Multivariate Classification of Cardiac Autonomic Function and Echocardiographic Abnormalities

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Abstract

Abnormalities in the function, physiology and the regulation of the heart can be diagnosed using echocardiography (ECHO) and analysis of heart rate variability (HRV). Patients with transthyretin amyloidosis often present increased wall thickness in the myocardium and/or autonomic dysfunction. We used a novel approach to analyse the relationship between these findings, using a combination of dimension reduction techniques and model based clustering.

1. Introduction

The function of the heart can be investigated using many different modalities, such as echocardiography (ECHO) and analysis of heart rate variability (HRV). In the present study, the relationships between data from these two modalities are assessed in both a multimodal and multivariate setting. The analyses are based on recordings from patients with hereditary transthyretin amyloidosis (ATTR amyloidosis) a severe fatal disease where both cardiac hypertrophy and autonomic dysfunction are common findings. ATTR amyloidosis is characterised by extracellular deposition of amyloid fibrils in tissue and organs, causing dysfunction and ultimately death. The hereditary form of the disease caused by the TTR V30M mutation is also called Familial amyloidotic polyneuropathy (FAP), and clusters of patients are noted, in Portugal, Japan, and Sweden[1]. Our aim was to analyse the relationship between these multimodal findings, using a combination of dimension reduction techniques and model based clustering.

2. Methods

2.1. Data acquisition

Data were obtained from previously performed clinical recordings from 39 adult patients and 62 healthy controls. HRV indices were calculated from 24-hour electrocardiographic recordings (Holter): the mean RR interval; the power of the very low-frequency (PVLF 0.003-0.04Hz), low-frequency(PLF 0.04-0.15Hz) and high-frequency components (PHF 0.15-0.5Hz). From standard echocardiographical examinations M-mode and Doppler measures were used: posterior wall thickness (PWT), septal thickness (IVS), left ventricular end diastolic dimension (LVDD), isovolumetric relaxation time (IVRT) and deceleration time (DT). The ECHO variable selection was based on a preliminary nonparametric univariate analysis, where variables were included for further analysis if they separated patients from controls in univariate statistical analyses ($p < 0.2$).

2.1.1. Statistical analysis

Principal component analysis (PCA) was performed for dimension reduction and to model the within modality variability of each group of variables, HRV and ECHO. The data were mean centered and scaled to unit variance before transformation. The number of significant PCA components were determined using a bootstrap-resamling based stopping method[2]. The factor loadings, describing the transformation of the original data onto the principal components, then were examined and interpreted. The significance of the loadings coefficients were estimated using 95% basic bootstrap intervals, and considered as significant if the zero was found outside the interval. The components scores were calculated by projections of the original data onto the principal components.

To identify sub-populations within the component scores, a hierarchical Gaussian mixture modeling method, Mclust[3], was used to find clusters of subjects in the resulting component scores. Each observation was assigned to a multidimensional gaussian ellipsoid Φ_k

$$\Phi_k(\mathbf{x}|\mu_\mathbf{k}, \mathbf{\Sigma_k}) = (2\pi)^{-\frac{p}{2}}|\Sigma_k|^{-\frac{1}{2}} \exp\{-\frac{1}{2}(\mathbf{x}-\mu_\mathbf{k})'\mathbf{\Sigma_k^{-1}}(\mathbf{x}-\mu_\mathbf{k})\}. \quad (1)$$

where each cluster Φ_k is centered at μ_k. The elliptic shape of each cluster is determined by the covariance matrix $\Sigma : k$, which is parameterized as

$$\Sigma_k = \lambda_k D_k A_k D_k^T. \quad (2)$$

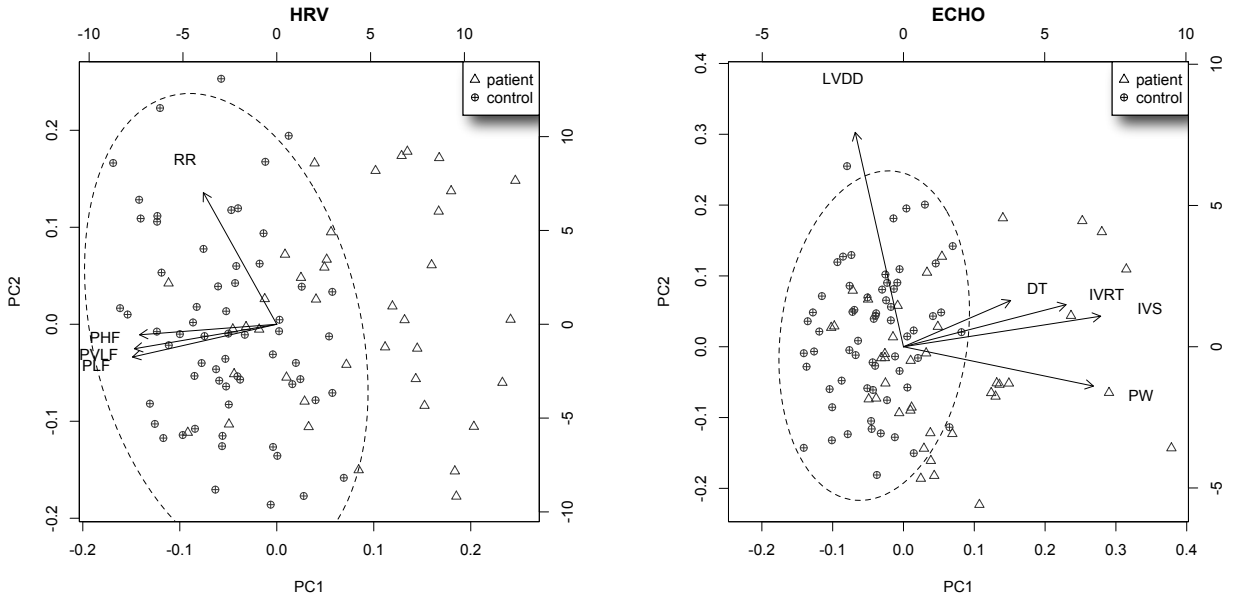

Figure 1. Biplot of PCA analysis of HRV (left) and ECHO (right) variables. The component loadings are visualized by arrows for each of the original variables. The component scores for controls and patients are plotted together with a 90% confidence ellipsis for the control group

Here, λ_k determines the shape, D_k the volume, and A_k the orientation of the ellipsoid [3]. The parameter estimation of the ellipsoids was made using the iterative EM-algorithm and the determination of the optimal number of clusters was based on the Bayesian information criteria.

To further analyze the interaction between the two sets of variables, a canonical correlation analysis(CCA) was performed on controls and patients separately. The CCA procedure creates linear combinations of the two sets of variables that maximizes the between set correlation. The linear combinations are called canonical covariates. The first canonical correlation was used as a measure of the connection between HRV and ECHO. The structural correlations are correlations between the original variables and the canonical covariates, and was used to describe the canonical correlations in terms of the original variables. The output from the CCA was validated using a bootstrap procedure similar to the one for the PCA loadings.

3. Results

The PCA resulted in two significant components(PC) for HRV, explaining 92% of the total variability and two significant components for ECHO, explaining 65% of the total variability. The contribution from each variable to the components are visualized in a biplot together with the component scores(Figure 1).

In HRV, the first principal component was dominated by the spectral parameters which all had similar contribution. The second component had most contribution from RR, while the effect from PHF could not be separated from zero. For ECHO, the first component had highest contributions from the anatomic measurements IVS and PW together with IVRT and DT, while the influence of LVDD was absent. PC2 was dominated by LVDD, which had the only significant contribution to this component.

For each modality, the cluster algorithm was applied to divide the components scores into three clusters. The cluster that mainly consisted of controls was denoted as Normal. The most diverging cluster was denoted Abnormal. The last cluster was denoted Borderline". The distribution of subjects into clusters are presented in Table 1

Nearly all controls (61/62) were classified as normal in ECHO, and as normal (young and middle-aged subjects) or borderline (middle-aged and old) in HRV, reflecting the well-known successive decrease in HRV with age in healthy subjects. For patients, the classification was related to the progress of disease: 36% had normal or borderline HRV and normal ECHO; 18% had abnormal HRV and normal ECHO; while 46% were classified as borderline or abnormal in both examinations.

The canonical correlation for controls was 0.43 and 0.55 for patients (Figure 2). Structrual correaltions for PVLF and PLF were high in both patients and controls. RR had lower influence while the relation with PHF was stronger in controls than in patients. For controls IVS and DT had

Table 1. Distribution of controls and patients from clustering, Control/Patients.

	E_N	E_B	E_A	Σ
H_N	42/6	1/0	0/0	43/6
H_B	19/8	1/3	0/3	19/14
H_A	0/7	1/9	0/3	0/19
Σ	61/21	1/12	0/6	62/39

the highest correlations with the ECHO canonical covariate, and for patients PW, IVS and LVDD were more prominent.

4. Discussion

The PCA resulted in equal number of significant components for both ECHO and HRV, although they differed in their ability in capture the variability of the data.

The first HRV component, PC1, mainly reflected the total variability in heart rate and provided a good separation between patients and controls. Subjects with high (positive) scores presented reduced HRV. We also noted that older controls tended to have higher scores (lower HRV) than younger controls. Therefore, PC1 could be considered as a marker of the magnitude of fluctuations in autonomic modulation of the sinus node [4]. Alternatively, PC1 could be a marker of parasympathetic modulation, which is reduced with increasing age. As RR dominated PC2, it could be a marker of mean levels of autonomic inputs. PC2 could possibly also reflect sympathetic activity, as the effect from PHF was found not significant in this component. Hence, patients with low scores in PC1 and high scores in PC2 were found to be the subjects with most disturbed regulation pattern, with low heart rate combined with very low total HRV.

The significant components of ECHO captured less variation than the HRV components. This is probably a result from greater dispersion among the variables in ECHO than among the HRV variables, with the spectral components highly correlated with each other. The first ECHO component can be related to the presence of increased wall thickness as the contribution from PWT and IVS were prominent. Relaxation and deceleration times have previously documented positive correlations with wall thickness[5], which was also indicated by their contribution to PC1. PC2 was closely related to LVDD. Patients classified as borderline in ECHO tended to have a smaller LVDD than both subjects classified as normal and abnormal, and therefore PC2 was found to be discriminating among patients without increased myocardial dimensions. ECHO borderline patients could represent a different stage of heart disease than hypertrophy. By Frank Starling's law the end diastolic volume will increase the stroke volume. Thus, a low

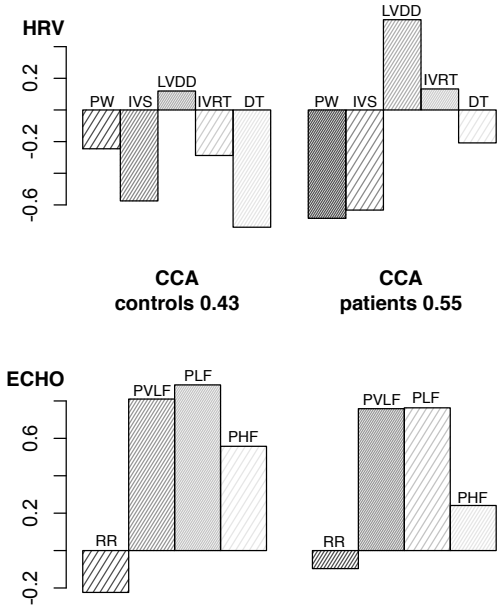

Figure 2. Canonical correlations for controls(left) and patients(right). Bars indicate the correlations between original variables and canonical covariates.

score in PC2 in ECHO and a high score in PC2 in HRV could imply a lower cardiac output.

Most patients were classified as borderline or abnormal in HRV, which can be explained by that a disturbance in the autonomic nervous system is a very common indication of TTR amyloidosis. Echocardiographic abnormalities are not always present in ATTR patients and 54% of the patients were classified as normal in ECHO. As shown in Table 1 the classification found 12 patients who were abnormal in HRV and borderline or abnormal in ECHO, which are the most affected patients with reduced heart function and probably with severe amyloid deposition in the myocardium.

The CCA was conducted on patients and controls separately to identify if the two groups had different relationships between modalities. Although the contribution from HRV variables to the canonical correlation was similar in both patients and controls, the two groups showed different patterns in ECHO. The patients tended to have a more anatomical driven effect on HRV as PW, IVS and LVDD had the largest contributions to the canonical correlation. This indicates a relation between increased wall thickness and lower total heart rate variability. It would have been desirable to examine the canonical correlations in the different cluster groups but unfortunately the sample sizes in the subgroups were to small to permit this analysis.

5. Conclusions

The analysis successfully separated between patients with regulatory involvement but only minor structural abnormalities, from those with both structural abnormalities and severe autonomic dysfunction. The presented method may also be used to model patterns in other diseases with cardiac and autonomic involvement.

References

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