455...	7.17022...	16358.5...	0.0
3	Statistics	stdv		0.083...	0.07308...	0.04629...	0.0453...	1.387...	0.447...	280.097579...	1.7398777...	6.50212...	6.5864...	0.321922...	0.0154...	1.27934...	1176.67...	0.0

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contains the parameters of all segments, their average, median and standard deviation as well as criteria for the goodness-of-fit across the segments.

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** button in the **Tools** list.

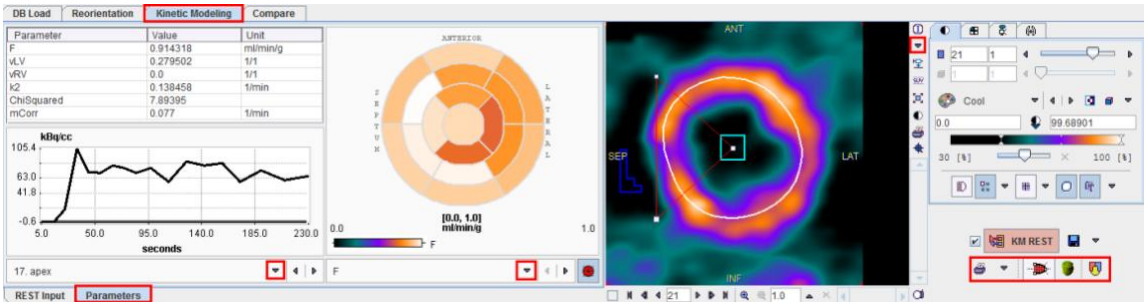
Returning to the Cardiac Tool

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 PCARD tool.

For a thorough explanation of the kinetic modeling tool and the calculated information please refer to the PMOD Kinetic Modeling Tool User's Guide.

Single Study Results

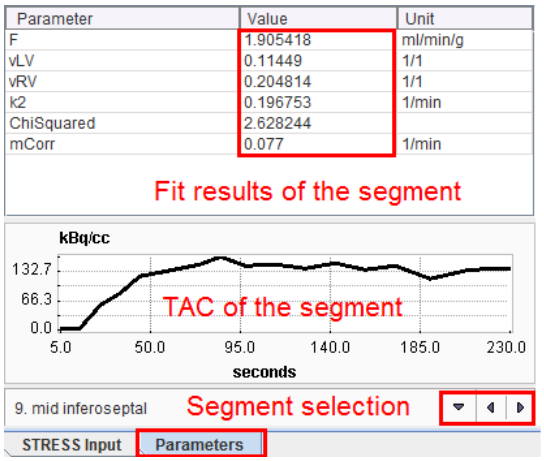
After fitting of the kinetic model has completed, the information on the **Kinetic Modeling** page is updated to allow for results inspection and documentation. The section below illustrates the situation when the **Wide Screen** layout has been *configured* (on page 7), and when the polar plot interpolation is set to **No**. (In the **Normal Screen** configuration the same information is distributed to more tabs.)



Examining the Results

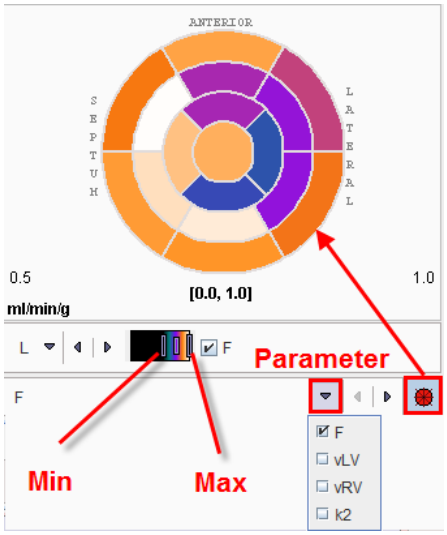
Parameters per Segment

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 overlayed. These can be easily switched off selecting the toogle button available on the lower right corner of the polar plot. A list selection is available at the bottom to switch between the parameters. When the cursor is moved about the polar plot the instantaneous 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 can be documented by the **Polar Plot** report.

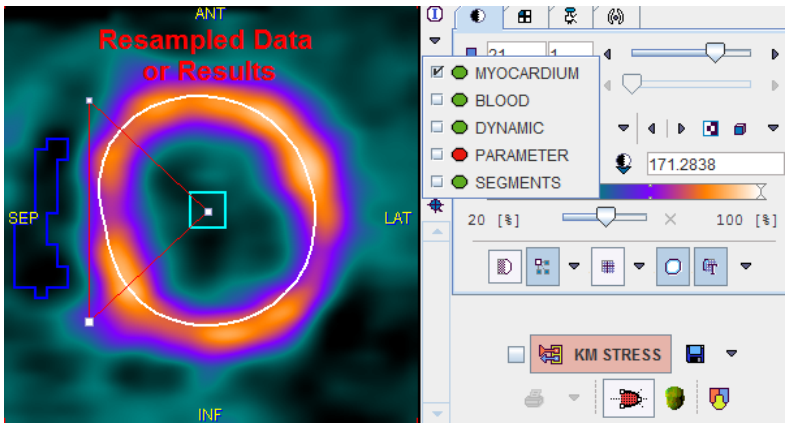


The polar plot display control can be easily switch on/off right clicking on the polar plot area and selecting the **Hide/Show Controls** option.

Activating the last option on the list, **Properties**, the display properties like **Description's font size** can be changed.

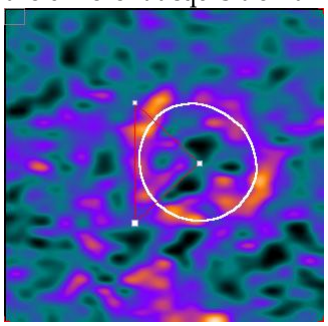
Resampled Data and Parameter Images

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).

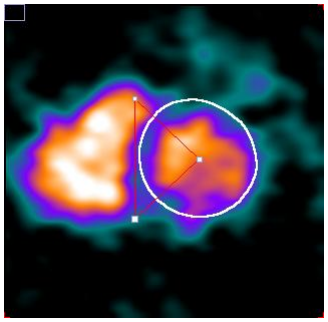


All this data has been resampled based on the **Myocard** VOI, so that the 20 slices cover the area from the apex to the base, plus some additional bounding box.

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

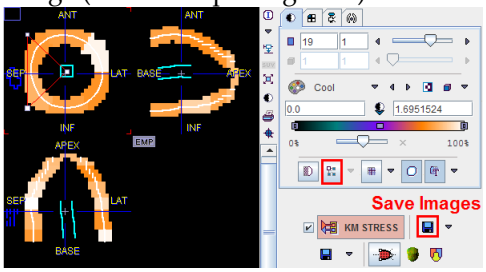


BLOOD The data calculated in the pre-processing step as a representation of blood.



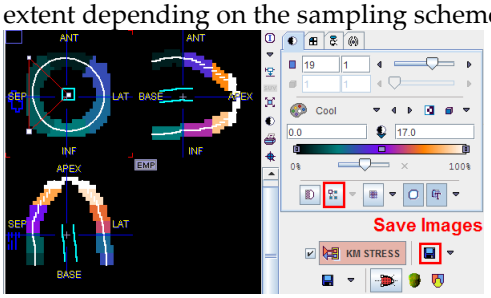
MYOCARDIUM The data calculated in the pre-processing step as a representation of myocardium (already illustrated above).

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. The actually sampled voxels may differ to some extent depending on the sampling scheme.

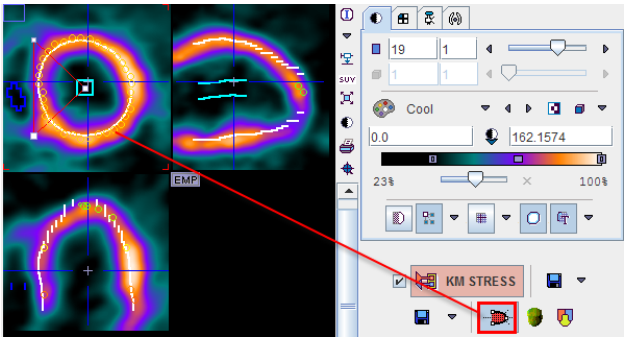


Note: If you click into the polar plot, the image to the right is adjusted so that the corresponding slice is shown. With an orthogonal image layout, the cross is positioned at the sampling location corresponding to the polar plot point.

Visualization of the Samples found by Polar Sampling

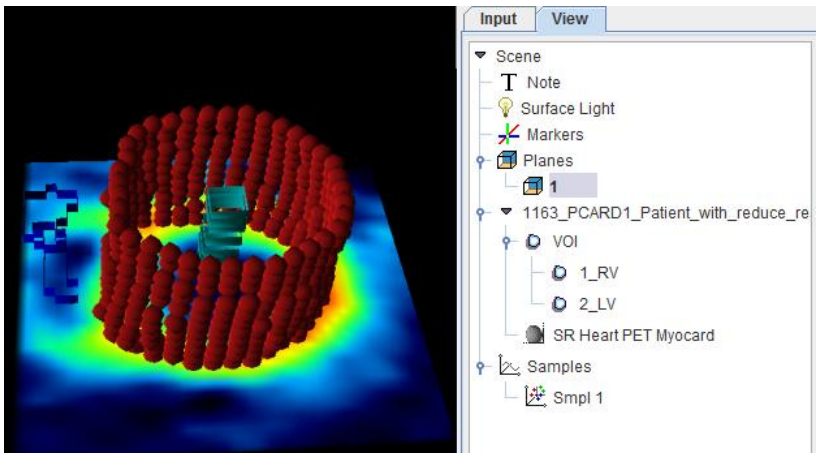
The pixels found during the sampling process can be visualized together with the short axis images. As soon as the button

is activated, small circles are shown in the overlay. They represent the intersection of a sphere around the sampling point with the imaging plane. Therefore, particularly in the apical segments, the circles can be of different diameter because of the there-dimensional geometric arrangement.

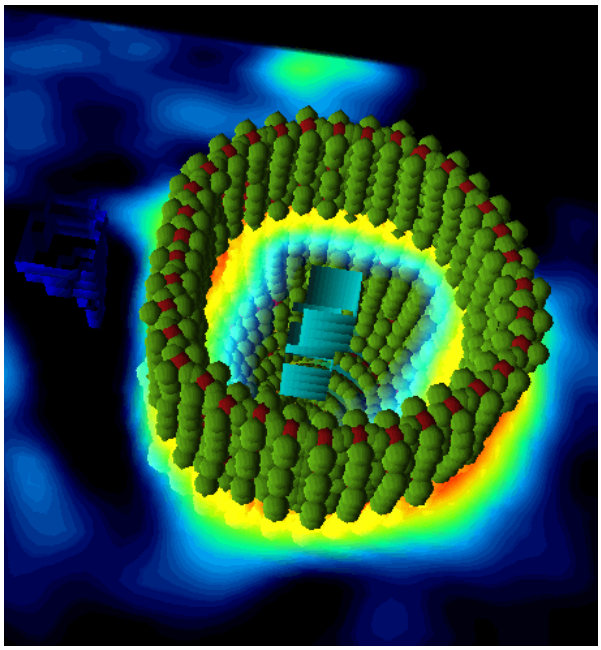


A better representation of the sampling points can be obtained by a 3D representation, which is only available if the **P3D** option has been purchased. In this case, the

button is present. When it is activated, the shape of the myocardium model is rendered together with the sampling points. The example below shows the sampling points as red spheres, the myocardium model as a surface with the texture of the MYOCARDIUM image, and a short axis slice of the anatomical images with transparency.



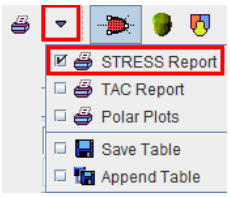
If a sampling scheme with averaging has been selected, the neighbor points are rendered as separate sphere objects in green as illustrated below.



To learn more about the many possibilities exploring the data in P3D please refer to the P3D User's Guide.

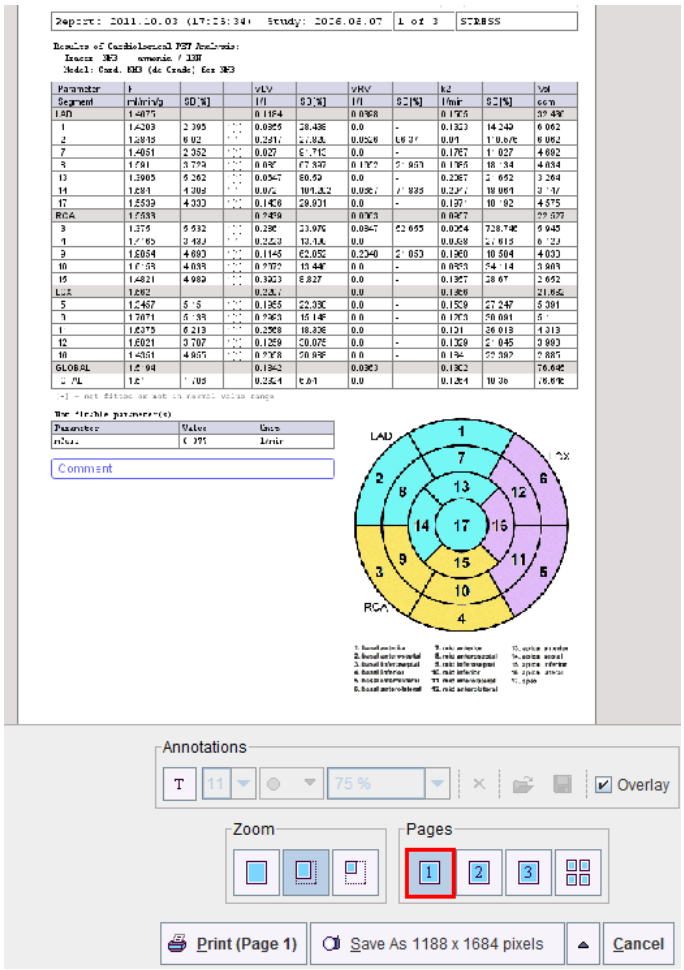
Documentation

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



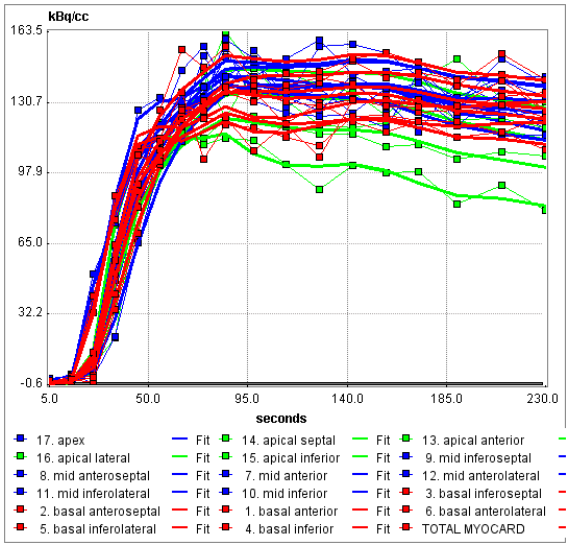
Main Report (STRESS, REST separate)

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.

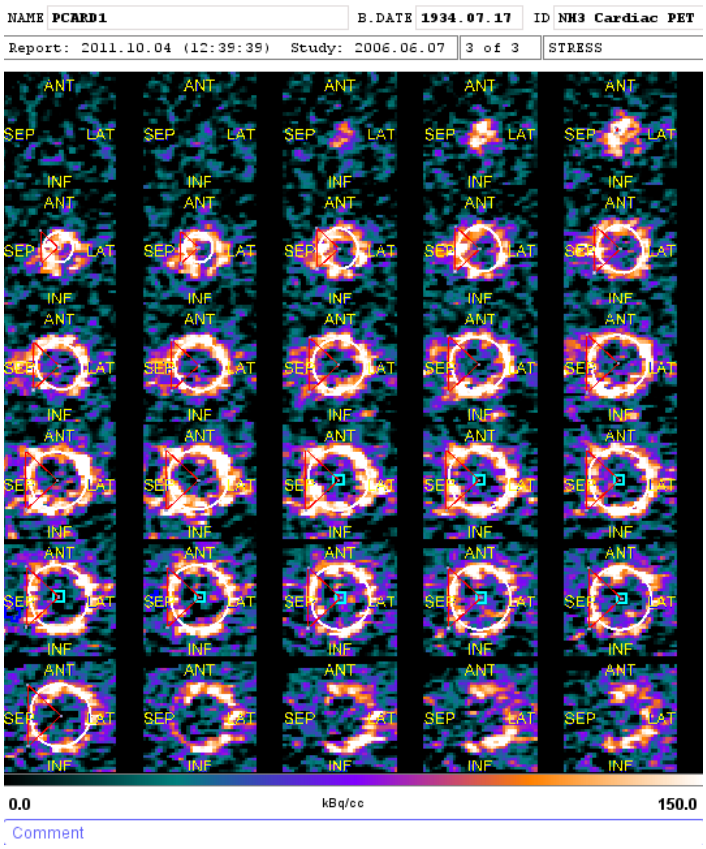


Note the buttons **Print** for printing a hardcopy of the report, and **Save as** for saving the report in a graphic format (JPEG, TIFF) or in DICOM. The latter button can be switched to generate a capture with lower resolution.

The second page of the main report shows the segmental TACs

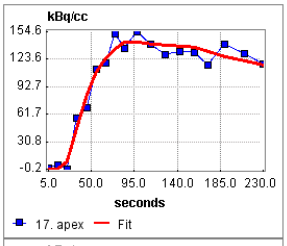


The third page allows to print images from the dynamic study in SA orientation. The report layout is fixed to 6x5 images such that 30 slices images are always visible. To change the appearance just click into the image area and adjust the visible frame and the color display range.



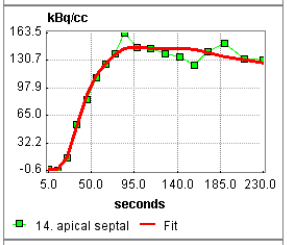
TAC Report

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.



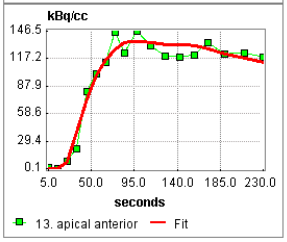
Parameter	Value	Unit
F	1.438424	ml/min/g
vLV	0.128252	1/1
vRV	0.0	1/1
k2	0.195835	1/min
ChiSquared	4.187918	
mCorr	0.077	1/min

[**] = not in range, * = not fitted



Parameter	Value	Unit
F	1.472186	ml/min/g
vLV	0.130254	1/1
vRV	0.022842	1/1
k2	0.160934	1/min
ChiSquared	2.777885	
mCorr	0.077	1/min

[**] = not in range, * = not fitted

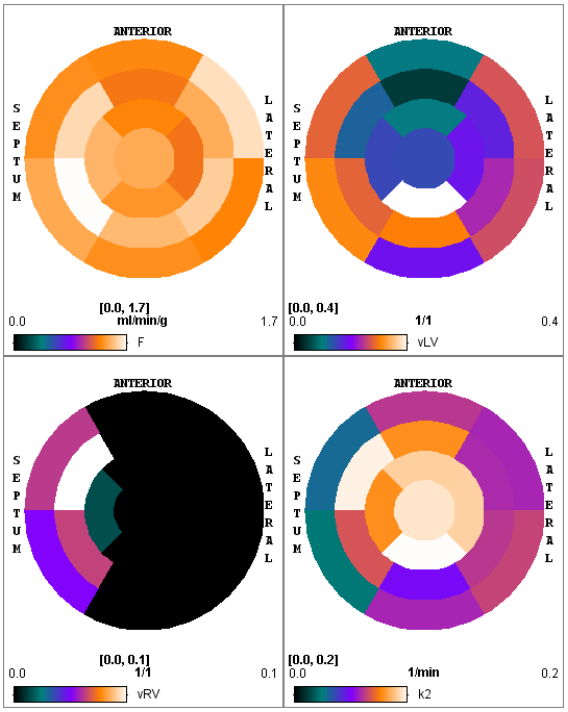


Parameter	Value	Unit
F	1.309092	ml/min/g
vLV	0.092456	1/1
vRV	0.0	1/1
k2	0.186929	1/min
ChiSquared	4.31955	
mCorr	0.077	1/min

[**] = not in range, * = not fitted

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.

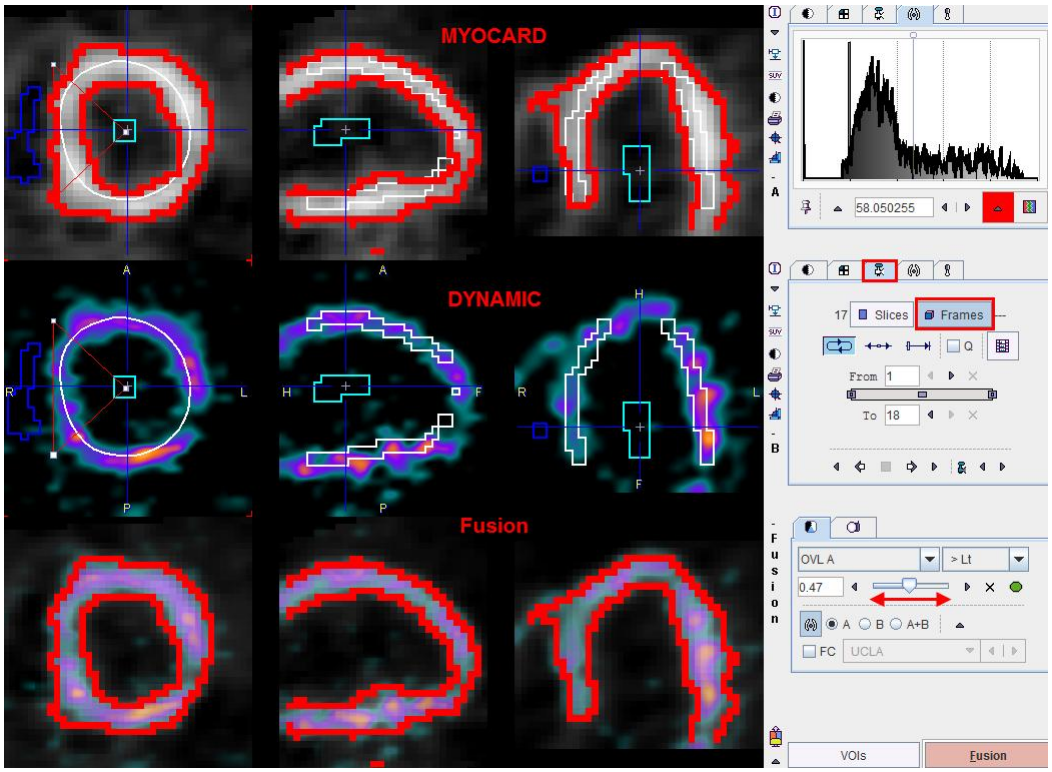
Advanced Data Exploration (Options)

Although PCARD 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 option (P3D), he has versatile tools available which can be readily employed as outlined below.

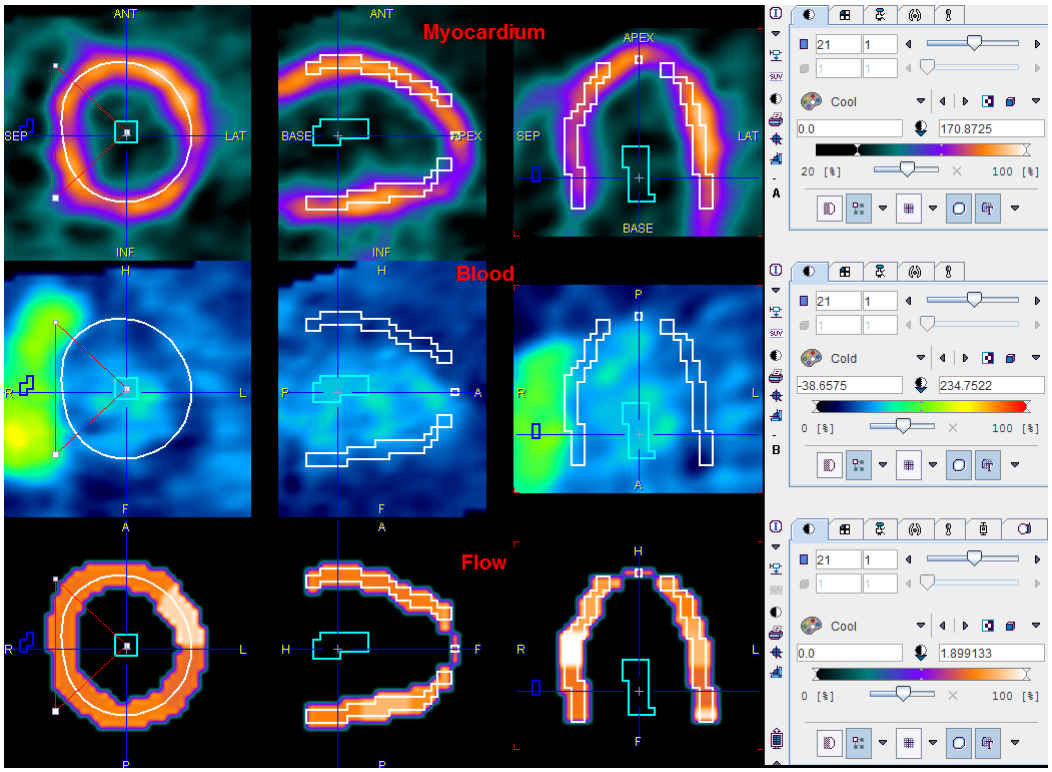
Fusion Display of all Data Sets

During processing, PCARD 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 capabilites.

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.



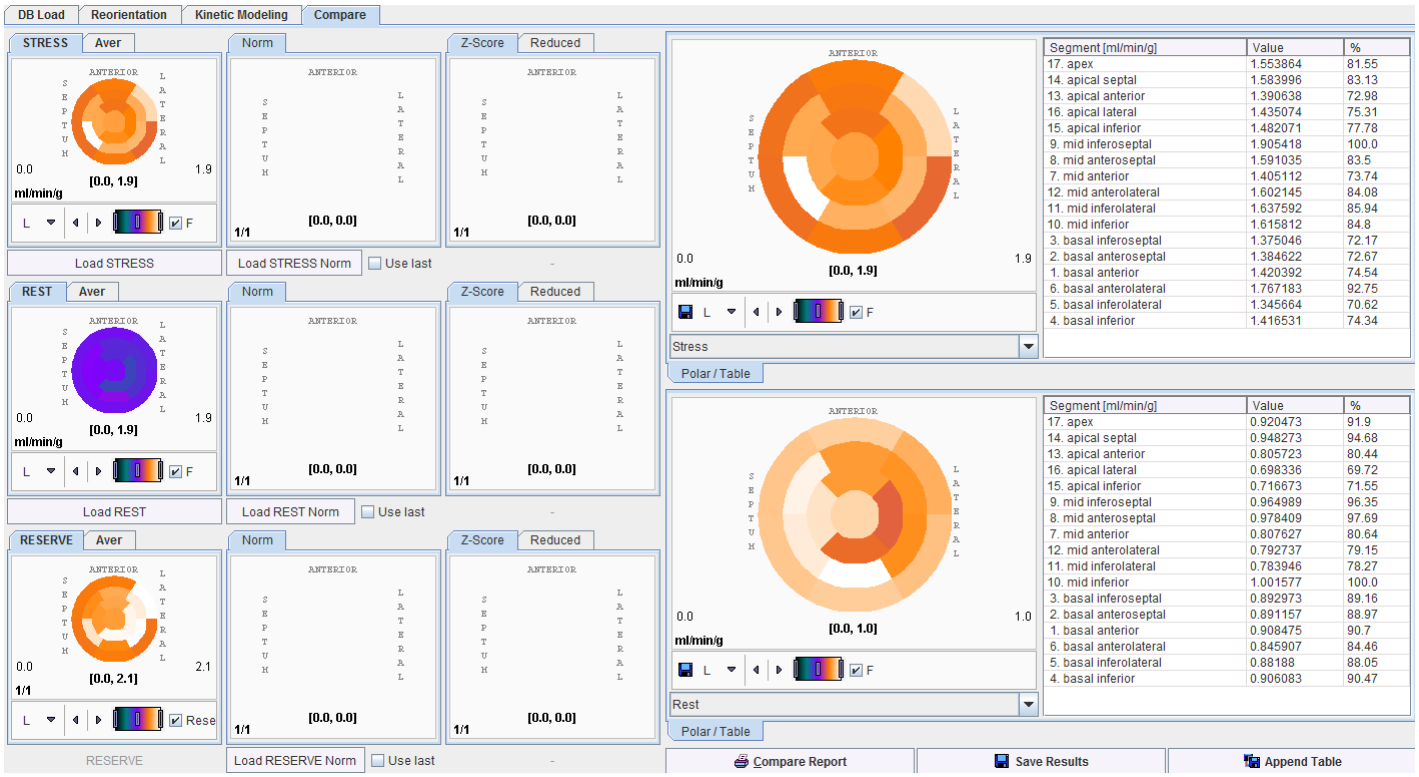
Rest/Stress and Database Comparison

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 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.

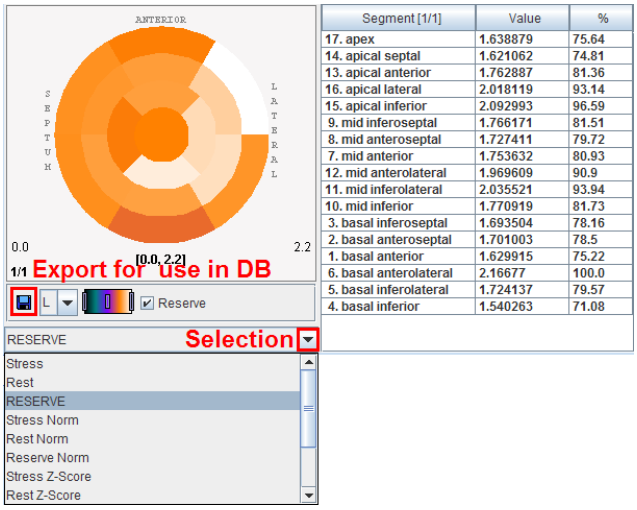
Please activate the **Compare** button on the **Kinetic Modeling** page to start the result comparison and continue on the now active **Compare** page.



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 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.

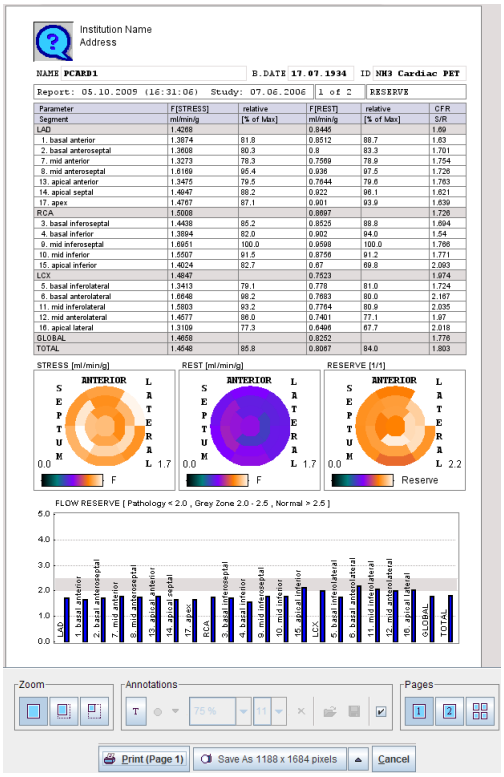
The right side of the page contains two enlarged polar plots with their numeric values shown in a table next to them. Initially, they show the stress and rest information, but the user can switch them, for instance to show the perfusion reserve as illustrated below.



Segment [1/1]	Value	%
17. apex	1.638879	75.64
14. apical septal	1.621062	74.81
13. apical anterior	1.762887	81.36
16. apical lateral	2.018119	93.14
15. apical inferior	2.092993	96.59
9. mid inferoseptal	1.766171	81.51
8. mid anteroseptal	1.727411	79.72
7. mid anterior	1.753632	80.93
12. mid anterolateral	1.969609	90.9
11. mid inferolateral	2.035521	93.94
10. mid inferior	1.770919	81.73
3. basal inferoseptal	1.693504	78.16
2. basal anteroseptal	1.701003	78.5
1. basal anterior	1.629915	75.22
6. basal anterolateral	2.16677	100.0
5. basal inferolateral	1.724137	79.57
4. basal inferior	1.540263	71.08

Note the  button which allows saving the polar plot information for later inclusion into a cardiac normal database.

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.

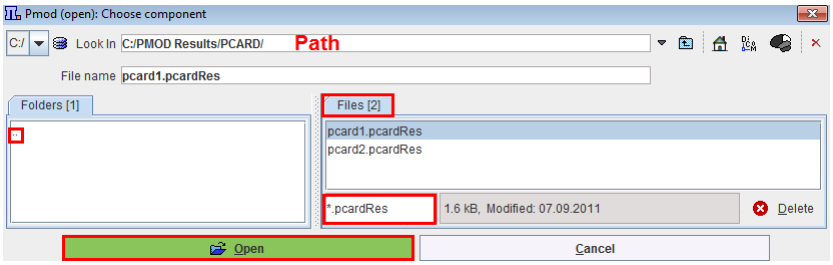


Parameter / Segment	F[STRESS] ml/min/g	relative [% of Max]	F[REST] ml/min/g	relative [% of Max]	CFR S/R
LAD	1.4268		0.8445		1.69
1. basal anterior	1.3874	81.8	0.8512	88.7	1.63
2. basal anteroseptal	1.3608	80.3	0.8	83.3	1.701
7. mid anterior	1.3273	78.3	0.7569	78.9	1.754
8. mid anteroseptal	1.5169	89.4	0.838	87.5	1.726
13. apical anterior	1.3475	79.5	0.7644	79.6	1.763
14. apical septal	1.4047	88.2	0.822	86.1	1.621
17. apex	1.4767	87.1	0.901	93.9	1.639
RCA	1.5008		0.8897		1.726
3. basal inferoseptal	1.4438	85.2	0.8525	88.8	1.694
4. basal inferior	1.3894	82.0	0.902	94.0	1.54
9. mid inferoseptal	1.6951	100.0	0.9599	100.0	1.766
10. mid inferior	1.5507	91.5	0.8756	91.2	1.771
15. apical inferior	1.4024	82.7	0.87	90.8	2.093
LCX	1.4847		0.7523		1.974
5. basal inferolateral	1.3413	79.1	0.778	81.0	1.724
6. basal anterolateral	1.6648	98.2	0.7883	80.0	2.167
11. mid inferolateral	1.5803	93.2	0.7764	80.9	2.035
12. mid anterolateral	1.4577	86.0	0.7401	77.1	1.97
16. apical lateral	1.3109	77.3	0.8409	87.7	2.018
GLOBAL	1.4658		0.8252		1.776
TOTAL	1.4548	85.8	0.8067	84.0	1.803

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

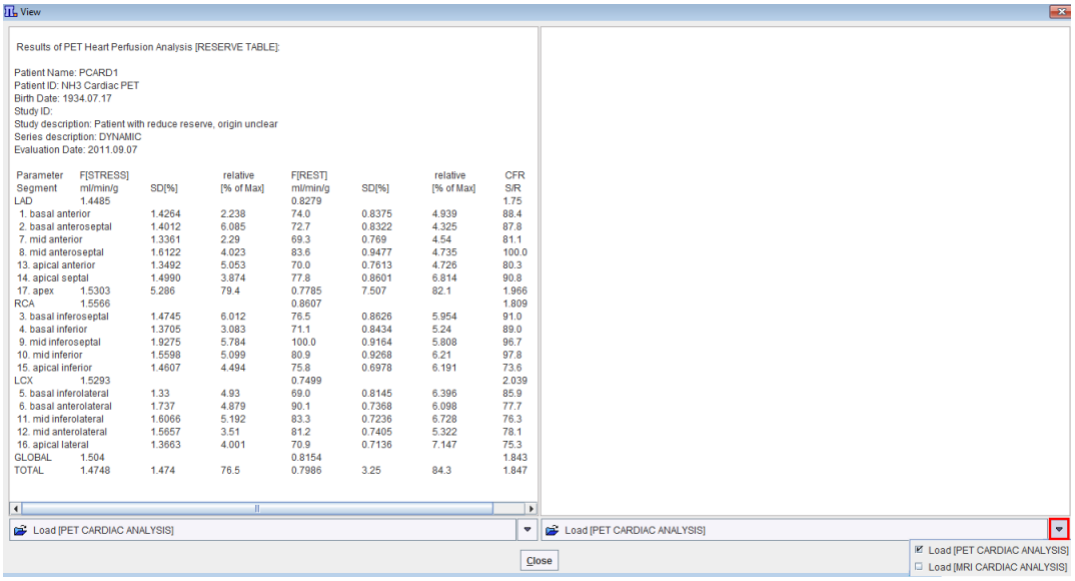
The numeric information of the table can also be saved or appended to a text file using the **Save Results** and the **Append Results** buttons, respectively. The saved file receives a **.pcardRes** suffix and can be visualized in Excel or a text editor (e.g Notepad).

Two different numeric results can be opened and compared within PCARD module. This can be easily achived activating the **View Results** View Results option from the bottom status line. Initially, a window appears allowing to select either a file from the database or a file located on your system. The Load from File System button activation 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:



Parameter	F[STRESS]		relative	F[REST]		relative	CFR
Segment	ml/min/g	SD[%]	[% of Max]	ml/min/g	SD[%]	[% of Max]	S/R
LAD	1.4485			0.8279			1.75
1. basal anterior	1.4264	2.238	74.0	0.8375	4.939		88.4
2. basal anteroseptal	1.4012	6.085	72.7	0.8322	4.325		87.8
7. mid anterior	1.3361	2.29	69.3	0.769	4.54		81.1
8. mid anteroseptal	1.6122	4.023	83.6	0.9477	4.735		100.0
13. apical anterior	1.3492	5.053	70.0	0.7613	4.726		80.3
14. apical septal	1.4990	3.874	77.8	0.8601	6.814		90.8
17. apex	1.5303	5.286	79.4	0.7785	7.507		82.1
RCA	1.5566			0.8607			1.966
3. basal inferoseptal	1.4745	6.012	76.5	0.8626	5.954		91.0
4. basal inferior	1.3705	3.083	71.1	0.8434	5.24		89.0
9. mid inferoseptal	1.9275	5.784	100.0	0.9164	5.808		96.7
10. mid inferior	1.5598	5.099	80.9	0.9268	6.21		97.8
15. apical inferior	1.4607	4.494	75.8	0.6978	6.191		73.6
LCX	1.5293			0.7499			2.039
5. basal inferolateral	1.33	4.93	69.0	0.8145	6.396		85.9
6. basal anterolateral	1.737	4.879	90.1	0.7368	6.098		77.7
11. mid inferolateral	1.6066	5.192	83.3	0.7236	6.728		76.3
12. mid anterolateral	1.5657	3.51	81.2	0.7405	5.322		78.1
16. apical lateral	1.3663	4.001	70.9	0.7136	7.147		75.3
GLOBAL	1.504			0.8154			1.843
TOTAL	1.4748	1.474	76.5	0.7986	3.25	84.3	1.847

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

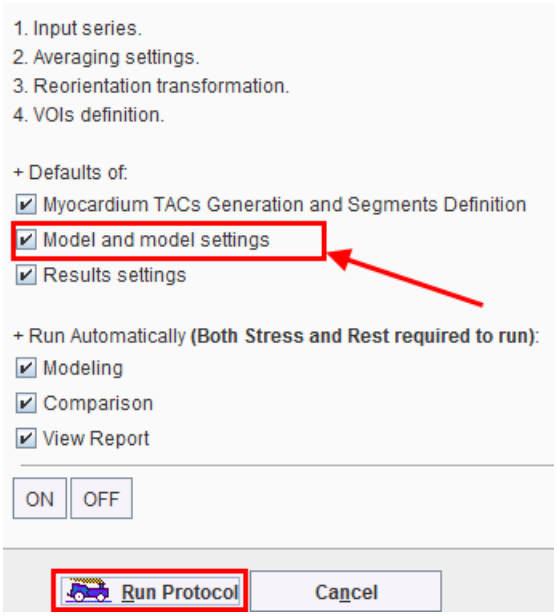
Database Comparison

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

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 PCARD analysis the entire set of definitions can be saved using the **Save Protocol** button which can be found in the lower status line. The selection of the **Save Protocol** button allows saving the work using a name of choice (for example Result of Automatic Procedure).

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



Processing of a Static Scan

The processing of static scans is much simpler than a full functional quantification, because kinetic modeling is not applicable. However, PCARD can generate a polar map and a numeric table of the uptake values.

Static Scan Processing

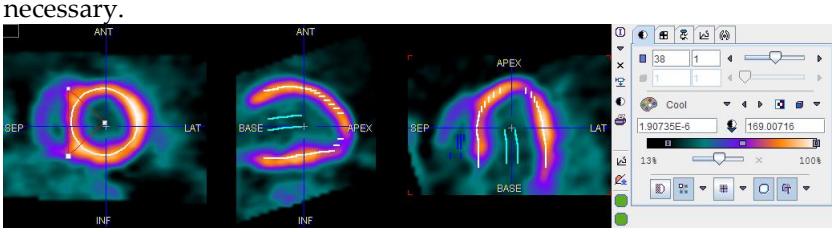
1) Load the image data in either row.

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

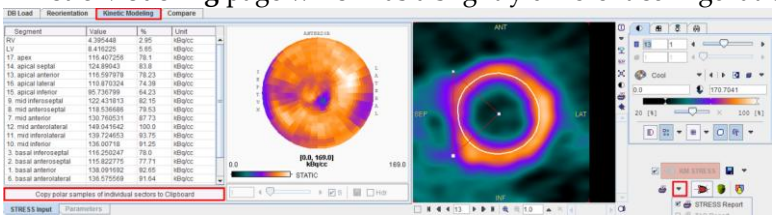
3) Define the five markers in the apex and at the basal locations using .

4) Activate the automatic contouring.

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



6) 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.

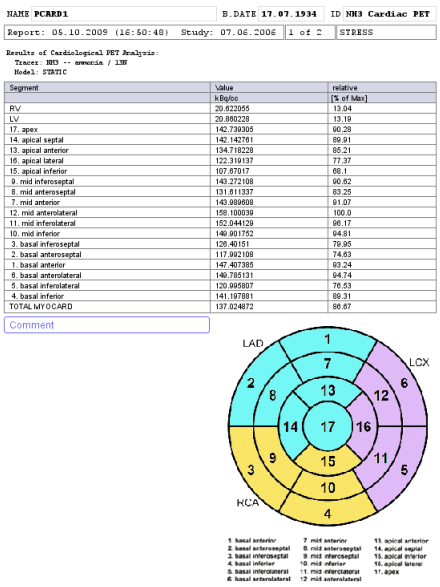


The table to the left contains the average uptake values in the different segments. The polar plot in the middle shows the uptake values obtained by the polar sampling process, and the images to the right illustrate the contour placement. Note that if you click into the polar plot, the image to the right 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.

7) 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**).

8) 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.



NAME PCARD1 B.DATE 17.07.1934 ID NH3 Cardiac PET

Report: 05.10.2009 (16:50:48) Study: 07.06.2006 1 of 2 STRESS

Results of Cardiological PET Analysis:
Tracer: NH3 -- ammonia / 13N
Model: STATIC

Segment	Value	relative
	kBq/cc	[% of Max]
RV	20.622055	13.04
LV	20.880228	13.19
17. apex	142.739305	90.28
14. apical septal	142.142781	89.91
13. apical anterior	134.718228	85.21
16. apical lateral	122.319137	77.37
15. apical inferior	107.87017	68.1
9. mid inferoseptal	143.272108	90.62
8. mid anteroseptal	131.611337	83.25
7. mid anterior	143.989008	91.07
12. mid anterolateral	158.100039	100.0
11. mid inferolateral	152.044129	96.17
10. mid inferior	149.901752	94.81
3. basal inferoseptal	126.40151	79.95
2. basal anteroseptal	117.992108	74.63
1. basal anterior	147.407385	93.24
6. basal anterolateral	149.785131	94.74
5. basal inferolateral	120.995807	76.53
4. basal inferior	141.197881	89.31
TOTAL MYOCARD	137.024872	86.67

Comment

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

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 are additionally required (identical zoom and offset values).

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.

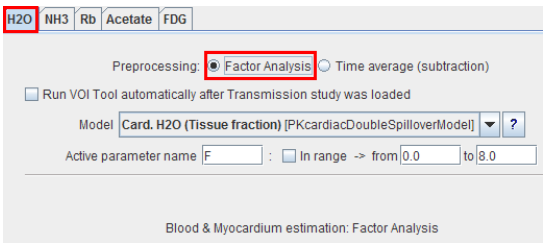
2) The expected uptake and washout in myocardium is calculated based on a 1-tissue compartment model, the blood activity as the input curve, and an average myocardial perfusion value.

3) 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.

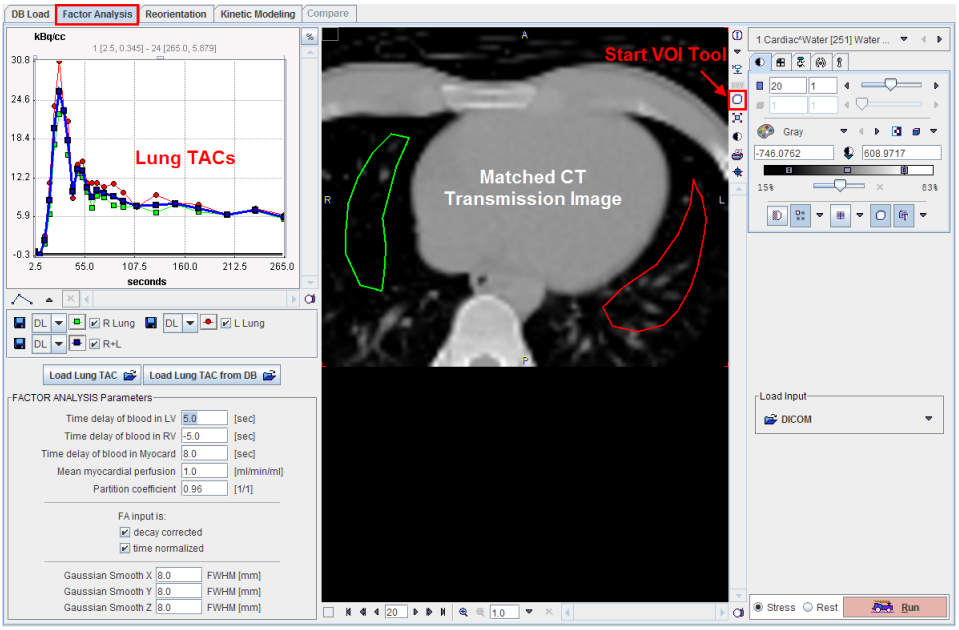
4) A myocardium factor image can then be obtained by summing the frames weighted by the m_i factors, and a blood factor image by summing the frames weighted by the b_i factors.

Factor Analysis Configuration

To use the factor analysis with cardiac $H_2^{15}O$-PET studies it must be ***configured*** (on page 7) by setting the radio button **Preprocessing** accordingly in the tracer configuration page as illustrated below.



When the configuration is closed, an additional page **Factor Analysis** shows up in PCARD.

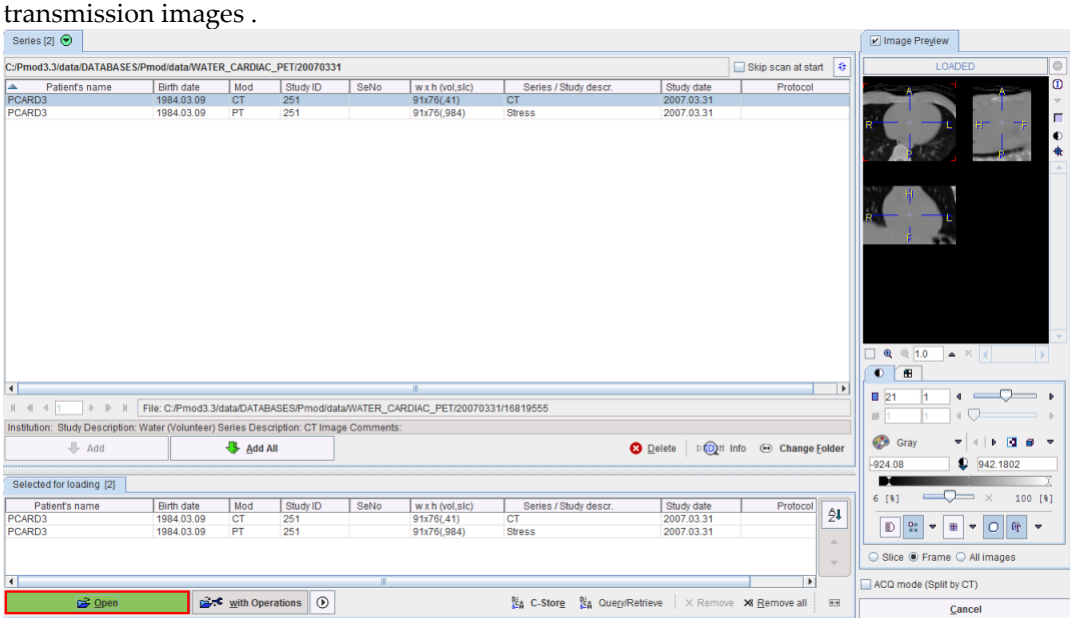


Derivation of the Lung TAC

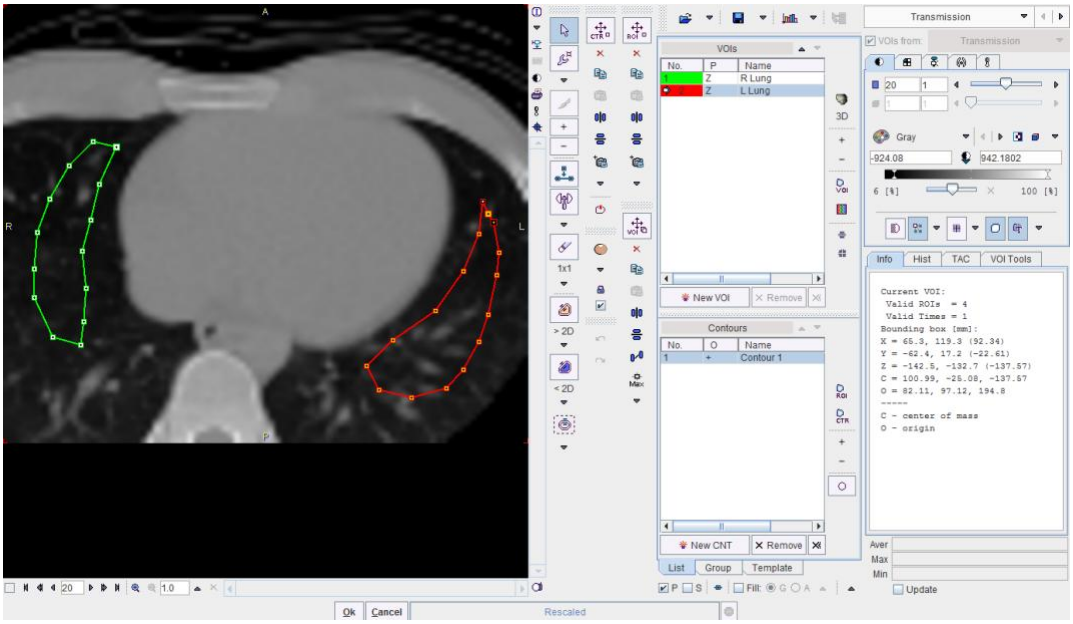
The TAC of the lungs provides a reasonable approximation of the shape of the blood curve. It is obtained in a lung VOI which must been outlined in transmission images, because there is not poor anatomical information in the water images. It is essential that the dynamic $H_2{}^{15}O$-PET images and the transmission images are exactly aligned.

Please perform the following steps which are illustrated above.

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

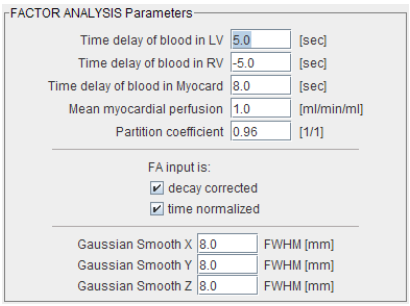
Factor Analysis

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}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.

2) 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.

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

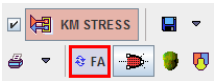
4) The smoothed factor images together with the dynamic images are transferred to the **Reorientation** page. To direct them into the right image container, please set the **Stress**/**Rest** radio button accordingly.

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**.

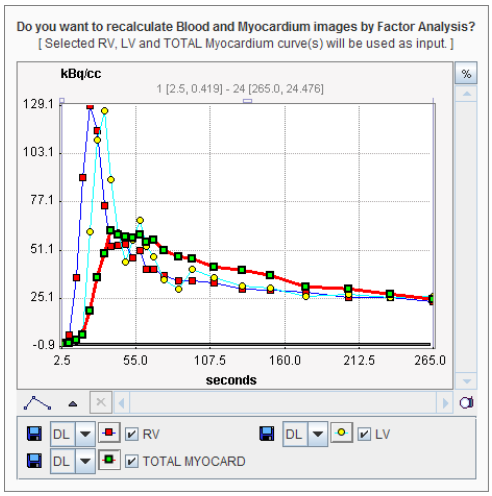
From then on processing continues with short axis reorientation, VOI definition and kinetic modeling as described ***above*** (on page 16) for the other tracers.

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 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 PCARD following a standard procedure. Note that the same kinetic and segment 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. PCARD 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.

This section will be completed. Please check for an update on
http://www.pmod.com/technologies/doc/index.html

Chapter 2

PCARD Reference

In This Chapter

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 cleanly 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.

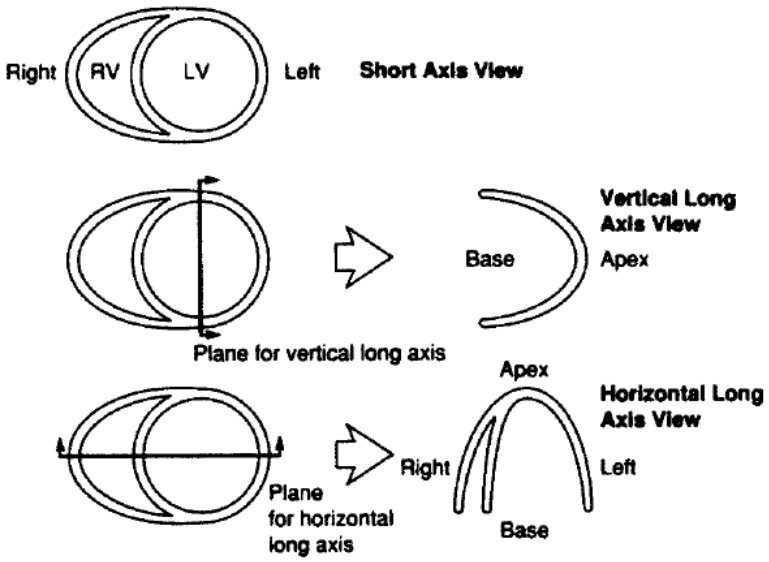


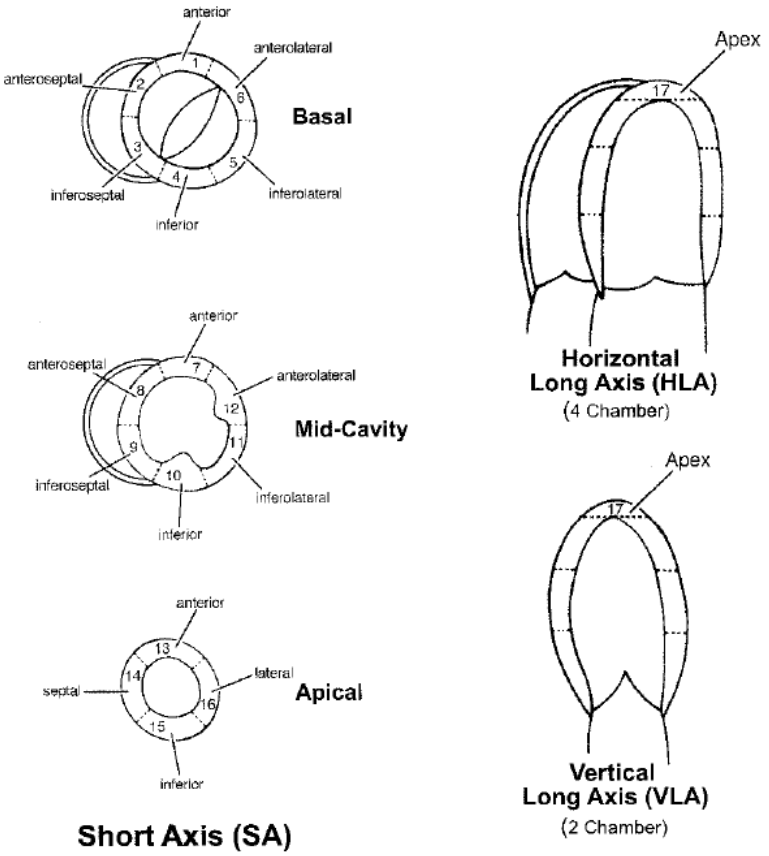
Figure 1. Cardiac plane definition and display for tomographic imaging modalities.[4]

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*.

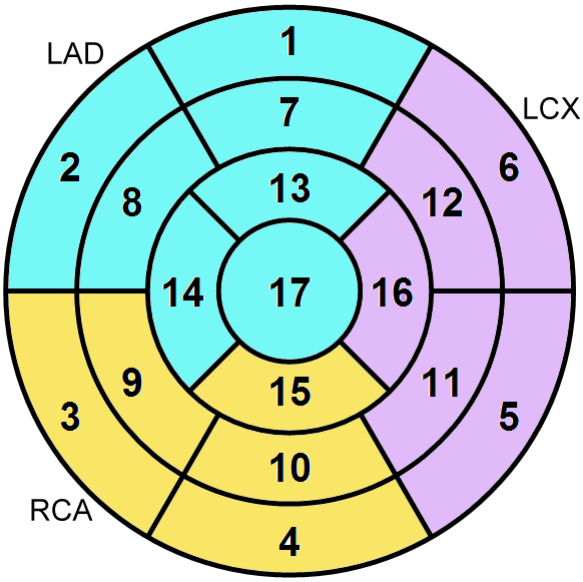


Polar Plots

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.

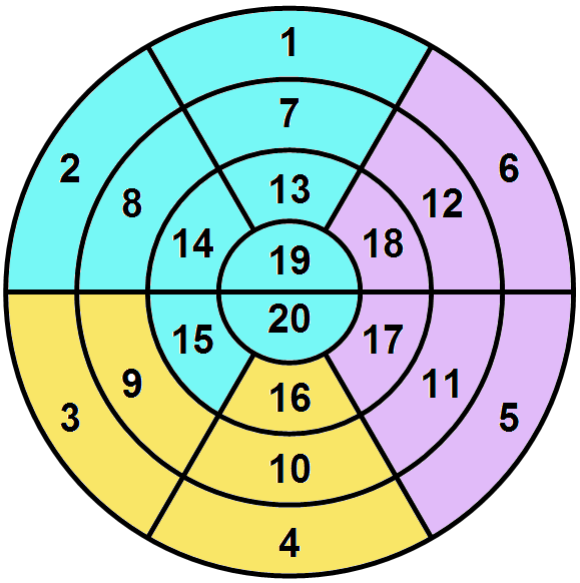
Coronary Artery Territories

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
5. basal inferolateral
6. basal anterolateral
10. mid inferior
11. mid inferolateral
12. mid anterolateral
16. apical inferior
17. apical inferolateral
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 blood spaces.

PCARD 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 PCARD 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.

2) **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 (^{1}C-acetate)
- FDG (^{18}F-Deoxygluose)

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.

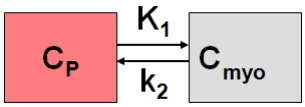
Exceptions to these rules are specified in the description of the individual models.

Cardiac Flow from Ammonia PET

Two models are 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)

This 1-tissue compartment model has been developed by DeGrado et al. [30] for cardiac PET studies using $^{13}NH_3$ ammonia bolus injection.



It includes a linear metabolite correction and describes the exchange of the NH_3 between blood and the myocardium by the following differential equation

$$\frac{dC_{myo}(t)}{dt} = K_1(1 - mCorr * t)C_{lv}(t) - k_2 C_{myo}(t)$$

The factor *mCorr* represents the metabolite correction factor. A value of 0.077 [1/min] has been found for *mCorr* in humans [30].

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

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

where

V_{lv} = spill-over fraction 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 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 two purposes: (1) multiplied by the metabolite correction (1-mCorr*t) it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- 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 reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.
- To set *mCorr* to a different value in all regions (eg. for animal studies) proceed as described for V_{rv} above.

Abstract [30]

"BACKGROUND: Although several modeling strategies have been developed and validated for quantification of myocardial blood flow (MBF) from ^{13}N- labeled ammonia positron emission tomographic data, a comparison of noise characteristics of the various techniques in serial studies is lacking. METHODS AND RESULTS: Dynamic ^{13}N-labeled ammonia positron emission tomographic imaging was performed at baseline and after pharmacologic stress in (1) single studies of four dogs with concomitant measurement of microsphere blood flow and (2) initial and follow-up studies of eight normal volunteers. Data were obtained from short-axis images for the blood pool and myocardial regions corresponding to the three arterial vascular territories. Indexes of MBF were obtained by four distinct techniques: (1) University of California, Los Angeles, two-compartment model, (2) Michigan two-compartment model, and (3) a one- compartment model with variable blood volume term. Coronary flow reserve (CFR) was measured as the ratio of stress/rest MBF. The estimated standard deviation of the measurement error for the relative change between studies of rest and stress MBF and CFR was determined for each technique. Estimates of MBF from all techniques showed good correlation with microsphere blood flow (r = 0.95 to 0.96) in canine myocardium. In human studies, similar mean estimates of MBF were found with all

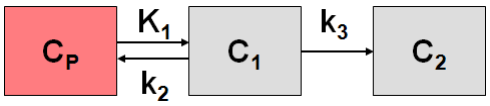
techniques. Techniques 1 and 3 showed the smallest interstudy variability in MBF and CFR. The estimated standard deviations for these techniques were approximately 20%, 30%, and 27% for rest MBF, stress MBF, and CFR, respectively. CONCLUSION: Noninvasive quantification of MBF and CFR from dynamic ^{13}N-labeled ammonia positron emission tomography is most reproducible with technique 1 or 3. The ability to account for differences in myocardial partial volume gives preference to technique 3. However, substantial interstudy variability in regional MBF remains, suggesting the importance of procedural factors or real temporal fluctuations in MBF."

Card. NH3 (Geometrical corr.)

This model is exactly the same model as the Card. NH_3 (Metabolite corr.) model described above with the single exception that no metabolite correction is applied, ie $mCorr \equiv 0$.

Card. NH3 (2 Compartments)

The **Card NH3 (2-Tissue)** model developed by Hutchins et al. [45] is an implementation of the irreversible 2-tissue-compartment model for cardiac PET studies using $^{13}NH_3$ 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}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.

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. [46]

$$C_P(t) = \begin{cases} C_{lv}(t) & t \le t_0 \\ e^{-\ln 2 (t - t_0)/T_{1/2}} C_{lv}(t) & t > t_0 \end{cases}$$

with 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 ventricle, including metabolites.

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

$$C_{PET}(t) = (1 - V_{lv} - V_{rv})\,(C_1(t) + C_2(t)) + V_{lv} C_{lv}(t) + V_{rv} C_{rv}(t)$$

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 $C_{rv}(t)$.

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, K1/k2)** has been developed using the parameter K_1/k_2 (DV, distribution volume of free tracer is used as a fit parameter instead of k_2, and k_2 is derived from the estimated K_1 and K_1/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.

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 two purposes: (1) corrected for metabolites it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- The delay and half-time of the metabolite correction are input parameters of the kinetic 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 reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

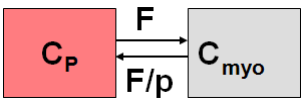
Abstract [45]

"Evaluation of regional myocardial blood flow by conventional scintigraphic techniques is limited to the qualitative assessment of regional tracer distribution. Dynamic imaging with positron emission tomography allows the quantitative delineation of myocardial tracer kinetics and, hence, the measurement of physiologic processes such as myocardial blood flow. To test this hypothesis, positron emission tomographic imaging in combination with N-13 ammonia was performed at rest and after pharmacologically induced vasodilation in seven healthy volunteers. Myocardial and blood time-activity curves derived from regions of interest over the heart and ventricular chamber were fitted using a three compartment model for N-13 ammonia, yielding rate constants for tracer uptake and retention. Myocardial blood flow (K1) averaged 88 +/- 17 ml/min per 100 g at rest and increased to 417 +/- 112 ml/min per 100 g after dipyridamole infusion (0.56 mg/kg) and handgrip exercise. The coronary reserve averaged 4.8 +/- 1.3 and was not significantly different in the septal, anterior and lateral walls of the left ventricle. Blood flow values showed only a minor dependence on the correction for blood metabolites of N-13 ammonia. These data demonstrate that quantification of regional myocardial blood flow is feasible by dynamic positron emission tomographic imaging. The observed coronary flow reserve after

dipyridamole is in close agreement with the results obtained by invasive techniques, indicating accurate flow estimates over a wide range. Thus, positron emission tomography may provide accurate and noninvasive definition of the functional significance of coronary artery disease and may allow the improved selection of patients for revascularization."

Cardiac Flow from Water PET

Two models are available for the quantification of myocardial perfusion PET studies using $H_2{}^{15}O$ water bolus injection. They only differ in the way how they handle spill-over correction. The model configuration is a 1-tissue compartment model below.



The distribution of the freely diffusible inert tracer $H_2{}^{15}O$ in myocardium can be described by a 1-tissue compartment model

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

with the myocardial blood flow F and the myocardium to blood partition coefficient of water p.

Card. H2O (Tissue fraction)

This model has been developed by Hermannsen et al. [27] for cardiac PET studies using $H_2{}^{15}O$ water bolus injection. It incorporates two spill-over terms from blood in the left and the right ventricles which are relatively displaced in time. So the operational equation which is fitted to the measured data is

$$C_{PET}(t) = TF\, C_{myo}(t) + V_{lv}C_{lv}(t) + V_{rv}C_{rv}(t)$$

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

Implementation Notes

As opposed to standard PKIN models a tissue fraction is used rather than a strict geometrical correction for compliance with the original model. 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 PCARD tool.

Abstract [27]

"Positron emission tomography (PET) in conjunction with $C^{15}O_2$ or $H_2^{15}O$ can be used to measure myocardial blood flow (MBF) and tissue fraction (TF), i.e. the fraction of the tissue mass in the volume of the region of interest. However, with $C^{15}O_2$ inhalation, the tissue fraction in the septum is overestimated. Bolus injection of $H_2^{15}O$ together with arterial cannulation gives very precise results but is invasive. The purpose of this study was to develop a method which circumvents these problems. A four- parameter model with parameters for MBF, TF and spill- over fractions from both left and right ventricular cavities was developed. This method was compared with a three- parameter model (no right ventricular cavity spill-over) in both septal and non-septal regions of interest for three different administration protocols: bolus injection of $H_2^{15}O$, infusion of $H_2^{15}O$ and inhalation of $C^{15}O_2$. It was found that MBF can be measured with intravenous administration of $H_2^{15}O$ without the requirement for arterial cannulation. The four-parameter protocol with bolus injection was stable in clinical studies. The four-parameter model proved essential for the septum, where it gave highly significantly better fits than did the three-parameter model ($P<0.00003$ in each of 15 subjects). Administration of $H_2^{15}O$ together with this four-parameter model also circumvented the problem of overestimation of TF in the septum seen with $C^{15}O_2$ inhalation. In addition, the radiation dose of $H_2^{15}O$ protocols is lower than that of $C^{15}O_2$ inhalation. Using a left atrial input curve instead of a left ventricular cavity input curve gave the same mean MBF and TF."

Card. H2O (Geometrical corr.)

This model is the same as the one above developed by Hermannsen 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 PCARD tool.

Cardiac Flow from Rubidium-82 PET

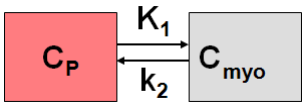
Two kinetic models are available for the quantification of myocardial perfusion from ^{82}Rb bolus PET data.

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

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

Card. Rb-82 (1 Compartment)

The model has the standard 1-compartment form



with the differential equation

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

The equation assumes that the activity in the left ventricle $C_{lv}(t)$ is used as the input curve.

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

$$K_1 = F\,E = F\,(1 - Ae^{-B/F})$$

The values of the correction factors reported by Lortie et al. [44] are

A = 0.77
B = 0.63 [ml/min/g]

The model implements a geometric double spillover correction for activity from the left and right ventricle in the form

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

where

V_{lv} = spill-over fraction 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:

- 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 two purposes: (1) as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- In practice, the expression for K_1 is inserted into the differential equation, so that F becomes a fit parameter, and K_1 is a derived parameter.
- To allow the user to change the form of the extraction function the scale factor A and the exponent B an be entered as input parameters.
- 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 of the regional TAC. The assumption is that

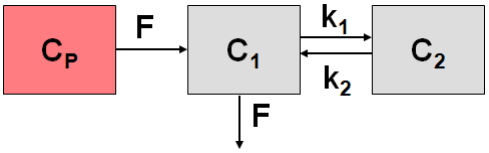
such a TAC is not from septal tissue and should thus be modeled with spill-over from the left ventricle only. The reason for this automatism is usage of the model in the **PCARD** tool.

- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

This model is also usable in the cardiac modeling tool **PCARD**.

Card. Rb-82 (2 Compartments)

The model has been implemented according to the method described and evaluated by Herrero et al [35]. Their ^{82}Rb 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.

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

$$\frac{dC_1(t)}{dt} = F(C_a(t) - C_1(t)/V_d) - k_1 C_1(t) + k_2 C_2(t)$$
$$\frac{dC_2(t)}{dt} = k_1\, C_1(t) - k_2 C_2(t)$$

with the arterial blood activity C_P and a fractional volume of distribution V_d in the first compartment .

The operational equation which is fitted to the measured data is

$$C_{PET} = F_{MM}\,(C_1(t) + C_2(t)) + F_{BM} C_a(t)$$

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

The model encompasses 6 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 distribution volume V_d and the recovery coefficient F_{MM} are usually fixed (proposed values from [35]: 0.75 and 0.65 respectively). The recovery coefficient depends on the image resolution and should be determined experimentally.

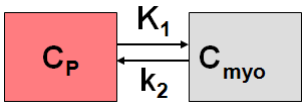
This model is also usable in the cardiac modeling tool **PCARD**.

Abstract [35]

"Positron emission tomography offers the ability to noninvasively assess regional myocardial perfusion in absolute terms (i.e., milliliters per gram per minute). Accurate estimates have been difficult to achieve with generator-produced 82Rb because of the complex behavior of this tracer in the myocardium. The aim of the present study was to determine whether regional myocardial blood flow could be assessed quantitatively with 82Rb and positron emission tomography by using a two-compartment kinetic model. Regional perfusion in milliliters per gram per minute was estimated from dynamic tomographic scans after intravenous administration of 82Rb in 18 studies in 13 intact dogs studied without intervention, after 2 and 24 hours of induced ischemia, during reperfusion after transient occlusion, or at rest and after pharmacological hyperemia after induced coronary artery stenosis. Regional flow was estimated along with the forward and backward rates of transport (k1 and k2 [minutes-1]) after the relative volume of distribution of the first compartment was fixed to 0.53 ml/ml and the tomographic parameters, the recovery and spillover fractions, were fixed to averaged values obtained in previous studies. In 36 comparisons, estimates of regional flow with 82Rb correlated well with flow measured with concomitantly administered radiolabeled microspheres (r = 0.91, p less than 0.05) over the flow range from 0.14 to 4.25 ml/g/min. A putative index of viability, k2, increased significantly in regions with severe ischemia. The results suggest that quantification of regional myocardial perfusion is possible in centers using 82Rb for estimates of myocardial perfusion when a physiologically appropriate, two-compartment model is used. Positron emission tomography offers the ability to noninvasively assess regional myocardial perfusion in absolute terms (i.e., milliliters per gram per minute). Accurate estimates have been difficult to achieve with generator-produced 82Rb because of the complex behavior of this tracer in the myocardium. The aim of the present study was to determine whether regional myocardial blood flow could be assessed quantitatively with 82Rb and positron emission tomography by using a two-compartment kinetic model. Regional perfusion in milliliters per gram per minute was estimated from dynamic tomographic scans after intravenous administration of 82Rb in 18 studies in 13 intact dogs studied without intervention, after 2 and 24 hours of induced ischemia, during reperfusion after transient occlusion, or at rest and after pharmacological hyperemia after induced coronary artery stenosis. Regional flow was estimated along with the forward and backward rates of transport (k1 and k2 [minutes-1]) after the relative volume of distribution of the first compartment was fixed to 0.53 ml/ml and the tomographic parameters, the recovery and spillover fractions, were fixed to averaged values obtained in previous studies. In 36 comparisons, estimates of regional flow with 82Rb correlated well with flow measured with concomitantly administered radiolabeled microspheres (r = 0.91, p less than 0.05) over the flow range from 0.14 to 4.25 ml/g/min. A putative index of viability, k2, increased significantly in regions with severe ischemia. The results suggest that quantification of regional myocardial perfusion is possible in centers using 82Rb for estimates of myocardial perfusion when a physiologically appropriate, two-compartment model is used."

Cardiac Flow from Acetate PET

Van den Hoff et al. [46] have investigated and validated ^{11}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_a and myocardial tissue C_{myo} and a differential equation

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

A metabolite correction is necessary to derive the plasma activity from whole blood measured in the left cavity.

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

with $T_{1/2}$=5.3 min. K_1 is the product of flow F and extraction E which is flow dependent for acetate. The relation found [46] is described by the following relation

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

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

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

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:

- 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 two purposes: (1) corrected by the metabolite buildup it serves as the input curve, (2) it is used for spillover correction of all myocardial TACs. It must be loaded as the **Input curve**.
- 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 reason for this automatism is usage of the model in the **PCARD** tool.
- To set $V_{rv} = 0$ in all regional models proceed as follows: in one region, set $V_{rv} = 0$ and disable the fit checkbox; fit the region; configure the button below **Copy to all regions** to **Model and Par.** and activate it.

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

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

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 $K_1k_3/(k_2+k_3)$ 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.

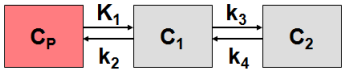
For FDG data, the Lumped constant (LC) and the plasma glucose level (PG) of the patient should be entered. The metabolic rate of glucose MRGlu is then obtained from the regression slope by MRGlu = slope * PG / LC.

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_1, 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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PMOD Technologies Ltd
Sumatrastrasse 25
8006 Zürich
Switzerland
+41 (44) 350 46 00
support@pmod.com
http://www.pmod.com

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