The revised role of left ventricular dilatation and ACE-inhibition after myocardial infarction

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Approaches to statistical analysis of repeated echocardiographic measurements after myocardial infarction and its relation to heart failure – application of a random-effects model

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ABSTRACT

Background: Extensive left ventricular (LV) dilatation after myocardial infarction is associated with increased heart failure risk.

Aims: To investigate whether the power to demonstrate the relation between LV dilatation and heart failure depends on the method applied to predict LV dilatation after myocardial infarction.

Methods: A random-effects model and ANOVA model for repeated measurements (MANOVA) were applied to predict LV volume index during 1 year for 298 post-myocardial infarction patients. Spearman correlation coefficients (r) were calculated and Cox regression analysis was used to calculate risk ratio’s (RR).

Results: LV volume indices were more accurately predicted by a random-effects model than by a MANOVA model (systolic/diastolic respectively r=0.93/0.91 versus r=0.67/0.64). Furthermore, patients with high LV volume index as predicted by the random-effects model, had significantly increased heart failure risk (systolic RR 2.04 (95% CI: 1.31 to 3.17; p=0.001), diastolic RR 1.80 (95% CI: 1.16 to 2.78; p=0.007). Using the same data, MANOVA failed to demonstrate this relation significantly (systolic RR 1.77 (95% CI: 0.79 to 3.98; p=0.16), diastolic RR 1.49 (95% CI: 0.68 to 3.30; p=0.31).

Conclusions: When analysing repeated measurement data, random-effect models are often more powerful in detecting clinical relations than are MANOVA models, especially in the presence of missing values.

INTRODUCTION

Patients with extensive left ventricular (LV) dilatation after myocardial infarction are at increased risk to develop heart failure. To determine the extent of LV dilatation after myocardial infarction, repeated 2-D echocardiography is frequently applied. However, the analysis of repeated echocardiographic measurements is often not optimal, and echocardiographic studies are amongst those who may benefit from a more sophisticated statistical analysis. Many echocardiographic studies have been performed after myocardial infarction, and applied either analysis of variance (ANOVA) models, or ANOVA models for repeated measurements (MANOVA) to assess the extend of LV dilatation after myocardial infarction. However, applying a random-effects model may result in more
accurate prediction of LV dilatation, and may prove to be a more powerful approach to detect the relation between LV dilatation and mortality and cardiac morbidity (e.g. heart failure) after myocardial infarction. The aim of the present study was to investigate whether the power to demonstrate the relation between LV dilatation and heart failure depends on the method applied to predict LV dilatation after myocardial infarction. This evaluation was performed in two steps, using the data of the Captopril And Thrombolysis Study (CATS) study with five repeated echocardiographic assessments during one year after myocardial infarction. Firstly, we explored whether a random-effects model better predicted the repeated LV volume measurements than the MANOVA model. Secondly, we investigated whether the 1-year volume measurements as predicted by the applied random-effects model were more powerful than the 1-year predictions of the MANOVA model to detect the relation between extensive LV dilatation and increased risk on heart failure.

METHODS

Patient population
In the present study, the data of the CATS study was used to evaluate whether the power to demonstrate the relation between LV dilatation and heart failure is dependent on the method applied to predict LV dilatation after myocardial infarction. CATS was a multi-centre double-blind, placebo-controlled trial in 298 patients with a first anterior myocardial infarction, in which repeated echocardiographic measurements were used to investigate the process of LV dilatation or remodeling. Thirteen Dutch centres participated in CATS. The CATS study conformed with the principles outlined in the Declaration of Helsinki. LV volume was measured by serial 2D-echocardiograms at 1, 3, and 10 days and at 3 and 12 months after myocardial infarction. Two parameters of LV volume were determined: LV diastolic volume index and LV systolic volume index. These two parameters were calculated from the end-diastolic and end-systolic left ventricular dimensions, using Simpsons rule and divided by body surface area. All echocardiograms were evaluated in an echocardiographic core lab by one single person.

Applied statistical models
In the present study, two models were applied to assess LV dilatation after myocardial infarction: an ANOVA model for repeated measurements (often referred to as a MANOVA
model) and a random-effects model. A suitable approach for the analysis of repeated measurements is MANOVA. In MANOVA, the relation between volume index and time can be represented by regression lines, constructed for each patient separately, however only for patients with a complete sequence of volume indices. In the applied MANOVA model, two sources of variation were distinguished: between subject variation (variation in the course of these regression lines) and residual variation (calculated from the differences of the measured LV volume indices to each regression line). The dependency between the LV volume indices in time, or the covariance structure was fixed in the MANOVA model (compound symmetry).

In the applied random-effects model the relation between LV volume index and time can be represented by an overall regression line. Two sources of variation were distinguished: the between-subject variation, by adding random variation to both the intercept and the slope, and the residual variation. When constructing a random-effect model, an appropriate variance-covariance structures should be selected. The covariance structure incorporates the dependency between the LV volume indices as measured at the different time-points. A good first impression of the dependency between echocardiographic measurements in time was obtained by constructing a sample variogram. The sample variogram for both LV diastolic and systolic volume index clearly showed that there was more dependency between LV volume indices when measured a few days apart than between LV volume indices measured weeks or months apart. Based on the sample variogram and also based on clinical considerations, the first order auto-regressive variance-covariance matrix seemed to be a good assumption. However, since the time-interval between two subsequent echocardiographic assessments increased during the study (i.e. echocardiographic assessments were performed at day 1, 3, 10, 90 and 360), the heterogeneous variant of the first order auto-regressive variance-covariance was selected. This variance-covariance structure also proved to be a good assumption after a post-hoc comparison of similar random-effects models with different covariance structures.

**Comparison of model results**

To compare the model results, the progression of LV volume indices in (log) time was modelled with the same selection of baseline characteristics (table 1). Furthermore, the LV volume indices were logarithmically transformed for both models. To explore the extent to which the echocardiographic measurements were better predicted by a random-effects model than by a MANOVA model, the predicted echocardiographic volume indices were plotted
coefficient (r) was calculated. A higher Spearman correlation coefficient was an indication of a better fit of the model to the measured LV volume indices. The assumption of normality was explored by constructing residual plots, in which the residuals were plotted as a function of the predicted value for both the MANOVA and random-effects model. Furthermore, two steps were distinguished to investigate whether the applied random-effects model achieved higher power in demonstrating the relation between LV dilatation and heart failure than the MANOVA model. Firstly, for each applied model, patients with significant LV diastolic dilatation and significant systolic dilatation were identified, based on the predicted LV volume index at 1 year. To obtain a prediction of 1 year LV systolic dilatation and diastolic dilatation by the random-effects model, we excluded all LV volume indices measured after the heart failure event. Since previous studies reported that 25% of all patients developed significant LV dilatation after myocardial infarction $^{15,16}$, CATS patients with LV diastolic dilatation were identified as the 25% of the patients with highest predicted LV diastolic volume index at 1 year, and patients with LV systolic dilatation as the 25% of the patients with highest predicted LV systolic volume index at 1 year. Secondly, we determined the cumulative incidences of heart failure by Kaplan-Meier survival analysis, and compared the cumulative incidences of heart failure between patients with and without predicted LV diastolic dilatation and between patients with and without LV systolic dilatation predicted as determined for each model separately. A log-rank test was used to evaluate statistical difference. In addition, a Cox regression analysis was performed to determine risk-ratios and 95% confidence intervals.

SAS (Cary, North Carolina) version 6.12 was used for all statistical analyses. PROC MIXED was used to fit the applied random-effects model. All tests were two-sided, and a p-value $\leq 0.05$ was considered statistically significant.

**RESULTS**

*Patient Population*

Of the 298 randomized patients, for 272 patients at least one, and for 122 patients all five repetitive assessments of LV volume were performed during one year after myocardial infarction. The main baseline characteristics of these 272 CATS patients are presented in Table 1. The median baseline left ventricular diastolic volume index was 55 ml/m$^2$ (range 24 - 105 ml/m$^2$) and the median baseline left ventricular systolic volume index 24 ml/m$^2$ (range 9 – 70).
Table 1: Baseline characteristics included for the prediction of LV dilatation for both the MANOVA and random-effects model

<table>
<thead>
<tr>
<th>Baseline characteristic (N=272)</th>
<th>Summary statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>59 (10)</td>
</tr>
<tr>
<td>Number of males (%)</td>
<td>209 (77)</td>
</tr>
<tr>
<td>Number of smokers (%)</td>
<td>171 (64)</td>
</tr>
<tr>
<td>Mean heart rate in beats/min (SD)</td>
<td>81 (15)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure in mmHg (SD)</td>
<td>77 (13)</td>
</tr>
<tr>
<td>Mean systolic blood pressure in mmHg (SD)</td>
<td>126 (20)</td>
</tr>
<tr>
<td>Median infarct size in U/l (min - max)*</td>
<td>1311 (17 - 6799)</td>
</tr>
<tr>
<td>Number of small infarcts (%)</td>
<td>87 (32)</td>
</tr>
<tr>
<td>Number of medium infarcts (%)</td>
<td>88 (32)</td>
</tr>
<tr>
<td>Number of large infarcts (%)</td>
<td>88 (32)</td>
</tr>
<tr>
<td>Number of patients with β-blockers at admission (%)</td>
<td>56 (21)</td>
</tr>
</tbody>
</table>

* The cumulative α-hydroxybutyrate dehydrogenase release (α-HBDH) was used as measure of infarct size, additionally, small, medium and large infarcts were defined by the tertiles of the infarct size distribution.

Figure 1: Progression of left ventricular diastolic volume index after myocardial infarction (for six randomly selected patients a regression line was fitted)
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ml/m²). There was substantial variation of volume indices at baseline and course of ventricular volume index over time (Fig. 1). Generally, LV volume index gradually increased over time, and patients with a lower volume index at baseline tended to remain lower during follow-up. The measured LV diastolic indices correlated better with the predicted diastolic volume indices of the random-effects model than with those of the MANOVA model (Fig. 2).

![Figure 2: Correlations between the measured left ventricular diastolic volume indices, and the volume indices as predicted by the MANOVA model and random-effects model](image)

In agreement with this finding, the measured systolic volume indices correlated better with the predicted systolic volume indices of the random-effects model ($r=0.93$) than with the predictions of the MANOVA model ($r=0.67$).

Infarct size, classified in small, medium or large was the most powerful determinant of LV volume index for both models. Patients with larger infarct size showed larger volume indices at study entry, and more pronounced progression of LV volume index in time. In addition, male gender was associated with higher LV volume indices. However, the estimation of the effect of baseline characteristics on progression of LV volume index was more accurate for the random-effects model than for the MANOVA model as expressed by smaller 95% confidence intervals. Furthermore, the important assumption of normality was assessed by constructing residual plots (Fig. 3). By analysing the LV volume indices on the logarithmic scale, an evenly distribution of the residuals above and below zero for
every associated variable was demonstrated, which indicated that the assumption of normality was justified. We defined patients with significant LV diastolic dilatation and significant LV systolic dilatation as 25% of all patients with highest predicted 1 year LV diastolic indices and LV systolic indices respectively. This resulted in the conclusion of LV diastolic dilatation if the predicted 1 year LV diastolic volume index exceeded 60 ml/m² and the conclusion of LV systolic dilatation if the predicted 1 year LV systolic volume index exceeded 26 ml/m² (differing only slightly between the applied models).

Figure 3: Residual plots for LV diastolic volume index, residuals and predicted values were obtained from both the MANOVA model and random-effects model; LVEDVI, left ventricular diastolic volume index.

If LV dilatation was predicted by the applied random-effects model, a statistically significant relation between LV dilatation and the development of heart failure was demonstrated (LV diastolic dilatation $p=0.007$: RR=1.80 (95% CI 1.16 to 2.78) (Fig. 4), LV systolic dilatation $p=0.001$: RR=2.04 (95% CI 1.31 to 3.17). In contrast, based on the applied MANOVA model, the relation between extensive LV dilatation and heart failure could not be detected significantly (LV diastolic dilatation $p=0.31$: RR=1.49 (95% CI 0.68 to 3.30) (Fig. 4), LV systolic dilatation $p=0.16$: RR=1.77 (95% CI 0.79 to 3.98).
Progression of LV dilatation may occur after myocardial infarction and is a dynamic and time-dependent process starting in the first days after infarction often proceeding over months to years after myocardial infarction. Along with progression of LV dilatation, the incidence of heart failure increases during the years after myocardial infarction. Previous large studies showed that patients with extensive LV dilatation are at high risk to develop heart failure. In the present study we demonstrated that the power to demonstrate the relation between LV dilatation and heart failure depends on the method applied to predict LV dilatation after myocardial infarction. The results of our study suggest that the more accurate prediction of the LV volume indices during one year after first anterior infarction by the random-effects model (Fig. 2), resulted in a more powerful detection of the positive relation between extensive LV dilatation and heart failure (Fig. 4). Furthermore, in accordance of the results of previous studies, the results of the present study showed that extensive progression of systolic volume index was a stronger predictor of heart failure than extensive progression of diastolic volume index.

The properties of the data in this longitudinal echocardiographic study after myocardial infarction, are common for many other repeated measures studies. These properties are: (1) the correlation of volume indices within a patient over time, (2) the variation in volume
indices between patients at baseline, (3) the variation between patients in LV enlargement over time, (4) the variation in observation time during follow-up, and (5) the relatively high number of missing LV volume indices. The ideal statistical model should take into account all of these properties, because neglecting them may potentially bias the model results. In the MANOVA model the correlation of repeated measurements within a patient was included by a pre-specified (fixed) correlation structure. However, in the random-effects model an appropriate correlation structure was selected, based on clinical and statistical considerations. The selection of an appropriate covariance structure may have contributed to the gain in accuracy of the results produced by the random effect model.

Both the random-effects model and the MANOVA model distinguish the variation between patients and variation within patients. As opposed to the MANOVA model however, the random-effect model could more efficiently modulate the between subject variation by separation of the between patient variation at baseline and the between patient variation in progression of LV volume index in time. The distinction of variation between patients and variation within patients is characteristic of repeated measurement data and enables better extrapolation of conclusions to the total population of interest. An important consequence of modelling two variation terms instead of one (ANOVA) is that generally larger samples sizes are needed to statistically significantly demonstrate relations or effects of trial medication. Another advantage of the random-effects model over the MANOVA model was the ability to handle the variation in observation time, because of its ‘parametric model approach’\textsuperscript{12}. This approach does not require that the repeated measurements are assessed exactly at predetermined points in time as MANOVA does, and consequently can adequately deal with diverging time sequences of repeated measures between patients.

The main reason for the more efficient prediction of the relation between extensive LV dilatation and the development of heart failure of the random-effects model as compared to the MANOVA model may be the handling of missing values. Missing values often complicate the analysis of many longitudinal studies. The presence of missing data is common in longitudinal echocardiographic studies after myocardial infarction. In the present study, only 31% of all patients had complete LV volume measurements. Volume measurements were mainly intermittently missing, due to logistic reasons and reasons directly related to LV volume (e.g. temporary hospitalization due to progressive heart failure). A smaller proportion of the missing data is missing due to drop-out (death, lost to follow-up). Currently, a well-developed missing values in longitudinal data is still in research\textsuperscript{12}.  

For the random-effects model, all measured volume indices were included to predict LV dilatation. In contrast, MANOVA models only included patients with complete sequences of repeated measurements in their calculations. Therefore, in the present study, the MANOVA model could only include 58% of all available LV volume measurements and calculations included 42% of all occurrences of heart failure. Consequently, the MANOVA model possibly disregarded important echocardiographic information of patients for whom for any reason one or more assessment of LV volume could not be obtained.

Finally, although ANOVA or repeated t-testing is frequently applied in the analysis of repeated measurement data, it is inappropriate and may lead to wrong conclusions. Since ANOVA acts as if the data repeatedly measured on the same patient are single observations obtained from different patients, two unique characteristics of repeated measurement data are ignored: the dependency between the repeated measurements in time and the separation of variation between subjects and variation within subjects.

**CONCLUSIONS**

In the present study we demonstrated that the LV volume indices as predicted by the applied random-effects model are much more powerful in detecting the relation between extensive LV dilatation and heart failure than are the predictions of the MANOVA model. The random-effects model optimally handles most of the complexities characteristic for repeated measurement data, while the major disadvantage of MANOVA is that only patients with complete sequences of repeated measurements are included. The results of the present study encourage more systematic use of random-effects models instead of MANOVA in the analysis of repeated measurements, especially in the presence of missing values.

**REFERENCES**


