# Visual Analysis of Heart Reinervation after Transplantation

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*Abstract*—During heart transplantation complete denervation of allograft occurs. Partial reinnervation may develop after one year or later. It can be detected by different methods i.e., iodine-123-meta-iodobenziylguanidine (MIBG) scintigraphy, positron emission tomography (PET), heart rate variability (HRV), etc. We propose an alternative noninvasive method based on visual diagnostics (VD) and supported by a custom developed tool (ComVis), which enables interactive visual analysis of large data sets by exploiting focus and context (simultaneous local and global view), multiple coordinated views and advanced interaction. Measurements of patients with transplanted heart are rare and valuable, therefore they should be analyzed in all details. Different statistical characteristics and time series from ECG and respiration measurements from fifteen patients and twelve healthy controls have been analyzed using the ComVis tool. MIBG scintigraphy imaging was included, as well. Heart to mediastinum ratio (HMR) was used as a measure of the ventricular reinnervation. HRV was analyzed to evaluate sinus node reinnervation. HRV was synchronized on well defined expiration moment and analyzed in time-domain. We will describe some new diagnostic results or rules that were deduced from interactive visual analysis and may help in the future investigation of heart reinnervation.

## I. INTRODUCTION

Donor heart is completely denervated after heart transplantation procedure (HTx). Previous studies demonstrated that sympathetic reinnervation after HTx can occur one or more years after transplantation. Reinnervation process is very slow and time dependent and may still not be completed up to 15 years after transplantation procedure [1]. Studies regarding sympathetic reinnervation extent and localization showed spatially heterogeneous process [1], [2], [3], [4]. Sympathetic nerve terminal growth was demonstrated first in anterior and septal parts of the left ventricle, than in the lateral parts, but inferior segments were frequently without substantial reinnervation [1].

Different methodologies have been used to investigate sympathetic reinnervation, either for sinus node reinnervation or for ventricular reinnervation. Sinus node sympathetic reinnervation was most frequently shown by studies with tyramine (an agent that causes norepinephrine release from intact sympathetic nerve terminals) injection into the artery that perfuses the sinus node and with heart rate variability analysis (HRV) [5], [6], [7], [8], [9], [10]. The most convincing biochemical and spatial evidences of ventricular sympathetic reinnervation are from studies with radiolabeled norepinephrine ana-

TABLE I
DATA OF HTX PATIENTS AND CONTROLS.

| | Patients | Controls |
|---|---|---|
| Number in group | 15 | 12 |
| Gender (female:male) | 3:12 | 3:9 |
| Underlying disease | | |
| Dilated CMP | 10 | 0 |
| Ishemic CMP | 5 | 0 |
| Time after HTx in months, mean SD (min-max) | 51.0 22.4(12-97) | |
| Age at time of study in years, mean SD (min-max) | 54.4 11.4 (30-71) | 49.79.6 (31-70) |

logues, such as iodine-123-meta-iodobenzylguanidine scintigraphy (MIBG) and positron emission tomography (PET) with C-11 Hydroxyephedrine (HED), which are taken up by myocardial sympathetic nerves [1], [2], [3], [4], [10].

## II. METHODS

### A. Patients

Fifteen HTx patients, 12 months or more after orthotopic heart transplantation, were included in the study. No patient received any medication known to interfere with catecholamine uptake in presynaptic nerve terminals. Beta blocking agents were withdrawn 24h before the study. For comparison, a control group of twelve healthy volunteers with presumably normal cardiac innervation was enrolled in this study. None of those subjects was receiving any medications or have history of cardiovascular disease. The study was approved by Slovenian ethical committee. Written informed consent was obtained from all the subjects before the study. Patients and controls data are shown in Table I.

### B. HMR

Iodine-123-meta-iodobenziylguanidine (MIBG) scintigraphy was performed. Regions of interest (ROI) were used for semiquantitative evaluation of MIBG uptake in left ventricular myocardium (heart, H) and in the mediastinum (M). H/M ratio (HMR), was calculated as index of MIBG uptake in the myocardium. HMR > 1.3 was considered for allograft left ventricular sympathetic reinnervation [3]. After HMR calculation, HTx patients were divided in two groups: patients with left ventricular sympathetic reinnervation and without left ventricular sympathetic reinnervation (denervated). Examples
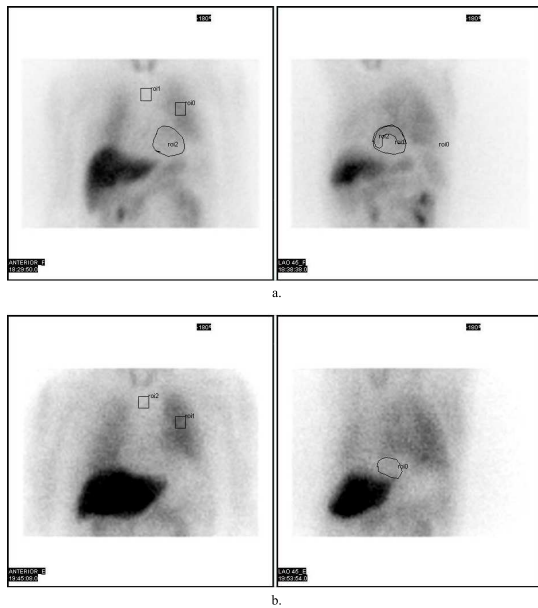
Fig. 1. Planar imaging in early phase, 20 minutes after MIBG application. a. Patient with reinnervated heart (HMR 1.42; 66 months after HTx). b. Patient with denervated heart (HMR 1.25; 52 months after HTx). Left parts are anterior projection and right parts the left anterior oblique projection. ROI in the myocardium and in the mediastinum is drawn for HMR calculation.
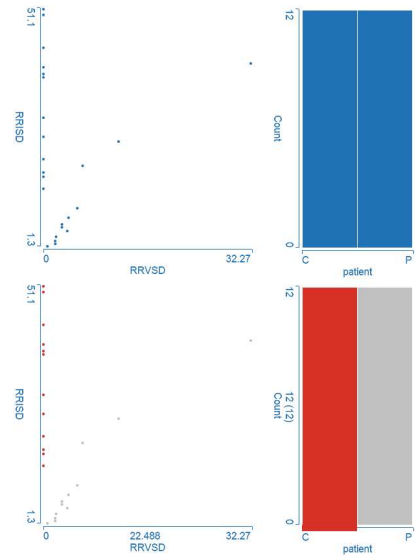


Fig. 2. Basic linking and brushing principle. The top row shows a scatterplot and a histogram. In the bottom row the user has selected (*brushed*) only one histogram bin, C-patients. In the linked scatterplot, on the left, corresponding points are highlighted as well. In this way we can clearly see a strong correlation between patient type and clustering in the scatterplot.

of MIBG planar imaging in early and late phase of a patient with reinnervated heart (HMR 1.42, 66 months after HTx) and a patient with denervated heart (HMR 1.25, 52 months after HTx) are shown in Figure 1a. and Figure 1b., respectively. For detailed description of MIBG protocol see [11].

### C. R-R intervals

The surface electrocardiogram, using bipolar lead CM5, was recorded with a high sampling rate (1800Hz) and resolution (2 $\mu$V). An 8.5-minute ECG recording was obtained with a patient in the supine position. Immediately after ECG, MIBG scintigraphy was performed. The spontaneous breathing of the patients was recorded simultaneously with a thermistor based detector. The recordings were analyzed offline. R-wave peaks were identified by an automated computer-based peak detection algorithm. To improve the time resolution, quadratic polynomial interpolation [12] was used. A 5-minute part with the lowest artifacts of the whole recording was used in the analysis of intervals between nearest R-waves (RRI).

### D. Time-analysis

Although the analysis of respiration induced heart rate variations has often been made in frequency-domain, the variations can also be analysed in time-domain by proper alignment of ECG signal to the breathing cycles. We developed also a time-domain method for the investigation of respiratory sinus arrhythmia (RSA) after HTx. Some similar methods have been proposed in the past [13] for the exploration of signal phases, however, they base on averaging and interpolation. The proposed procedure is sensitive enough to show small RRI found in patients after heart transplantation, even in cases

with spontaneous breathing (no metronome). Furthermore, the evolution of RRI corresponding to the respiration cycle is obtained, which is not the case in methods based on power spectral techniques.

The method does not require periodic signals and therefore allows spontaneous breathing. The method was further developed in order to be tailored for the signals with extremely low variability. It allows sub-interval analysis in order to explore time invariability of each measurement. Additionally, it preserves the form of the RRI variations together with its phase.

Because of the extremely small values of RRI in HTx patients, because of relatively small number of available measurements and because of their diversity, the statistical analysis or Fourier transform are not appropriate. We analyzed each HTx measurements separately and tried to find some added information using ComVis tool.

### III. COMVIS

ComVis is an interactive visualization tool based on coordinated multiple views principle. It supports well known views, such as, e.g., scatter plot, parallel coordinates, histogram, as well as a special curve view used for displaying families of function graphs. The combination of views makes it possible to analyze wide variety of data sets. The main idea of coordinated multiple views is to display more views simultaneously. Every view can be of any supported type. ComVis pays great attention to interaction. Linked views enable user to easily select a subset of data points in any view and all corresponding items in other views will be highlighted. This offers significant advantage compared to static views. Figure 2 illustrates the basic idea. A scatterplot (top left) shows relation between two
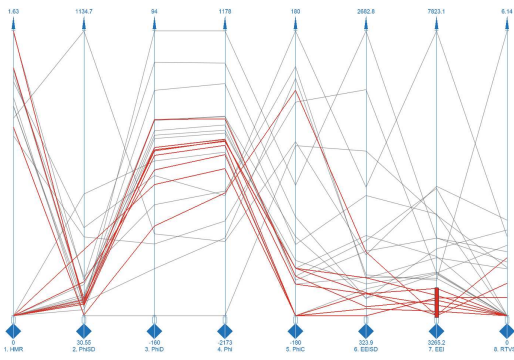
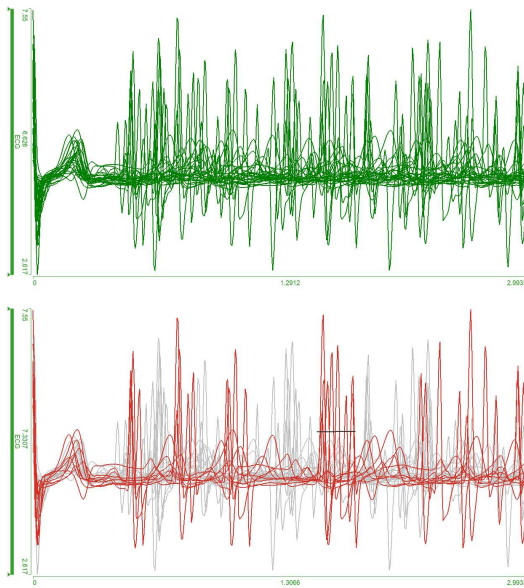Fig. 3. Parallel coordinates showing 8 dimesions simultaneousy. User has selected low EEI values.



Fig. 4. Curve view depicting a family of curves. All curves are shown simultaneously. The user can select a subset by simply drawing a line as shown in bottom image. All curves that cross the line will be selected. The view is linked with all other views.

parameters, RRISD on y-axis and RRVSD on x-axis. We can clearly see two clusters, one with almost linear correlation, and the second one with very low RRVSD values, independently of RRVSD. A simple histogram (top right) depicts patients status. Since status is binary variable, each patient can be either "P" or "C" (P stands for real patient and C for control person) histogram has only two bins. Each histogram bin represents count of patients having certain status. In our case we have 12 C-patients and 15 P-patients. Now, if we link the views and let the user select one subset, C-patients in our case, by simple graphical selection on histogram, points corresponding to the C-patients will be highlighted in the scatterplot. Figure 2 bottom shows the situation now. We can clearly see that C-patients do not show linear correlation. Note one point having low RRVSD and high RRISD which belongs to P-patients.

The context, items which are not selected, are always depicted as well. The simultaneous displaying of focus and con-

text significantly contributes to analysis. Advanced *brushing and linking* proved to be very powerful analytical tool. User can brush in any view, where he can use rectangular brush in the scatter plot, one dimensional brush in histogram, or on the parallel coordinates axis. Furthermore the user can use simple, yet powerful line brush in the curves view. Line brush selects all curves intersecting the line. Formal definition of such a brush is not straight forward, but its visual representation is immediately clear to the user. All brushes can be scaled and moved interactively.

Besides simple brushing ComVis supports composite brushing. Multiple brush mode makes it possible for the user to combine various brushes. The user selects brushes and boolean operations between them. AND, OR, and SUB are supported. Furthermore the tool creates composite brush in an iterative manner. This means that user selects current operation (AND, OR, or SUB) and draws a brush. The previous brushing state is combined with the new brush. The new state is computed and the new state is used when user draws a further brush. In this way user immediately gets visual feedback, and can very easily broaden his selection (using OR), or can further restrict selection (using AND or SUB). Although this mechanism is less formal then a real Boolean editor for brushes it is very efficient and allows very fast information drill-down. Once the user is satisfied with selection (or in the meantime) a tabular representation of selected data can be shown and exported on demand. Besides scatterplots and histogram we will use parallel coordinates and curve view in the analysis.

Parallel coordinates [15] are often used to explore multidimensional data sets. The main idea is to place more coordinate axes parallel to each other and to connect points representing values from a particular record on each axis with a line. In this way each record is represented with a poly line. Figure 3 illustrates the parallel coordinates view using our data set. Although it might seem confusing for a novice user, parallel coordinates are certainly very powerful analysis tool. Correlations between neighboring axis are clearly visible, and in combination with linking and brushing many unexpected patterns can be detected.

The curve view is used in case when we have data following a more complex data model [14]. In conventional tabular data data record can be considered to be a multidimensional point. Each dimension can be a scalar value in this case. Many applications require to have a function, or a data series in a single dimension. In our case, we do have various scalar data for each patient, but we also have various time series data. As there are more patients, we have a family of curves. E.g. ECG measurements of all patients form a family of ECG curves. At the same time there are many other parameters belonging to each patient. The curve view depicts all curves simultaneously, and user can intuitively select a subset by simply drawing a line across curves. All curves which cross the line will be selected. Figure 4 shows the curve view depicting ECG family of curves without (top) and with (bottom) user selection.
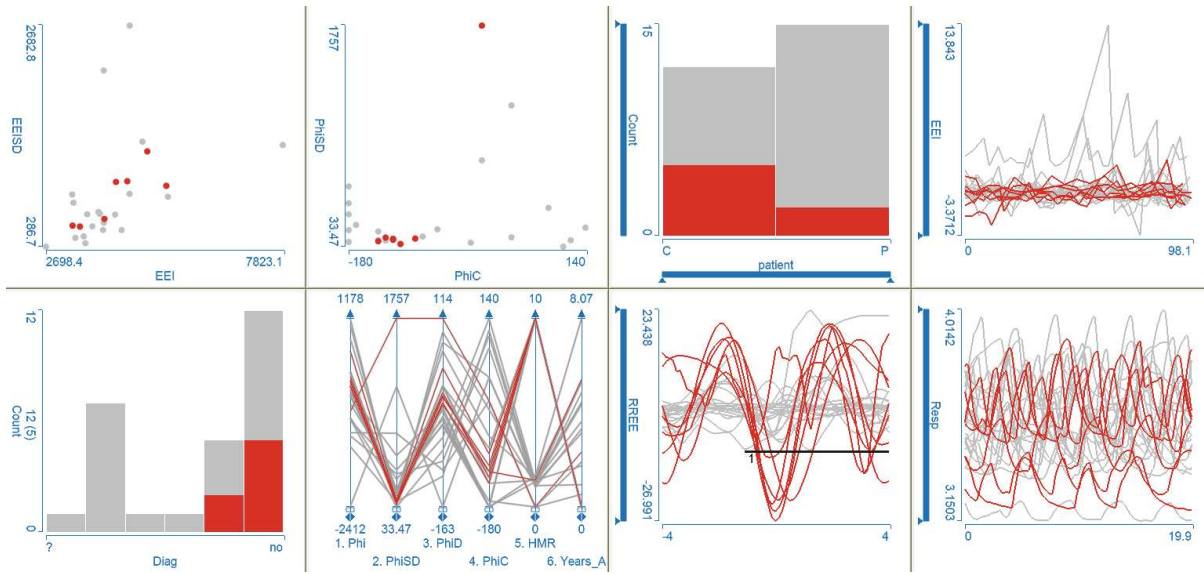
Fig. 5. Multiple coordinated views used for data analysis. User selected items having low values of RREE in the middle and right part of the curves. Corresponding items are selected in all views. Control patinets and real patients were selected (histogram in upper row) and there is an interesting cluster in PhiC/PhiSD scatterplot.
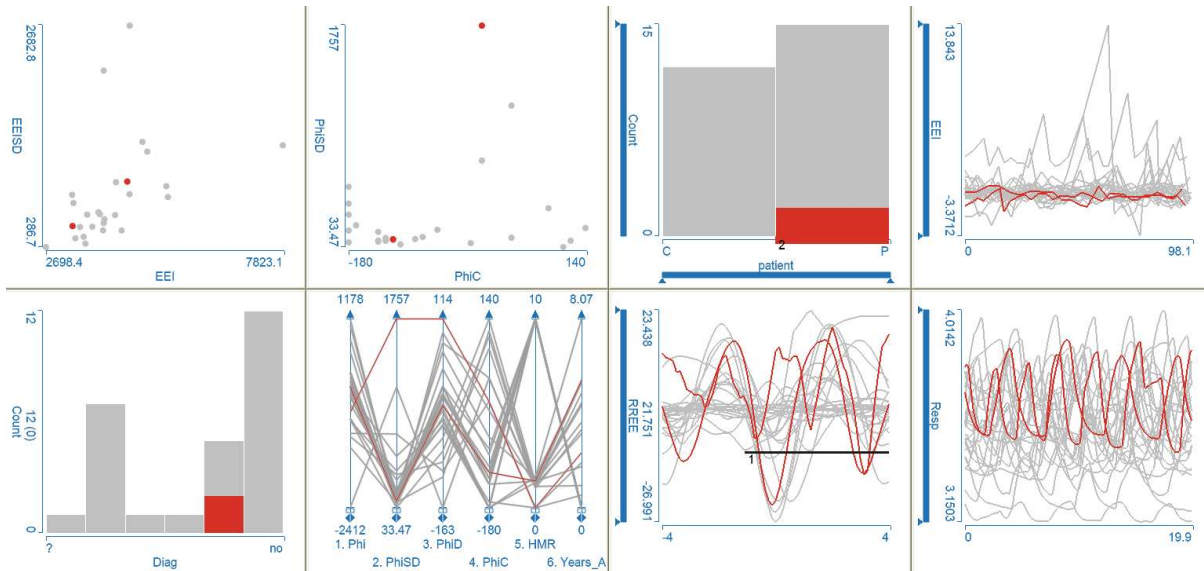


Fig. 6. The selection from Figure 5 is refined now. Only real patients are selected. All of them have ischemia as diagnosis (lower left histogram) and quite high values of resp curves.

## IV. INTERACTIVE VISUAL ANALYSIS

We will now illustrate how interactive visual analysis can help in understanding our data set. The data set is not large, there are only 27 patients. Nevertheless we have identified some interesting aspects which can serve as a basis for further investigation. We will start with RREE curves and select curves which have relatively low values in the middle and right hand part. Figure 5 bottom right shows the selection. The user simply draws a line (depicted with 1 in the figure) and all corresponding items are selected. The histogram in upper row shows that some real patients and some control patients belong to the selection. Note also very strong clustering in

the second scatterplot, depicting PhiC and PhiSD. There is one strong outlier in this scatterplot which certainly deserves our attention. The lower left histogram shows us that selected patients either have no diagnosis, or they are ischemic. We suppose that real patients correspond to ischemic and control patients to no diagnosis in this case. Let us refine the selection now. The user selected real patients only (Fig. 6) using AND brush (depicted with "2" in the figure.) Our suspicion about patients being ischemic confirmed. Note also EEI and Resp curves. In both views patients have lower values compared to control persons. Furthermore, the outlier in PhiC / PhiSD scatterplot remained. Actually, we can consider the bottom one
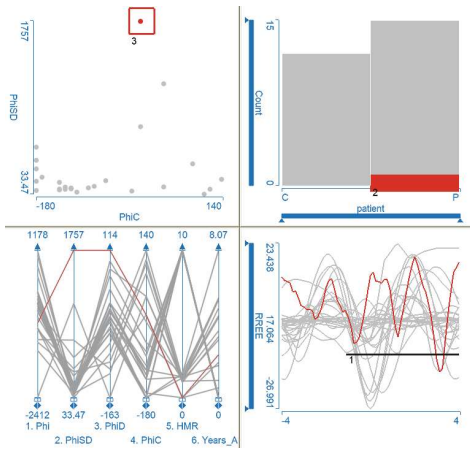
Fig. 7. Finally, the outlier form PhiC / PhiSD scatterplot has been isolated. Note his RREE curve, he hardly get into selection at very begin. It is an unusual RREE curve with low values on right hand side only.

to be outlier now since obviously this patient has characteristic similar to control persons (for this particular parameters.) If we finally select the outlier now we can see that his RREE curve is much higher than the rest in selection. It has low values in right most part only as shown in Figure 7.

Let us describe another example now. This time user selects curves with unusually high EEI curves. Figure 8a. shows this case. All selected items belong to real patients. If we look at the PhiC / PhiSD sctterplot again we can see that selected items form a cluster. There are two additional items in the cluster that are not selected. User selects them now using an OR brush (brush 2 in Figure 8)b. and sees that selected patients have one additional diagnosis now. We also see additional curves selected. The user wonders which is the patients with additional diagnosis, so he uses SUB brush and subtracts new diagnosis – diletative, idopative DKMP. The remaining selected diagnosis are diletative (left) and ischemic (right). Figure 8b. illustrates this case. We see that patient with idopative DKMP had the highest PhiC (this is gray now) and the Resp curves are of much more similar shape now. The idopative DKMP patient had significantly different shape of the Resp curve.

Finally we will illustrate a new finding, an unexpected discovery. Figure 9 illustrates this case. We can see two scatterplots, RRISD–ID and Phi–ID. Control persons are selected and depicted in red throughout this example. The first scatterplot shows that patients have (in general) lower RRISD values which is a well known fact. The second scatterplot shows that PHi seems to be larger for control persons, but not so dominantly. This was not well known to the domain experts before. The Phi parameter is a phase of the RREE signal (depicted in Figure 9, as well). We can see from the curve view that all control patients have approximately the same phase. The lower left scatterplot indicates the new finding. It seems that PHi increases as Years After Operation parameter increases. We could interpret this as normalization of the heart regulation system. Interestingly, the HMR (which represents
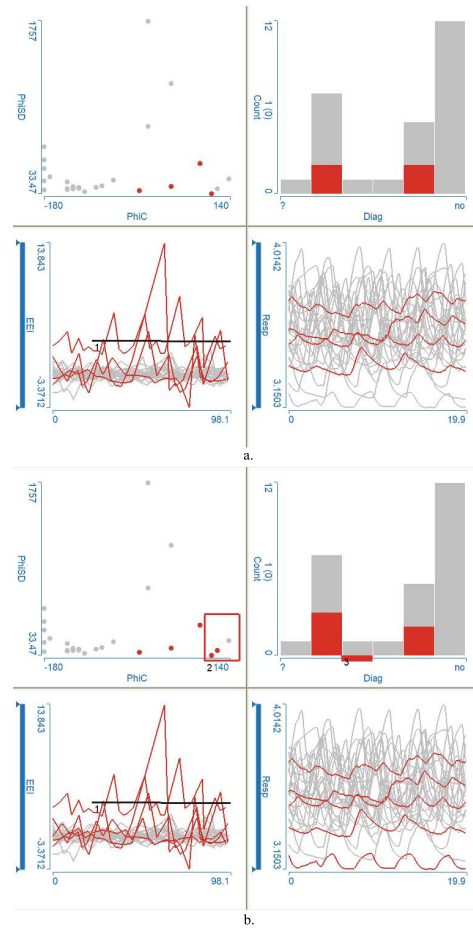


Fig. 8. a. The user selects unusually high EEI curves. A cluster is identified in PhiC / PhiSD scatterplot. All items belong to real patients having two different diagnosis. b. Further refinement is done by excluding idopative DKMP patient (brush 3 is SUBTRACT brush). This patient was on the border of the cluster, and Resp curves have more uniform shape now.

reinervation of transplanted heart) does not show such increase with time after operation. It seems that PHi might be a much better indicator of heart regulation normalization than HMR.

## V. CONCLUSION

The major finding of previous study [11] is that sympathetic reinnervation of the sinus node after HTx does not predict left ventricular sympathetic reinnervation and might have different time occurrence pattern. Sympathetic reinnervation was evaluated with two independent methods; MIBG was used to evaluate left ventricular sympathetic reinnervation and HRV to assess reinnervation of sinus node. Studies of sympathetic reinnervation after HTx based on investigation of sinus node function by HRV parameters, may be, regarding to our investigation, unreliable and possibly influenced by not well understood factors. Assessment of sympathetic ventricular reinnervation investigated by MIBG imaging seems to be more reliable.

At the end we have shown how interactive visual analysis can help us in gaining insight into the data set. We have
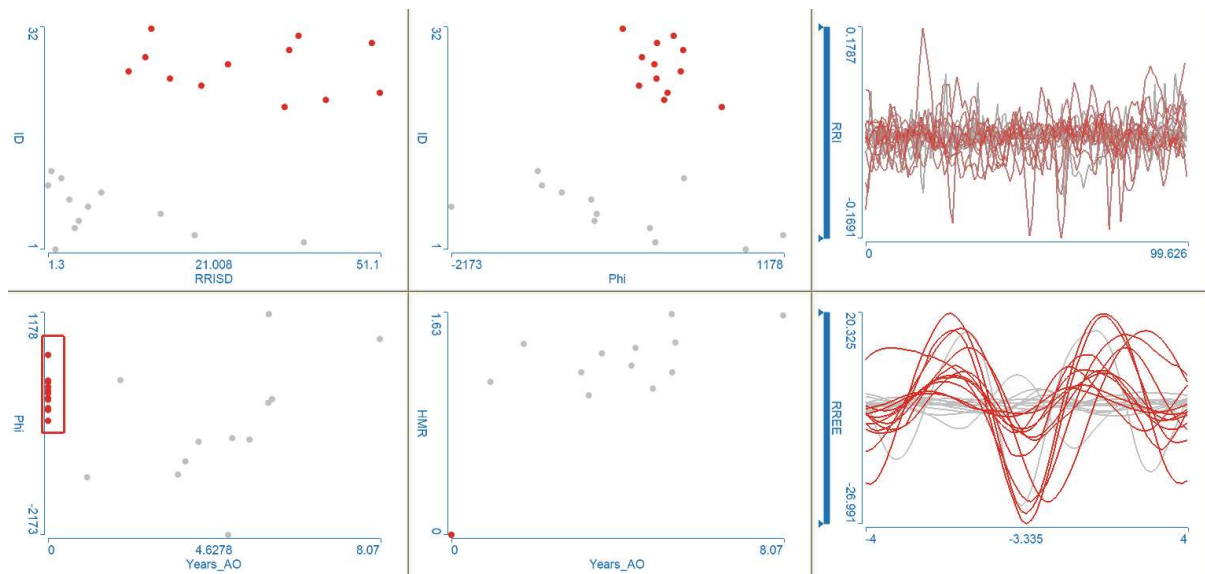
Fig. 9. An unexpected discovery. The control persons are selected and depicted in red. The lower left scatterplot illustrates the increase of Phi with increase of time after operation. After some time the phase of RREE signal (PHi) will become similar to the phase of control persons. This indicates a possibility of using PHi as a measure of the heart regulation normalization level, rather then using HMR which represents reinervation of transplanted heart.

detected some unexpected behavior and further study of described phenomena can certainly help domain experts in understanding complex interplay of parameters. Such unexpected findings can trigger new ideas and often act as a seed of new solution or theory.

In the future we will further exploit potentials of interactive visual analysis and design new views and analysis techniques suitable for medical experts.

## ACKNOWLEDGMENTS

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